Response to Omalizumab in Black and White Patients with Allergic Asthma

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BACKGROUND: Higher asthma burden is more likely to be experienced by Black than White patients. In clinical research, underrepresentation of minority populations is observed.

OBJECTIVE: To estimate response to omalizumab in Black and White patients in North America with moderate to severe asthma.

METHODS: Data from placebo-controlled (EXTRA) and single-armed (PROSPERO) omalizumab studies were used for this post hoc analysis. We used a Poisson regression model to examine exacerbation rates. An analysis of covariance model was used to estimate placebo-corrected change in FEV1 and Asthma Quality of Life Questionnaire (AQLQ) by racial group.

RESULTS: This analysis included 631 White and 176 Black patients from EXTRA and 567 White and 130 Black patients from PROSPERO. In EXTRA, placebo-corrected exacerbation rate reductions (relative rate change [95% confidence interval], 22.6% [2.0-38.9%] vs 22.0% [−18.0% to 48.4%]) and FEV1 improvements were similar for White and Black patients. There was a trend toward greater AQLQ improvements for Black versus White patients (least squares mean treatment differences: 0.0 vs 0.3, 0.6 vs 0.4, and 0.6 vs 0.2 at weeks 16, 32, and 48, respectively) throughout the study. In PROSPERO, on-study exacerbation rates (0.76 [0.65-0.88] vs 0.77 [0.56-1.10]) and AQLQ improvements (least squares mean change from baseline: 1.2 vs 1.2 and 1.3 vs 1.2 at month 6 and end of study, respectively) were similar for White versus Black patients. A trend toward greater FEV1 improvement was observed in White versus Black patients throughout the study.

CONCLUSIONS: This analysis of EXTRA and PROSPERO suggests that Black and White patients with moderate to severe asthma experience similar improvements in exacerbations, FEV1, and quality of life with omalizumab.

INTRODUCTION

An increased burden of asthma is frequently experienced by racial minorities compared with White patients. Long-term systemic corticosteroid use, poorly controlled disease, reduced
quality of life, higher total serum IgE, worse eosinophilic airway inflammation, and requirement for emergency department visits are more common in Black patients than in White patients.1-3 Furthermore, asthma-related mortality is two to three times more likely to be experienced by Black and Hispanic patients than White patients.

The cause of these observed racial disparities in asthma outcomes remains a topic of debate. Some studies have indicated that these differences could be due to genetic or biological factors. However, evidence suggests that environmental exposures and social determinants of health also contribute to the observed disparities.4-6 Factors leading to worse asthma outcomes include worse air quality, limited access to quality health care, and suboptimal living conditions, which are often observed in urban areas where there is likely a larger Black population.7-10 In addition, some studies indicated that response to treatment may differ between White and Black populations with asthma, with steroid-insensitive asthma more common in Black populations.11 Together, the differences in asthma outcomes suggest the need for increased awareness and improved approaches to disease management among racial subgroups. However, despite the increased prevalence of chronic diseases, including asthma, among racial minorities, there is underrepresentation of these populations in clinical research.12 Specifically, about 6% of federally funded clinical trial participants are Black or Latino, even though these groups represent 30% of the general population.13-19 This gap exists despite the 1993 National Institutes of Health Revitalization Act, which aimed to ensure the inclusion of racial minorities in clinical research.15 Potential reasons for lower participation in clinical research by racial minorities include time constraints, financial costs, lack of will to enroll, and mistrust.14,18 Although racial minorities continue to be underrepresented in clinical trials, it is prudent to assess interracial responses and outcomes from these studies when possible, particularly for diseases in which evidence suggests the potential for disparities, such as asthma.

