

Preseasonal treatment with either omalizumab or an inhaled corticosteroid boost to prevent fall asthma exacerbations

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Background: Short-term targeted treatment can potentially prevent fall asthma exacerbations while limiting therapy exposure.

Objective: We sought to compare (1) omalizumab with placebo and (2) omalizumab with an inhaled corticosteroid (ICS) boost with regard to fall exacerbation rates when initiated 4 to 6 weeks before return to school.

Methods: A 3-arm, randomized, double-blind, double placebo-controlled, multicenter clinical trial was conducted among inner-city asthmatic children aged 6 to 17 years with 1 or more recent exacerbations (clinicaltrials.gov #NCT01430403).

Guidelines-based therapy was continued over a 4- to 9-month run-in phase and a 4-month intervention phase. In a subset the effects of omalizumab on IFN- α responses to rhinovirus in PBMCs were examined.

Results: Before the falls of 2012 and 2013, 727 children were enrolled, 513 were randomized, and 478 were analyzed. The fall exacerbation rate was significantly lower in the omalizumab versus placebo arms (11.3% vs 21.0%; odds ratio [OR], 0.48;

95% CI, 0.25-0.92), but there was no significant difference between omalizumab and ICS boost (8.4% vs 11.1%; OR, 0.73; 95% CI, 0.33-1.64). In a prespecified subgroup analysis, among participants with an exacerbation during the run-in phase, omalizumab was significantly more efficacious than both placebo (6.4% vs 36.3%; OR, 0.12; 95% CI, 0.02-0.64) and ICS boost (2.0% vs 27.8%; OR, 0.05; 95% CI, 0.002-0.98).

Omalizumab improved IFN- α responses to rhinovirus, and within the omalizumab group, greater IFN- α increases were associated with fewer exacerbations (OR, 0.14; 95% CI, 0.01-0.88). Adverse events were rare and similar among arms. **Conclusions:** Adding omalizumab before return to school to ongoing guidelines-based care among inner-city youth reduces fall asthma exacerbations, particularly among those with a recent exacerbation. (J Allergy Clin Immunol 2015;■■■■-■■■■-■■■■.)

Key words: Asthma, fall season, omalizumab, inhaled corticosteroid, asthma exacerbations, rhinovirus, IFN- α

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Abbreviations used

AE:	Adverse event
EPR3:	Expert Panel Report-3
FENO:	Fraction of exhaled nitric oxide
ICAC:	Inner-City Asthma Consortium
ICATA:	Inner-City Anti-IgE Therapy for Asthma
ICS:	Inhaled corticosteroid
mITT:	Modified intention-to-treat
NIAID:	National Institute of Allergy and Infectious Diseases
OR:	Odds ratio
PROSE:	Preventative Omalizumab or Step-up Therapy for Fall Exacerbations

Although implementation and adherence to asthma guidelines improves disease control,¹ some children and adolescents continue to experience exacerbations despite treatment with doses of inhaled corticosteroids (ICSs) and long-acting β -agonists that reduce levels of impairment.^{2,3} The consequences of exacerbations are significant: greater morbidity, higher health care costs,⁴ and, possibly, disease progression.⁵ Furthermore, asthma exacerbations can occur at any time in any patient, but those with more severe disease, greater degrees of atopy, viral infection, and recent exacerbations appear most susceptible to recurrences, particularly during the fall after school resumes.⁶ These risks of exacerbations indicate that both innovative treatment approaches and a more specific targeting of treatment to mechanistic interactions between allergic sensitization and viral respiratory tract infections are necessary to reduce the frequency of these events.

Two prior Inner-City Asthma Consortium (ICAC) studies found the frequency of exacerbations was reduced with higher daily doses of ICSs² or with omalizumab (anti-IgE mAb)³ when added to year-round guidelines-based treatment, with the effects of omalizumab being most striking during the fall season.³ Because continuous treatment with both therapeutic modalities can impart certain risks and increased costs and because the fall season is the peak period for exacerbations among the inner-city population,⁶ we designed the Preventative Omalizumab or Step-up Therapy for Fall Exacerbations (PROSE) study to determine whether a targeted strategy of beginning preventative therapy with omalizumab 4 to 6 weeks before the start of school and continuing it for the next 4 months would be more efficacious than (1) placebo or (2) an ICS boost in preventing fall asthma exacerbations among children already receiving guidelines-based therapy.

It is necessary to understand that viral respiratory tract infections, particularly rhinovirus infections, and underlying allergic sensitization are strong risk factors for fall asthma exacerbations to determine and possibly target the mechanisms of treatment in this setting.⁶⁻⁸ Consequently and based on findings that some patients with asthma have reduced antiviral type I and III interferon responses,^{9,10} a defect also noted with peripheral blood plasmacytoid dendritic cells isolated from asthmatic patients and associated with IgE concentration on the cell surface,^{11,12} we formulated the additional hypothesis that the beneficial effects of omalizumab on seasonal asthma exacerbations can be explained in part by an increased release of IFN- α from plasmacytoid dendritic cells on rhinovirus exposure.

