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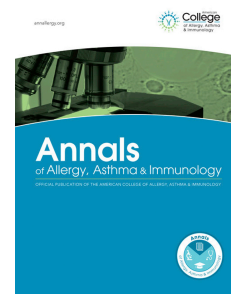
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No difference in omalizumab efficacy in patients with asthma ~~Efficacy of omalizumab therapy in patients with asthma~~ **by number of asthma-related/allergic comorbidities**

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Conflict of Interest

Dr Chen is a former employee of Genentech, Inc., and received fellowship grant support from Genentech, Inc. E. Choo is an advisory board member for Teva Respiratory, and is on the speaker board for AstraZeneca. Dr Yoo, Mr Raut, Dr Pazwash, and Dr Holweg are employees of Genentech, Inc. Dr Haselkorn is a former consultant for Genentech, Inc. and Novartis Pharmaceuticals Corporation. Dr Hudes receives research grant support from AstraZeneca, Genentech, Inc., and Merck, and is an advisory board member for AstraZeneca and GlaxoSmithKline.

Funding Source

Included studies (008/009; EXTRA [NCT00314574]; INNOVATE [NCT00046748]; PROSPERO [NCT01922037]) and this analysis were funded by Genentech, Inc., a member of the Roche Group, and Novartis Pharma AG.

Clinical Trial Registration

EXTRA: NCT00314574 (<https://clinicaltrials.gov/ct2/show/NCT00314574>); INNOVATE: NCT00046748 (<https://clinicaltrials.gov/ct2/show/NCT00046748>); PROSPERO: NCT01922037 (<https://clinicaltrials.gov/ct2/show/NCT01922037>)

Key words

Allergic asthma, comorbidity, exacerbations, forced expiratory volume, omalizumab

Abbreviations/Acronyms

AR, allergic rhinitis; CI, confidence interval; FEV₁, forced expiratory volume in 1 second; IgE, immunoglobulin E; Q2W, every 2 weeks; Q4W, every 4 weeks; RRR, relative rate reduction.

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Background: Comorbidities are common in asthma and may complicate treatment response. Objective: To examine response to omalizumab in patients with moderate-to-severe allergic asthma by asthma-related/allergic comorbidities. Methods: Patients aged 12 years or more from placebo-controlled 008/009 (n = 1071), EXTRA (n = 848), and INNOVATE (n = 419), and single-armed PROSPERO (n = 801) omalizumab studies were included. Poisson regression/analysis of covariance models were used to estimate adjusted exacerbation rates/forced expiratory volume in 1 second (FEV1) change from baseline after omalizumab initiation for subgroups by number of comorbidities (0/1 [008/009]; 0/1/≥2 [EXTRA/INNOVATE]; 0/1/2/≥3 [PROSPERO]). Self-reported comorbidities included allergic rhinoconjunctivitis, chronic rhinosinusitis, recurrent acute sinusitis, nasal polyps, atopic/contact dermatitis, urticaria, food allergy, anaphylaxis, other allergies, gastroesophageal reflux disease, eosinophilic esophagitis, and eosinophilic granulomatosis with polyangiitis. Results: In EXTRA/INNOVATE, no consistent pattern was observed for placebo-corrected relative rate reduction in normalized asthma exacerbations among omalizumab-treated comorbidity subgroups. In PROSPERO, on-study exacerbation rates in the comorbidity subgroups were similar (0, 0.68; 1, 0.70; 2, 0.77; ≥3, 0.80). FEV1 improvements were observed throughout the study for omalizumab vs placebo for all comorbidity subgroups. There were no consistent differences in FEV1 improvements among comorbidity subgroups in 008/009, EXTRA, or INNOVATE. Similarly, no among-group differences were observed for FEV1 change from baseline at month 12 in PROSPERO (0, 0.05 L; 1, 0.08 L; 2, 0.00 L; ≥3, 0.04 L). 95% confidence intervals overlapped substantially in all instances. Conclusion: In these analyses of placebo-controlled/single-armed studies, on-study exacerbation rates/FEV1 improvements with omalizumab treatment were similar irrespective of comorbidity burden.

1 Introduction

2 Patients with asthma have a higher prevalence of comorbid conditions, such as
3 gastroesophageal reflux disease (GERD),¹ allergic rhinitis (AR),^{1,2} nasal polyps,¹ urticaria,³
4 atopic dermatitis,^{2,3} and food allergy.² The presence of comorbidities is associated with
5 poorer asthma control,⁴⁻⁶ inadequate response to treatment,⁷ and higher health care resource
6 utilization.^{5,8} Patients with severe asthma have a particularly high prevalence of
7 comorbidities,⁴ which may contribute to uncontrolled disease and complicate asthma
8 management.⁹

9 The link among asthma and comorbidities is complex; however, studies suggest a
10 shared underlying inflammatory pathophysiological mechanism. The allergic asthma
11 endotype, characterized by elevated levels of allergen-specific immunoglobulin E (IgE)
12 antibodies and a type 2 dominant immune response, is highly associated with a cluster of
13 other allergic conditions, such as atopic dermatitis, food allergy, and AR.¹⁰ Multimorbid
14 asthma, the presence of 1 or more comorbid conditions, is further associated with an IgE-
15 polysensitized phenotype, which is accompanied by high allergen-specific IgE, high total
16 IgE, and type 2 inflammation.¹⁰