Omalizumab is an anti-IgE monoclonal antibody that has been approved for moderate to severe asthma in the United States since 2003 for patients aged 12 years and older, and since 2012 for patients aged 6 years and older with moderate to severe allergic asthma.17 Omalizumab binds to free IgE, inhibiting its interaction with FcεRI and CD23 (FcεRII), with long-term use potentially leading to the downregulation of these receptors on their respective cells.20-23 Omalizumab reduces the frequency of clinically significant asthma exacerbations and the requirement for inhaled corticosteroids while improving asthma symptoms, lung function, and asthma-related quality of life.20,24-27 Omalizumab has also been shown to have a favorable safety profile and is well tolerated.28 Two prospective, randomized, US-based clinical trials evaluating pediatric and adolescent patients with allergic asthma have shown the efficacy of omalizumab in decreasing exacerbations in inner-city populations, which are represented by greater than 90% Black or Hispanic race or ethnicity.29,30 However, response to omalizumab is not as well characterized in adult patients with allergic asthma from these different racial backgrounds. Given the burden of asthma in racial minorities and the potential for differing responses to treatment between races, we examined the effect of omalizumab in Black and White adolescent and adult patients with moderate to severe asthma using data from randomized controlled trials (EXTRA; NCT00314574)26 and single-armed real-world studies (PROSPERO; NCT01922037)27 of omalizumab in North America.

METHODS

Study design and patients

This was a post hoc analysis of placebo-controlled (EXTRA) and single-armed (PROSPERO) studies of omalizumab in adolescent and adult patients with moderate to severe allergic asthma. Detailed methods were published previously for EXTRA26 and PROSPERO,27 but are summarized briefly here.

EXTRA26 was a 48-week, prospective, multicenter, randomized, double-blind, placebo-controlled study of omalizumab in patients aged 12 to 75 years who had uncontrolled allergic asthma despite high-dose inhaled corticosteroids and long-acting β-agonists. Patients were required to have one or more protocol-defined asthma exacerbations during the past 12 months and baseline prebronchodilator FEV1 of 40% to 80% of predicted levels. Bronchodilator reversibility was not a requirement for enrollment. In addition, patients were required to have total IgE levels between 30 and 700 IU/mL and body weight between 30 and 150 kg for omalizumab dosing according to the US package insert.

PROSPERO27 was a 48-week, multicenter, prospective, single-armed study of omalizumab in which patients aged 12 years or greater with allergic asthma received omalizumab based on physician-assessed need. There were no restrictions for total IgE levels or weight, but patients were required to have access to omalizumab through insurance or other funding. There was no requirement for bronchodilator reversibility for enrollment into PROSPERO.

All study participants provided written informed consent; both studies were approved by an institutional review board. These studies were conducted according to the International Conference on Harmonisation E6 Guidelines for Good Clinical Practice and the principles of the Declaration of Helsinki, US Food and Drug Administration regulations, and any applicable local, state, and national laws.

Assessments

In this analysis, exacerbations, changes in lung function (measured by FEV1 in milliliters), changes in Asthma Quality of Life Questionnaire (AQLQ) score, and changes in asthma control (evaluated using Total Asthma Symptom Score [TASS] in EXTRA and Asthma Control Test [ACT] in PROSPERO) were assessed by racial groups in EXTRA and PROSPERO. Patients were categorized as White, Black, or other (Asian American, Native American or Alaska Native, or Native Hawaiian or Other Pacific Islander) based on self-report at baseline. Other racial groups were not reported in this analysis because too few patients identified in other racial groups to perform a meaningful analysis.
Exacerbations were recorded throughout the study in EXTRA and PROSPERO. For EXTRA, a protocol-defined asthma exacerbation was defined as worsening of asthma symptoms requiring treatment with rescue systemic (oral or intravenous) corticosteroids for 3 days or more as determined by the investigator. For patients taking chronic oral corticosteroids, a protocol-defined asthma exacerbation was any clinically significant worsening of asthma requiring 3 days or more of treatment, with a 20-mg or greater increase in average daily dose of oral prednisone or a comparable dose of systemic corticosteroids. For PROSPERO, a protocol-defined asthma exacerbation was defined as worsening of asthma symptoms that required treatment with systemic corticosteroids, a visit to the emergency department, or hospitalization.