METHODS**Study design**

The PROSE study (clinicaltrials.gov #NCT01430403) was a 3-arm, randomized, double-blind, double placebo-controlled, multicenter clinical trial conducted among participants receiving ongoing guidelines-based asthma care (Expert Panel Report-3 [EPR3]).¹ The study enrolled 2 cohorts at 8 urban clinical research sites before the fall seasons of 2012 and 2013. The primary study objectives were to compare (1) omalizumab with placebo and (2) omalizumab with a boost in ICS (with total daily dose not to exceed 1000 μ g of fluticasone propionate equivalent) in preventing fall exacerbations. After enrollment (November-March for each cohort), participants completed a 4- to 9-month run-in phase during which guidelines-based care was delivered to achieve asthma control. Study intervention treatments were then added to ongoing guidelines-based treatment beginning 4 to 6 weeks before each participant's school start date and ending 90 days after the school start date. The protocol (available in this article's [Online Repository](http://www.jacionline.org) at www.jacionline.org) was approved by all 8 institutional review boards. Written informed consent was obtained from each participant's legal guardian. Participants provided assent according to local guidelines.

Participants

Eligibility criteria included age of 6 to 17 years, asthma diagnosis or symptoms for more than 1 year, 1 or more asthma exacerbations (requiring systemic corticosteroids) or hospitalization within the prior 19 months, a positive skin test response to 1 or more perennial allergens, body weight and total serum IgE levels suitable for omalizumab dosing based on the ICAC's prior study (see [Table E1, A](http://www.jacionline.org), in this article's [Online Repository](http://www.jacionline.org) at www.jacionline.org),^{3,13} school attendance beginning the following August or September, residence in a low-income census tract in predefined inner-city areas, and insurance covering standard medications.

Randomization and masking

By using a predefined EPR3-based treatment algorithm (see [Table E1, B](http://www.jacionline.org)), clinicians determined each participant's controller regimen (step level; see [Table E1, C](http://www.jacionline.org)) based on symptoms, spirometric results, and exacerbation history (see [Table E1, D](http://www.jacionline.org)), with assessments performed at 4 visits during the run-in phase. During the intervention period, step levels remained fixed. Randomization was done by using a blind, centralized, computer-based random allocation scheme. Participants had to require the equivalent of 200 μ g/d or greater fluticasone propionate to be eligible for randomization. Because evidence suggests that using more than 1000 μ g/d fluticasone propionate equivalent provides limited additional efficacy¹⁴ and increases the risk of side effects,¹⁵ participants requiring 500 μ g of fluticasone or equivalent twice daily for control during the run-in phase (step 5) were not entered into the ICS boost arm. Instead, they were randomized at a ratio of 3:1 to omalizumab or injected placebo ([Fig 1](http://www.jacionline.org)). The remaining participants (those receiving <500 μ g of fluticasone propionate equivalence twice daily [steps 2-4]) were randomized at a ratio of 3:3:1 to omalizumab (with inhaled placebo), ICS boost (with injected placebo), or guidelines-based care with injected placebo and inhaled placebo. During the intervention, all participants (steps 2-5) had 2 inhalers, one obtained by prescription for ongoing guidelines-based care and one provided by blinded staff (a Diskus device [GlaxoSmithKline, Research Triangle Park, NC] containing either fluticasone propionate or placebo) for the ICS boost. The study Diskus provided to participants at step 5 always contained placebo.

Omalizumab or its placebo was administered every 2 or 4 weeks by means of subcutaneous injection by unblinded nurses who had no other role in the trial, with dosing based on weight and serum IgE levels, as described previously (see [Table E1, A](http://www.jacionline.org)).^{3,13} The ICS boost, fluticasone propionate inhalation powder (100 or 250 μ g twice daily), effectively doubled the ICS dose of those patients at steps 2 to 4 at randomization (see [Table E1, E](http://www.jacionline.org)).