17 Omalizumab, an anti-IgE antibody, has demonstrated efficacy in reducing asthma
18 exacerbations and improving asthma control in patients with moderate-to-severe allergic
19 asthma in large randomized controlled trials and real-world observational studies.^{11,12}
20 However, the response to omalizumab in patients with or without asthma-related or allergic
21 comorbidities has not been previously examined. We conducted post hoc exploratory
22 analyses using data from key placebo-controlled (008/009, INNOVATE, EXTRA) and real-
23 world (PROSPERO) omalizumab studies to investigate the impact of comorbidity burden and
24 type on asthma treatment outcomes with omalizumab in patients with allergic asthma.¹³⁻¹⁸

25

Methods

Study Design

Exploratory analyses were conducted in patients with moderate-to-severe allergic asthma from the 008/009, EXTRA (NCT00314574), INNOVATE (NCT00046748), and PROSPERO (NCT01922037) omalizumab studies. Patients were aged 12 to 75 years in the 008/009, EXTRA, and INNOVATE studies, and 12 years or more in PROSPERO. Full study details, including overall safety results, have been published previously.¹³⁻¹⁸

Briefly, studies 008 and 009 were methodologically identical, randomized, double-blind, placebo-controlled trials in patients with moderate or severe allergic asthma and persistent symptoms while on inhaled corticosteroids.^{13,14} EXTRA and INNOVATE were randomized, double-blind, placebo-controlled studies in patients with severe allergic asthma and persistent symptoms despite use of inhaled corticosteroids and long-acting β_2 -agonists.^{15,16,19}

PROSPERO was a US-based, multicenter, single-arm, prospective, observational study in patients with allergic asthma initiating omalizumab based on physician-assessed need.^{17,18} EXTRA and PROSPERO did not require reversibility of 12% or more as an inclusion criterion, and also enrolled patients who demonstrated low or no bronchodilator reversibility. In all studies except PROSPERO, dosing of omalizumab was based on body weight and total serum IgE per the prescribing information.²⁰ Because PROSPERO was an observational study, patients were evaluated and treated according to the investigator's standard practice.

All studies were approved by an institutional review board and were conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Written informed consent was obtained from each participant or their guardian.

Assessments and Comorbidity Burden

Studies 008 and 009 comprised a 4- to 6-week run-in period, 16-week steroid-stable phase, and 12-week steroid-reduction phase^{13,14}; EXTRA was a 48-week study¹⁹; INNOVATE was a 52-week study comprising an 8-week run-in phase, 28-week drug add-on phase, and 16-week follow-up phase¹⁵; and PROSPERO was a 48-week study.²⁰ Forced expiratory volume in 1 second (FEV₁) improvements were reported for weeks 0, 4, 8, 12, and 16 of the steroid-stable phase of studies 008/009; weeks 0, 12, 24, 36, and 48 in EXTRA; weeks 0, 4, 12, 20, and 28 of the drug add-on phase in INNOVATE; and months 0, 6, and 12 in PROSPERO. Exacerbations were recorded throughout the study for EXTRA, INNOVATE, and PROSPERO. Because studies 008 and 009 were methodologically identical, data from these studies were pooled.

Comorbidities that were included in the present analysis were allergic rhinoconjunctivitis (AR), chronic rhinosinusitis, recurrent acute sinusitis, nasal polyps, atopic or contact dermatitis, urticaria, food allergy, anaphylaxis, other allergies (nonsteroidal anti-inflammatory drugs, aspirin, venom, chemical, latex), ~~gastroesophageal reflux disease~~ GERD, eosinophilic esophagitis, and eosinophilic granulomatosis with polyangiitis (Table 1). Ongoing comorbidities were captured from patient medical records or were self-reported as part of medical history at baseline.

Comorbidity burden was based on the distribution of the number of comorbidities for each study. For 008/009, the comorbidities were categorized as 0 or 1 comorbidities; for EXTRA and INNOVATE, comorbidities were categorized by as follows: 0, 1, and 2 or more comorbidities; and for ~~EXTRA and INNOVATE~~ PROSPERO, 0, 1, 2, and 3 or more comorbidities ~~for PROSPERO~~. The varied number of categories was due to differences in study size and capture of comorbidities.

The effect of comorbidity burden on the efficacy of omalizumab was evaluated by asthma exacerbations per study duration for PROSPERO and relative rate reduction (RRR) in asthma exacerbations per study duration for EXTRA and INNOVATE. Exacerbation analyses were not performed for studies 008/009 due to the short observation period. Change from baseline in FEV₁ at each study visit was analyzed for all studies.

Exacerbation and FEV₁ analyses were also carried out by specific common comorbidities (allergic rhinoconjunctivitis [AR] and gastroesophageal reflux disease [GERD]) reflecting allergic and non-allergic status, in EXTRA and PROSPERO, as patient numbers were sufficiently high for these comorbidities.