Lung function, assessed by FEV₁, was examined every 4 weeks in EXTRA and at baseline and 6 and 12 months (end of study/early termination) in PROSPERO. For spirometry measurements, race correction was used according to guidelines that were available at the time the studies were conducted. For EXTRA, the 1995 American Thoracic Society guidelines were used, whereas for PROSPERO, the 2005 American Thoracic Society guidelines were used.

The AQLQ, TASS, and ACT were completed at baseline and at weeks 16, 32, and 48 of EXTRA and at baseline, 6 months, and end of study for PROSPERO. Safety was evaluated throughout EXTRA and PROSPERO.

### Statistical analyses

Exacerbation rates were determined using a Poisson regression model. In EXTRA, the model accounted for treatment, dosing schedule, concomitant asthma medications, and number of exacerbations in the year before enrollment within each racial subgroup; in PROSPERO, the model included race and number of exacerbations in the past year. Because not all patients were in the study for the same duration, data were normalized by subject-time on study medication at risk for both studies.

Least squares mean (LSM) change from baseline in FEV₁, AQLQ score, TASS, and ACT score was estimated using an analysis of covariance (ANCOVA) model. In EXTRA, the ANCOVA model included baseline value for FEV₁, AQLQ score, TASS, or ACT score and treatment and their interaction; in PROSPERO, the ANCOVA model included race.

Safety data for racial subgroups were summarized according to reporting requirements per protocol for each study. Because of low numbers in some subgroups, only overall safety events are provided. P values were not calculated owing to the post hoc nature of the analysis. All results are presented descriptively, and 95% confidence intervals (CIs) are included where appropriate.

### RESULTS

#### Baseline demographics and clinical characteristics

**EXTRA.** Of 848 modified intention-to-treat patients in EXTRA, 807 (White, n = 631; Black, n = 176) were included in this analysis. Forty-one other racial self-reported patients were not included. Baseline demographics were generally similar between treatment groups within White and Black patients (Table 1). However, there was a higher percentage of male patients in the omalizumab arm (40.9%) compared with the placebo arm (31.1%) among White patients. Furthermore, median IgE level was lower in the omalizumab arm versus the placebo arm, and mean FeNO level was higher in the omalizumab arm compared with the placebo arm among Black patients.

There were some differences in baseline characteristics between Black and White patients (Table 1). There was a higher proportion of females, median IgE levels, mean FeNO levels, exacerbation rate, and bronchodilator reversibility, and a lower percent predicted FEV₁ and duration of asthma in Black patients compared with White patients.

**PROSPERO.** Of 801 omalizumab-treated patients in PROSPERO, 697 (White, n = 567; Black, n = 130) were included in this study. One hundred and four other racial self-reported patients were not included in this analysis. Baseline demographic and clinical characteristics were generally similar between White and Black patients in PROSPERO (Table 1), except that mean age was higher in White patients than in Black patients, and median IgE level was lower in White patients compared with Black patients.

### Exacerbation rate reduction

**EXTRA.** In EXTRA, a lower on-study exacerbation rate with omalizumab compared with placebo was demonstrated in both White (0.6 and 0.7, respectively) and Black (0.8 and 1.1, respectively) patients (Figure 1). The placebo-corrected reduction in exacerbation rate for White patients (relative rate change [95% CI], 22.6% [2.0% to 38.9%]) and Black patients (22.0% [−18.0% to 48.4%]) receiving omalizumab was similar over the 48-week study.

**PROSPERO.** In PROSPERO, the exacerbation rate for White and Black patients in the year before enrollment was comparable (mean [SD]: White patients, 2.9 [3.3]; Black patients, 2.9 [2.7]) (Figure 2, A), as was the mean (95% CI) on-study exacerbation rate after initiation of omalizumab treatment (White patients, 0.76 [0.65-0.88]/study period; Black patients, 0.77 [0.56-1.10]/study period) (Figure 2, B).

### Lung function changes

**EXTRA.** In EXTRA, despite low bronchodilator reversibility, there were placebo-corrected LSM improvements in lung function throughout the study for both White and Black patients (Figure 3, A). At the end of the study, the LSM (95% CI) difference in FEV₁ between omalizumab and placebo in White and Black patients was 0.04 L (−0.04 to 0.12 L) and 0.14 L (0.01-0.26 L), respectively. For all time points, there was substantial overlap of 95% CIs.