Statistical Analysis

Baseline demographics and clinical characteristics are presented by study. Categorical variables were summarized by frequencies and percentages, and continuous variables were summarized by means and standard deviations, or medians and interquartile ranges, as appropriate.

For the exacerbation analysis, Poisson regression, with the log of time at risk as the offset variable, was used to estimate the exacerbation rate and its associated 95% confidence interval (CI) by comorbidity burden. Variables included treatment (omalizumab vs placebo), prior exacerbations, asthma controller medication at baseline, and dosing schedule (every 2 weeks [Q2W] vs every 4 weeks [Q4W]). RRR could not be computed for PROSPERO due to the lack of a control arm, and exacerbation rates prior to and during the study are therefore reported.

For the lung function analysis, an analysis of covariance model was used to estimate adjusted mean change from baseline in FEV₁ (mL) or percent predicted FEV₁ at each postbaseline study week for comorbidity subgroups. The model included change from

baseline measurement as the outcome, and treatment (omalizumab vs placebo, where applicable), baseline FEV₁ or percent predicted FEV₁ as appropriate, and their interaction as covariates. Results are presented as least squares means of between-treatment differences in FEV₁ for studies 008/009, EXTRA, and INNOVATE.

Results

Demographic and Baseline Clinical Characteristics

Baseline demographics and clinical characteristics were generally similar across studies (Table 24). However, there was a lower proportion of female patients in PROSPERO (36.6%) compared with studies 008/009 (54.8%-55.0%), EXTRA (61.4%-70.1%), and INNOVATE (65.7%-67.5%). There was also a higher proportion of White patients in the pooled population from studies 008/009 (89.0%-91.1%) compared with EXTRA (73.3%-75.5%), INNOVATE (78.0%-78.1%), and PROSPERO (70.8%), and a higher proportion of Black patients in EXTRA (20.4%-21.1%) and PROSPERO (16.2%) compared with studies 008/009 (5.1%-5.9%) and INNOVATE (6.7%). Mean baseline FEV₁ reversibility following bronchodilator administration was lower in patients in EXTRA (11.7%-12.4%) and PROSPERO (7.9%) compared with patients in studies 008/009 (25.9%-26.6%) and INNOVATE (21.4%-22.1%).

An asthma exacerbation requiring treatment with systemic corticosteroids in the past 12 months was required for entry into EXTRA and INNOVATE, but not for PROSPERO. In the year before enrollment, the mean number of asthma exacerbations in patients randomized to omalizumab and placebo was broadly similar across comorbidity groups in EXTRA and INNOVATE. In EXTRA, the mean number of exacerbations in the year before enrollment in the omalizumab and placebo groups for the 0, 1, and 2 or more comorbidity subgroups was 1.9 and 1.9, 1.9 and 1.9, and 2.2 and 2.0, respectively. In INNOVATE, the mean number of

exacerbations in the year before enrollment and during run-in for the omalizumab and placebo groups for the 0, 1, and 2 or more comorbidity subgroups was 2.9 and 2.6, 3.1 and 2.6, and 2.9 and 3.0, respectively. The mean number of asthma exacerbations in the year before enrollment was also similar across the comorbidity subgroups in PROSPERO, with 3.3, 3.1, 2.8, and 3.1 in the 0, 1, 2, and 3 or more comorbidity subgroups, respectively (Fig 1C).

Rate of On-Study Asthma Exacerbations by Number of Comorbidities

There was no consistent impact of comorbidity burden on exacerbation rate reductions across studies included in this analysis (Fig 1). Within EXTRA, placebo-corrected rate reductions were greater in patients with 1 (33.9%) and 2 or more (21.5%) comorbidities vs patients with 0 comorbidities (12.9%) (Fig 1A). However, within INNOVATE, placebo-corrected RRR in asthma exacerbations showed the opposite trend, where patients without comorbidities had the best response (placebo-corrected RRR, 38.1%, 26.2%, and -8.4% for the 0, 1, and ≥ 2 comorbidity groups, respectively) (Fig 1B). In PROSPERO, on-study exacerbation rates were generally similar among comorbidity subgroups, despite small increases with increasing number of comorbidities (0.68, 0.70, 0.77, and 0.80 for 0, 1, 2, and ≥ 3 comorbidities, respectively) (Fig 1D). The 95% CIs highly overlapped in all 3 studies, suggesting that there was no difference in exacerbation rate reductions among the groups of different comorbidity burdens.

Change from Baseline in Absolute FEV₁ by Number of Comorbidities

Improvements in FEV₁ were observed with omalizumab across comorbidity subgroups in all studies, despite low FEV₁ reversibility in EXTRA and PROSPERO. Within

each of the studies, FEV₁ improvements with omalizumab were similar among patients with 0, 1, or 2 or more comorbidities present, with 95% CIs highly overlapping (Fig 2).

In studies 008/009 (FEV₁ assessed at baseline and Q4W up to week 16), placebo-corrected improvements in FEV₁ were observed as early as week 4 and were maintained over the study period. Improvements were similar for patients with 0 or 1 or more comorbidities, with overlapping 95% CIs for all groups (Fig 2A).