**PROSPERO.** In PROSPERO, despite low bronchodilator reversibility, FEV₁ LSM improvements at 6 months and end of study/early termination were similar for White and Black patients. A greater LSM improvement in FEV₁ at both time points was observed in White patients compared with Black patients; however, there was substantial overlap of 95% CIs (Figure 3, B).

### Asthma Quality of Life Questionnaire score improvements

**EXTRA.** In EXTRA, placebo-corrected LSM improvements in AQLQ score from baseline at all time points (0.3, 0.4, and 0.2 at weeks 16, 32, and 48, respectively) were observed in White patients. Although there was no improvement in AQLQ score at week 16 (0.0) in Black patients, improvements of 0.6 and 0.6 were observed at weeks 32 and 48 in Black patients. At week 48, a trend toward a greater placebo-corrected LSM improvement in AQLQ score was observed in Black compared with White patients.

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At the end of the study, the LSM (95% CI) difference in AQLQ score between omalizumab and placebo in White and Black patients was 0.18 (−0.01 to 0.37) and 0.58 (0.21-0.96), respectively. For all time points, there was a substantial overlap of 95% CIs.

In PROSPERO, LSM improvements in AQLQ scores from baseline to 6 months and end of study/early termination that were above the minimal clinically important difference of 0.5 points for AQLQ score were observed in Black and White patients.33 The improvements in AQLQ score (LSM

<table>
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<tr>
<th>Characteristic</th>
<th>EXTRA White</th>
<th>EXTRA Omalizumab</th>
<th>PROSPERO White</th>
<th>PROSPERO Black</th>
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<tr>
<td>Age, y (mean [SD])</td>
<td>46.2 (13.6)</td>
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<td>Male, n (%)</td>
<td>99 (31.1)</td>
<td>128 (40.9)</td>
<td>23 (26.7)</td>
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<td>Education level, n (%)</td>
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<td></td>
<td>169 (29.8)</td>
<td>22 (16.9)</td>
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<td>Some college/trade school</td>
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<td></td>
<td>139 (24.5)</td>
<td>41 (31.5)</td>
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<td>Some high school</td>
<td></td>
<td></td>
<td>31 (5.5)</td>
<td>15 (11.5)</td>
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<tr>
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<td></td>
<td>46 (8.1)</td>
<td>27 (20.8)</td>
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<tr>
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<td></td>
<td></td>
<td>279 (49.2)</td>
<td>37 (28.5)</td>
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<tr>
<td>Employed part time</td>
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<td></td>
<td>43 (7.6)</td>
<td>14 (10.8)</td>
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<td>Homemaker</td>
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<td>25 (4.4)</td>
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<td>107 (18.9)</td>
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<td>67 (11.8)</td>
<td>38 (29.2)</td>
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<tr>
<td>Smoker, n (%)</td>
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<tr>
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<td>9 (2.9)</td>
<td>3 (3.5)</td>
<td>1 (1.1)</td>
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<td>304 (97.1)</td>
<td>83 (96.5)</td>
<td>89 (98.9)</td>
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<td>Body mass index, kg/cm² (mean [SD])</td>
<td>31.5 (7.1)</td>
<td>32.2 (7.9)</td>
<td>32.4 (8.0)</td>
<td>32.1 (8.0)</td>
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<td>Eosinophils, cells/µL (median [Q1, Q3])</td>
<td>260.0 (150.0, 430.0)</td>
<td>270.0 (170.0, 430.0)</td>
<td>260.0 (190.0, 550.0)</td>
<td>220.0 (130.0, 405.0)</td>
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<td>Total IgE, IU/mL (median [Q1, Q3])</td>
<td>127.0 (63.0, 231.0)</td>
<td>136.0 (75.0, 249.0)</td>
<td>178.5 (95.0, 299.0)</td>
<td>139.0 (89.0, 240.0)</td>
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<tr>
<td>FeNO, ppb (mean [SD])</td>
<td>26.9 (26.6)</td>
<td>25.0 (22.4)</td>
<td>36.7 (38.5)</td>
<td>44.2 (40.3)</td>
</tr>
<tr>
<td>Reversibility, % (mean [SD])</td>
<td>10.9 (15.6)</td>
<td>12.5 (16.6)</td>
<td>15.2 (15.7)</td>
<td>12.6 (17.1)</td>
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<tr>
<td>Percent predicted FEV1, % (mean [SD])</td>
<td>65.8 (13.9)</td>
<td>66.5 (14.5)</td>
<td>60.1 (13.4)</td>
<td>60.7 (14.9)</td>
</tr>
<tr>
<td>Exacerbations, events/y (mean [SD])</td>
<td>1.9 (1.3)</td>
<td>1.9 (1.5)</td>
<td>2.2 (1.9)</td>
<td>2.4 (3.9)</td>
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<tr>
<td>Asthma duration, y (mean [SD])</td>
<td>25.1 (15.8)</td>
<td>23.7 (15.5)</td>
<td>24.0 (15.8)</td>
<td>20.7 (14.9)</td>
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</table>

Q, quartile.
change from baseline: 1.2 vs 1.2 and 1.3 vs 1.2 at month 6 and end of study, respectively) were similar for White versus Black patients (Figure 4, B).

Asthma control
EXTRA. In EXTRA, placebo-corrected LSM improvements in TASS from baseline at all time points (0.3, 0.4, and 0.1 at weeks 16, 32, and 48, respectively) were observed in White patients. There was a small decrease in TASS at week 16 (−0.1) in Black patients, with improvements of 0.4 and 0.6 observed at weeks 32 and 48, respectively.

PROSPERO. In PROSPERO, LSM improvements in ACT total scores from baseline to 6 months and end of study/early termination were 4.1 and 4.5 in White patients, respectively, and 4.0 and 4.1 in Black patients, respectively.

Safety
EXTRA. In EXTRA, the proportion of patients experiencing one or more adverse events (AEs) (81.2% vs 81.4%, respectively) or serious AEs (SAEs) (8.6% vs 8.8%, respectively) was similar between omalizumab and placebo in White patients (Table II). In contrast, the proportion of patients experiencing one or more AEs was higher for omalizumab than placebo in Black patients (80.0% vs 72.1%, respectively), whereas the opposite was observed for SAEs (11.1% vs 17.4%, respectively). A greater proportion of patients experiencing an SAE with both omalizumab (11.1% vs 8.6%, respectively) and placebo (17.4% vs 8.8%, respectively) was observed for Black versus White patients.

PROSPERO. Similar to EXTRA, the percentage of patients treated with omalizumab who experienced an SAE in PROSPERO was slightly higher in Black patients than in White patients (15.4% vs 10.4%, respectively) (Table III).

DISCUSSION
Disparities in asthma treatment outcomes remain a concern in racial minorities, particularly in Black populations, which experience a higher burden of disease and worse treatment outcomes.1,3,14 To address the question of whether omalizumab response is different in patients from diverse racial backgrounds, we performed a post hoc analysis of data from placebo-controlled (EXTRA) and single-armed (PROSPERO) studies of omalizumab. To our knowledge, the results of this analysis are the first data describing omalizumab response by racial background.

Several previously completed studies indicated racial differences in response to asthma therapies, possibly owing to variances in pharmacokinetics and pharmacodynamics and socioeconomic, environmental, and genetic factors.34 For example, it was shown that asthma-related and respiratory-related deaths are higher in Black but not White salmeterol-treated patients, compared with placebo.35 Furthermore, patients with steroid-insensitive asthma are more likely to be Black,11 whereas greater concentrations of oral glucocorticoids are required to suppress T-lymphocyte activation in Black patients compared with White patients.36 However, evidence suggests that the response to inhaled corticosteroids may not be affected by race.37 Similarly, the response to add-on long-acting β-agonist therapy in Black adolescents and adults is comparable with the response observed in White adults.38 In the current analysis, overall findings suggested that the response to omalizumab was not affected by racial background because improvements in efficacy outcomes, including exacerbation rate, lung function, and effect of asthma on quality of life as measured on the AQLQ in both EXTRA and PROSPERO, were similar for Black and White patients.29,30 In addition, these data corroborate findings from two prospective, randomized, US-based clinical trials that documented the efficacy of omalizumab in decreasing exacerbations in inner-city populations.29,30