In EXTRA (FEV₁ assessed at baseline and Q4W up to week 48), improvements fluctuated across the study period in all comorbidity subgroups. There were no clear differences in improvements among comorbidity subgroups over the study period, with substantial overlap in 95% CIs (Fig 2B).

In INNOVATE (FEV₁ assessed at baseline, week 4, and every 8 weeks thereafter up to week 28), all comorbidity subgroups demonstrated FEV₁ improvements by week 12 that were maintained (0 comorbidities) or improved upon (1 and ≥ 2 comorbidities) through the end of the study period. The patients without comorbidities demonstrated consistently lower mean improvements than patients with 1 and 2 or more comorbidities from week 12 onwards, and here again, the 95% CI intervals overlapped (Fig 2C).

In PROSPERO (FEV₁ assessed at baseline, month 6, and month 12), FEV₁ improvements were observed in all comorbidity subgroups at 6 months. Patients with 2 comorbidities had limited improvement in FEV₁ compared with patients with 0, 1, or 3 or more comorbidities. At 12 months, improvements were maintained for the 1 and 3 or more comorbidity subgroups, while patients with 0 comorbidities did not maintain their initial improvement (Fig 2D). Similar to the other studies, the 95% CIs overlapped.

Rate of On-Study Asthma Exacerbations by Type of Comorbidity

In EXTRA, the placebo-corrected exacerbation rate reductions (95% CI) were similar for patients with or without AR (26.0% [6.4, 41.5] and 21.0% [-18.3, 47.3]) and with or without GERD (24.0% [-9.0, 47.0] and 23.0% [1.7, 39.7], respectively).

Mean (SD) exacerbations in the 12 months prior to enrollment were 3.03 (3.33) and 3.01 (3.04) for patients with and without AR and 3.05 (3.04) and 3.00 (3.45) for patients with and without GERD. During the study, adjusted exacerbations (95% CI) were similar between patients with and without AR (0.75 [0.65, 0.87] and 0.75 [0.55, 1.02], respectively). However, patients with GERD appeared to have a lower on study exacerbation rate compared to patients without GERD (0.93 [0.78, 1.11] and 0.62 [0.52, 0.75], respectively).

Change from Baseline in Absolute FEV₁ by type of comorbidity

In the EXTRA study, improvements in FEV₁ varied across the study period for both comorbidities with overlapping 95% confidence intervals between patients with or without the comorbidities. For AR, similar improvements were noted in omalizumab-treated patients with or without AR. Interestingly, however, a larger placebo improvement was noted in patients with AR compared to patients without AR, resulting in a numerically larger placebo-corrected difference in patients with AR compared to patients without (Figure 3). Patients with or without GERD had comparable placebo-corrected differences in FEV₁. However, omalizumab-treated patients without GERD had numerically greater improvements at most timepoints compared to patients with GERD.

In PROSPERO, mean FEV₁ improvements were minimal, but were numerically greater for patients with AR versus without AR at 6 and 12 months (month 6: 63.3 [32.6, 94.0] versus 40.8 [-30.7, 112.3]; month 12: 42.0 [10.0, 74.1] versus 3.9 [-72.0, 79.7], respectively). Conversely for GERD, patients without GERD had greater improvements

compared to patients with GERD at both timepoints (month 6: 79.5 [42.5, 116.4] versus 33.7 [-9.9, 77.4]; month 12: 60.7 [21.9, 99.6] versus 5.7 [-39.6, 51.1], respectively).

Discussion

In this post hoc exploratory analysis of data obtained from placebo-controlled and real-world omalizumab studies, reductions in asthma exacerbations and improvements in FEV₁ were observed in response to omalizumab treatment. The overlapping 95% CIs, the lack of patterns in increasing or decreasing response by number and type (allergic, represented by AR or non-allergic, represented by GERD) of comorbidities, and the lack of consistent findings among the studies all suggest that improvements in exacerbations and FEV₁ are unaffected by comorbidity burden or the type of comorbidities present in these patients. Because multimorbidity is a frequent feature in patients with severe and poorly controlled asthma in the real world,²¹ the preservation of omalizumab effectiveness despite a high comorbidity burden is of particular significance to its target patient population, ~~which~~ ~~has~~ who have poorly controlled moderate-to-severe allergic asthma.

To our knowledge, the impact of comorbidity burden on the efficacy of biologics for the treatment of asthma has not been specifically evaluated previously. However, some biologics have studied asthma outcomes in the presence and absence of a single comorbidity. In a retrospective observational study in patients with uncontrolled allergic asthma receiving omalizumab in clinical practice, similar reductions in asthma exacerbations and improvements in FEV₁ were observed following omalizumab treatment in patients with asthma alone vs those with comorbid AR and/or nasal polyps.²² A linear regression model from that study confirmed these findings, with asthma exacerbations and FEV₁ found to be unaffected by the presence and severity of these upper respiratory comorbidities ($P = .618$ and $P = .442$, respectively).²² These results have been further demonstrated in this analysis of the

EXTRA and PROSPERO studies where response to omalizumab with respect to exacerbations and FEV₁ did not show a consistent better or worse response across studies in patients with or without AR or GERD, representing allergic or non-allergic comorbidities. In a post hoc analysis from a pivotal phase IIb dose-ranging study of dupilumab in patients with uncontrolled persistent asthma, the placebo-corrected risk reduction in annualized exacerbation rate was lower in patients with perennial AR compared with patients without perennial AR.²³ FEV₁ improvement was not impacted by comorbid perennial AR; the least squares mean (standard error) change in FEV₁ from baseline vs those without perennial AR was 0.25 (0.04) L vs 0.24 (0.06) L, respectively, in response to dupilumab 300 mg Q2W; however, for the 200-mg Q2W dose, mean change was lower for patients with AR vs without AR (0.22 [0.05] L vs 0.32 [0.05] L, respectively).²³ In a pooled analysis of the phase III SIROCCO and CALIMA benralizumab trials in severe eosinophilic asthma, the presence of comorbid nasal polyps predicted a greater reduction in asthma exacerbations and greater improvements in FEV₁ and asthma control compared with patients with asthma alone.²⁴ In post hoc analyses of pooled data from 2 phase III BREATH reslizumab studies, the reslizumab-induced rate reduction in asthma exacerbations was lower in patients with comorbid chronic rhinosinusitis with nasal polyps vs patients without chronic rhinosinusitis with nasal polyps (0.17 [95% CI, 0.09-0.32] vs 0.53 [95% CI, 0.4-0.69], respectively).²⁵

Our results are strengthened by the fact that data were derived from multiple studies with different designs. Inclusion of participants from both prospective, randomized, multicenter studies and the real-world observational PROSPERO study may provide a better reflection of the efficacy of a biologic in clinical trials when results are similar in the real-world asthma population. Importantly, the lack of a reversibility threshold inclusion criterion in EXTRA and PROSPERO means that the results are representative for patients with either high or low reversibility. This is especially important for changes in FEV₁. In our analysis,

the effects of omalizumab on FEV₁ were variable both between studies and within studies (as evidenced by the wide 95% CIs), reflecting the original overall findings of these studies.^{13,14,17,19} Analyses of studies 008 and 009 did show statistically significant improvements in FEV₁, while analyses of EXTRA and PROSPERO did not show statistically significant changes in FEV₁. There is, however, evidence that omalizumab treatment can result in clear meaningful improvements in FEV₁ over placebo and that these appear to be, at least in part, driven by baseline bronchodilator reversibility. Studies 008 and 009 specifically included patients with bronchodilator reversibility.^{13,14} In contrast, EXTRA and PROSPERO, did not stipulate reversibility as an eligibility criterion.¹⁶⁻¹⁹ Indeed, post-hoc analyses of 008/009, PROSPERO, and EXTRA data by FEV₁ reversibility at baseline, suggested that higher levels of reversibility were associated with greater improvements in FEV₁.²⁶⁻²⁸

However, this post hoc analysis must also be considered in light of its a number of limitations. For example, PROSPERO was an observational trial and patients were treated according to the standard practice of the investigator, which may have resulted in approximately 30% of patients not being dosed according to the US prescribing information (eg, baseline IgE or weight was out of range or not reported). Comorbidities were derived from patient medical records or were self-reported during medical history review. Further, although the sample sizes for the studies as a whole were large, the sample sizes for some comorbidity groups (eg, ≥ 2 comorbidities) were too small to reliably assess RRR in exacerbation rates for EXTRA and INNOVATE. Finally, comorbidities were grouped by number and not by severity of comorbid conditions, which may have underestimated the impact of some less frequent, but more severe comorbidities. Analyses by severity were not performed as severity data were not collected. Analyses by comorbidity type could only be performed for AR and GERD in EXTRA and PROSPERO as sample sizes for other

comorbidities were insufficient and precluded the ability to make meaningful conclusions from being drawn. The analysis of patients without AR or GERD may have been confounded by other comorbidities present in these patients. and severity were not performed because (1) analyzing the data by type would reduce the sample size in each subgroup to preclude meaningful conclusions from being drawn, and (2) severity data were not collected.

In this exploratory analysis from placebo-controlled and real-world omalizumab studies, reductions in asthma exacerbations and improvements in lung function were observed with omalizumab in patients with allergic asthma, irrespective of the degree of comorbidity burden or type of comorbidity. Response to omalizumab treatment in exacerbation rates and lung function was similar in patients with 0, 1, or 2 or more ongoing comorbidities and in patients with AR and GERD. The 95% CIs were highly overlapping, with no discernible pattern showing better or worse outcomes based on the comorbidity burden or with or without allergic or non-allergic comorbidities.