Although overall baseline characteristics were similar between Black and White subgroups in EXTRA and PROSPERO, in both trials, median total IgE levels at baseline were higher in the Black compared with the White subgroup. This observation is in line with the findings of several previous studies that also reported higher IgE levels in Black compared with White patients.3,39 The response to omalizumab in Black and White patients was comparable, as evidenced by improvements across all efficacy outcomes analyzed, indicating that these elevated baseline IgE levels did not affect outcomes, as previously reported.40 In addition, dosing for omalizumab is based on
pretreatment weight and total IgE levels, and therefore should account for these higher IgE levels.

In EXTRA, the percentage of patients experiencing an AE was generally similar between the placebo and omalizumab arms in both the White and Black subgroups. Also, the percentage of patients with an omalizumab-related AE in PROSPERO was similar between the White and Black subgroups. However, compared with White patients in both EXTRA and PROSPERO, a slightly higher percentage of Black patients experienced an SAE. In EXTRA, 8.6% (omalizumab) and 8.8% (placebo) of White patients experienced an SAE, compared with 11.1% (omalizumab) and 17.4% (placebo) of Black patients; in PROSPERO, 10.4% of White patients compared with 15.4% of Black patients experienced an SAE. The observation that placebo-treated Black patients in EXTRA experienced the highest rate of SAEs suggests that the higher rate of SAEs is not related to drug effects; rather, it may be inherent in individual characteristics.
An analysis of the effects of omalizumab by racial backgrounds was possible owing to the inclusion of a relatively large population of Black patients in the EXTRA (21%) and PROSPERO (16%) studies. The examination and agreement of data from both placebo-controlled and real-world studies also means that these data may be broadly applicable to patients in a variety of settings. However, this study is subject to certain inherent limitations. Because this was a post hoc subgroup analysis, the data may be prone to bias. The number of Black patients was low compared with that of White patients in both EXTRA and PROSPERO, potentially affecting the ability to detect differences. This also limited the ability to stratify patients further by additional factors such as asthma duration, blood eosinophil count, FeNO levels, total IgE levels, omalizumab dosing, sex, and background medications, which might have affected observing potential differences in outcomes.\(^{41}\) In addition, there was limited available information on socioeconomic factors, which restricted the ability to extrapolate the findings to other minority populations. Patients also self-reported race, which may have affected racial categorization. Furthermore, we could not directly compare outcomes in EXTRA and PROSPERO because EXTRA was a randomized placebo-controlled study and PROSPERO was a single-armed real-world study. Findings from PROSPERO should be considered with caution owing to the lack of blinding and placebo control. However, PROSPERO provided real-world data, with findings comparable with those of the placebo-controlled EXTRA study.

The totality of results from these post hoc analyses of the randomized controlled EXTRA trial and real-world PROSPERO study suggests that the response to omalizumab in terms of exacerbation rate and FEV\(_1\) and AQLQ score improvements was similar between Black and White patients with moderate to severe allergic asthma; however, a slightly higher percentage of patients experiencing an SAE were Black. These findings suggest that omalizumab treatment could be considered to treat allergic asthma, irrespective of whether the patient is Black or White.

Acknowledgments

The ClinicalTrials.gov registration number for EXTRA is NCT00314574, and for PROSPERO is NCT01922037. Qualified researchers may request access to individual patient level data through the clinical study data request platform (https://vivli.org/). Further details on Roche’s criteria for eligible studies are available here (https://vivli.org/members/ourmembers/). For further details on Roche’s Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see here (https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.html).

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