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1 **Table 1**

2 Number of patients with each specified comorbidity

Comorbidity, n (%)	Studies 008/009		EXTRA		INNOVATE		PROSPERO
	Omalizumab	Placebo	Omalizumab	Placebo	Omalizumab	Placebo	Omalizumab
	(n = 542)	(n = 529)	(n = 427)	(n = 421)	(n = 209)	(n = 210)	(N = 801)
Allergic rhinoconjunctivitis	64 (11.8)	42 (7.9)	298 (69.8)	298 (70.8)	85 (40.7)	70 (33.3)	665 (83.0)
NSAID-exacerbated respiratory disease	4 (0.7)	6 (1.1)	8 (1.9)	20 (4.8)	4 (1.9)	4 (1.9)	NR
Anaphylaxis	1 (0.2)	1 (0.2)	1 (0.2)	0 (0.0)	NR	NR	NR
Angioedema	NR	NR	0 (0.0)	1 (0.2)	3 (1.4)	1 (0.5)	NR
Atopic dermatitis	9 (1.7)	14 (2.6)	33 (7.7)	24 (5.7)	17 (8.1)	20 (9.5)	114 (14.2)
Chronic rhinosinusitis	12 (2.2)	18 (3.4)	41 (9.6)	36 (8.6)	15 (7.2)	20 (9.5)	217 (27.1)
Contact dermatitis	1 (0.2)	2 (0.4)	2 (0.5)	1 (0.2)	NR	NR	6 (0.7)
Eosinophilic granulomatosis with polyangiitis	NR	NR	1 (0.2)	0 (0.0)	NR	NR	NR

Eosinophilic esophagitis	NR	NR	1 (0.2)	0 (0.0)	NR	NR	6 (0.7)
Food allergy	7 (1.3)	6 (1.1)	18 (4.2)	12 (2.9)	3 (1.4)	4 (1.9)	139 (17.4)
GERD	25 (4.6)	25 (4.7)	115 (26.9)	114 (27.1)	35 (16.7)	41 (19.5)	334 (41.7)
Nasal polyposis	8 (1.5)	6 (1.1)	17 (4.0)	20 (4.8)	9 (4.3)	9 (4.3)	68 (8.5)
Other allergies	1 (0.2)	0 (0.0)	1 (0.2)	2 (0.5)	0 (0.0)	2 (1.0)	7 (0.9)
Recurrent acute sinusitis	1 (0.2)	1 (0.2)	1 (0.2)	2 (0.5)	1 (0.5)	1 (0.5)	NR
Urticaria	0 (0.0)	1 (0.2)	8 (1.9)	7 (1.7)	3 (1.4)	2 (1.0)	76 (9.5)

Abbreviations: GERD, gastroesophageal reflux disease; NR, not reported; NSAID, non-steroidal anti-inflammatory drug.

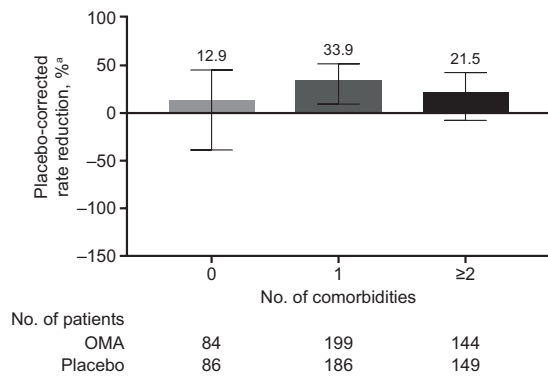
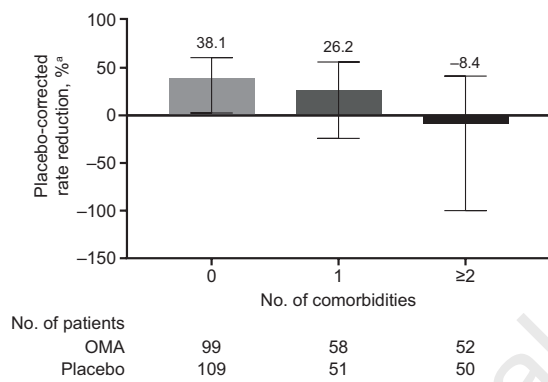
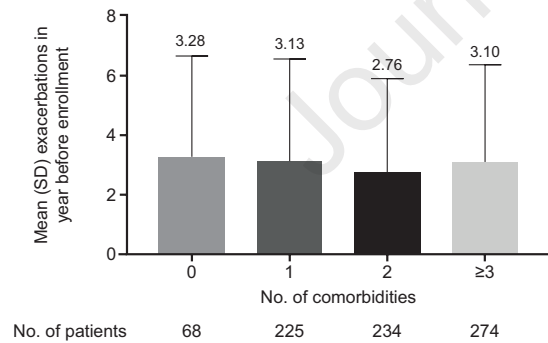
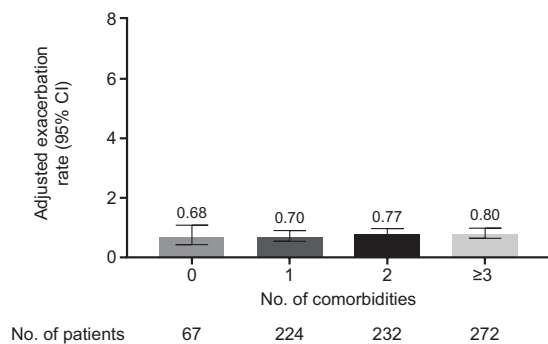
5 **Table 24**

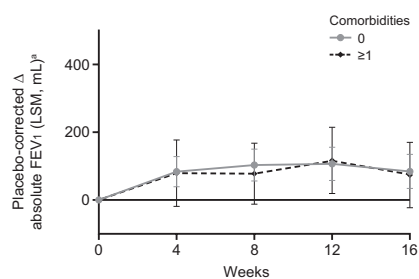
6 Baseline Demographics and Clinical Characteristics

Characteristic	Studies 008/009		EXTRA		INNOVATE		PROSPERO
	Omalizumab	Placebo	Omalizumab	Placebo	Omalizumab	Placebo	Omalizumab
	(n = 542)	(n = 529)	(n = 427)	(n = 421)	(n = 209)	(n = 210)	(N = 801)
Age (y), mean (SD)	39.7 (13.8)	39.1 (13.7)	43.7 (14.3)	45.3 (13.9)	43.4 (13.3)	43.3 (13.5)	47.2 (17.4)
Female, n (%)	297 (54.8)	291 (55.0)	262 (61.4)	295 (70.1)	141 (67.5)	138 (65.7)	293 (36.6)
Race, n (%)							
White	494 (91.1)	471 (89.0)	313 (73.3)	318 (75.5)	163 (78.0)	164 (78.1)	567 (70.8)
Black	32 (5.9)	27 (5.1)	90 (21.1)	86 (20.4)	14 (6.7)	14 (6.7)	130 (16.2)
Other	16 (3.0)	31 (5.9)	24 (5.6)	17 (4.0)	32 (15.3)	32 (15.2)	104 (13.0)
BMI (kg/m ²), mean (SD)	27.3 (6.1)	27.2 (6.1)	32.0 (7.8)	31.5 (7.3)	29.7 (6.9)	28.9 (6.1)	30.8 (8.2)
BMI category, n (%)							
<25 kg/m ²	203 (40.3)	194 (39.5)	61 (15.1)	67 (16.5)	66 (28.0)	68 (29.6)	146 (19.9)
≥25 to <30 kg/m ²	161 (31.9)	169 (34.4)	118 (29.2)	124 (30.6)	80 (33.9)	73 (31.7)	210 (28.7)
≥30 kg/m ²	140 (27.8)	128 (26.1)	225 (55.7)	213 (52.6)	90 (38.1)	89 (38.7)	375 (51.2)

Duration of asthma (y), mean (SD)	20.5 (13.6)	20.9 (14.0)	22.8 (15.4)	24.7 (15.8)	23.3 (15.2)	22.7 (14.7)	22.3 (18.0)
Asthma exacerbations in past year, mean (SD)	NR	NR	2.0 (2.2)	1.9 (1.5)	2.9 (1.5)	2.7 (1.2)	3.0 (3.3)
Prebronchodilator ppFEV ₁ , mean (SD)	69.0 (14.9)	68.8 (14.5)	65.4 (15.2)	64.4 (13.9)	61.0 (14.4)	61.6 (13.8)	75.4 (20.6)
FEV ₁ reversibility (%), mean (SD)	26.6 (14.8)	25.9 (13.6)	12.4 (16.5)	11.7 (15.5)	22.1 (27.7)	21.4 (25.7)	7.9 (13.9)
Total IgE (IU/mL), median (IQR)	155 (195)	156 (190)	138 (172)	140 (174)	150 (199)	138 (233)	193 (401)
Eosinophils (cells/ μ L), median (IQR)	250 (230)	280 (230)	270 (270)	260 (300)	300 (300)	300 (300)	230 (250)
Patients with ≥ 1 comorbidity, n (%)	111 (20.5)	97 (18.3)	343 (80.3)	335 (79.6)	110 (52.6)	101 (48.1)	733 (91.5)

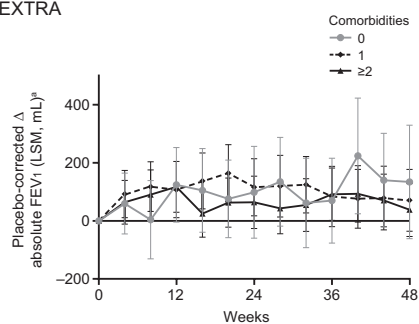
7 Abbreviations: BMI, body mass index; FEV₁, forced expiratory volume in 1 second; IQR, interquartile range; NR, not reported; ppFEV₁, percent
8 predicted forced expiratory volume in 1 second; SD, standard deviation.

(A) EXTRA**(B) INNOVATE****(C) PROSPERO: year before enrollment****(D) PROSPERO: on treatment**

(A) 008/009

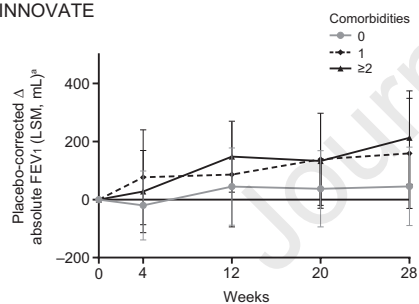
No. of patients

0 comorbidities	863	853	844	831	811
≥1 comorbidity	208	202	201	195	194

(B) EXTRA

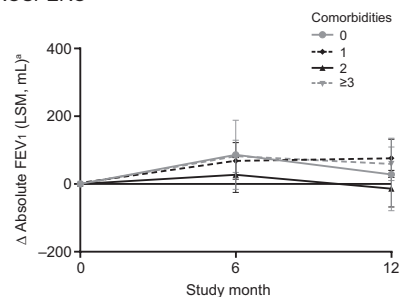
No. of patients

0 comorbidities	170	147	129	125	126
1 comorbidity	383	341	326	313	306
≥2 comorbidities	289	254	244	236	232

(C) INNOVATE

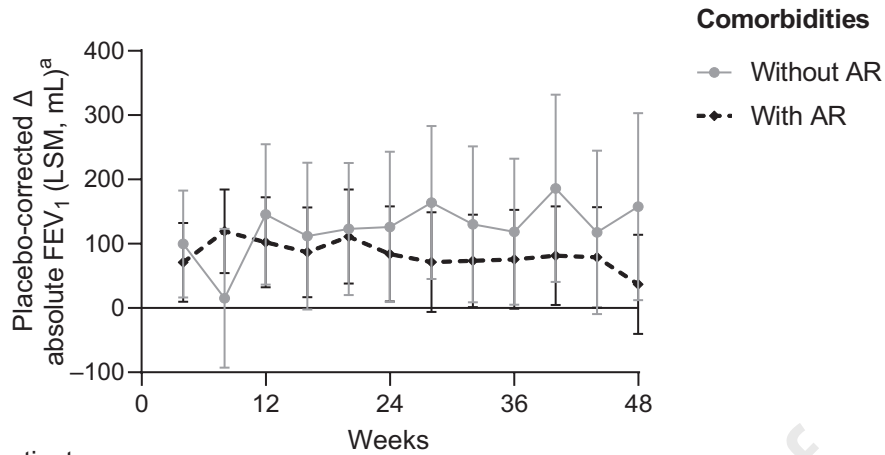
No. of patients

0 comorbidities	208	204	199	195	198
1 comorbidity	109	105	99	97	104
≥2 comorbidities	102	99	92	87	95

(D) PROSPERO

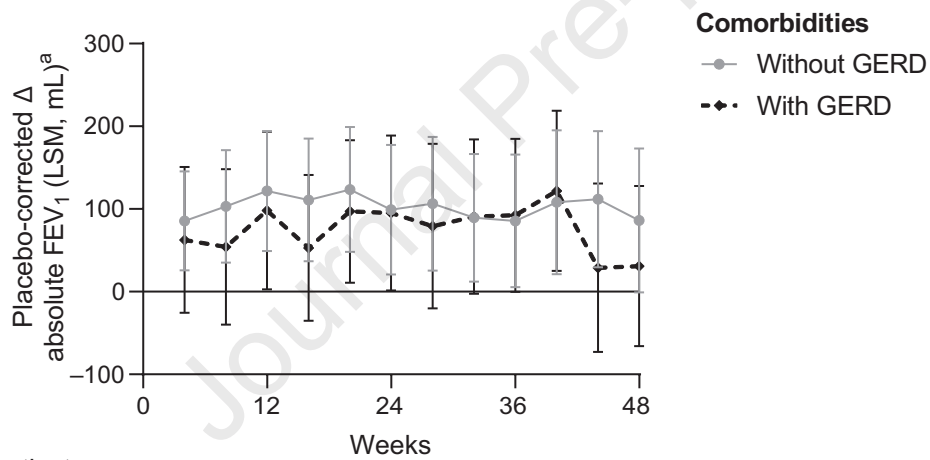
No. of patients

0 comorbidities	68	48	48
1 comorbidity	223	171	171
2 comorbidities	233	186	189
≥3 comorbidities	270	225	227

(A) AR

No. of patients

Without AR	252	219	195	189	191
With AR	596	523	504	485	473

(B) GERD

No. of patients

Without GERD	619	543	513	490	483
With GERD	229	199	186	184	181

Figure Legends

Figure 1. Placebo-corrected asthma exacerbation reduction rate for omalizumab (OMA) vs placebo in (A) EXTRA and (B) INNOVATE, and asthma exacerbation rate in PROSPERO (C) in the years before and (D) after treatment initiation by number of comorbidities. ^aData presented as a relative rate reduction for omalizumab vs placebo, with 95% confidence intervals (CIs) as error bars. SD, standard deviation.

Figure 2. Change from baseline in forced expiratory volume in 1 second (FEV₁) by number of comorbidities in (A) studies 008/009, (B) EXTRA, (C) INNOVATE, and (D) PROSPERO. ^aData presented with 95% confidence intervals. LSM, least squares mean.

Figure 3. Change from baseline in forced expiratory volume in 1 second (FEV₁) by (A) allergic rhinoconjunctivitis (AR) and (B) Gastroesophageal reflux disease (GERD) status in EXTRA. ^aData presented with 95% confidence intervals. LSM, least squares mean.