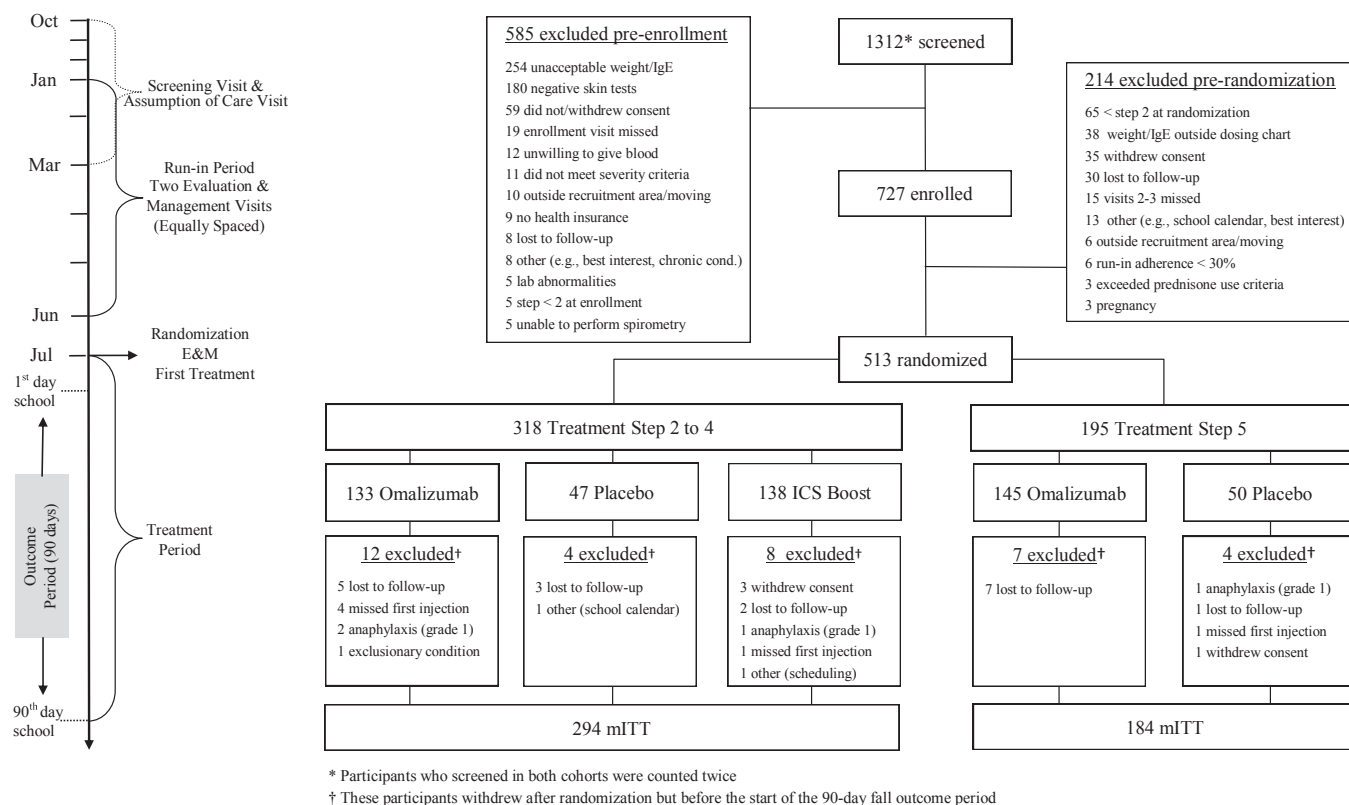


FIG 1. CONSORT diagram.

Procedures

Clinical assessments before randomization included skin prick tests to 14 aeroallergen extracts (Greer Laboratories, Lenoir, NC), total and allergen-specific serum IgE measurement, and spirometry. Questionnaires (administered every 4–8 weeks during the run-in phase and every 2–4 weeks during the intervention phase) assessed asthma symptoms, respiratory illnesses, exacerbations, and adverse events (AEs). Adherence was measured by means of self-report for the inhaler used for ongoing care, counter for the ICS boost Diskus, and injection records for omalizumab/placebo.

During the intervention period, weekly nasal mucus samples were collected for viral detection (Respiratory Viral Panel [Luminex, Austin, Tex] and/or rhinovirus detection), as previously described.¹⁶ Also, eosinophilic cationic protein levels were measured in the same samples monthly.

PBMCs from a subset of subjects ($n = 87$) were incubated *ex vivo* with rhinovirus with or without IgE cross-linking to simulate allergen activation and IFN- α levels were measured in culture supernatants to determine whether omalizumab affected antiviral responses.¹¹ Blood for these studies was obtained from subjects at 2 sites (UT Southwestern Medical Center, Dallas, Tex; National Jewish Health, Denver, Colo) before (prerandomization, at visit 3 or 4) and during (postrandomization, at visit 7 or 8) the intervention period. PBMCs were isolated by means of Ficoll-Paque (GE Healthcare, Fairfield, Conn) density gradient centrifugation and cultured at $0.5 \times 10^6/0.2$ mL in 96-well round-bottom plates in complete RPMI 1640 medium (supplemented with 10% heat-inactivated FBS, 1% penicillin-streptomycin, 1% sodium pyruvate, 1% HEPES buffer solution, 1% nonessential amino acids, 1% glutamate, 100 μ mol/L β -mercaptoethanol, and 10 ng/mL IL-3). PBMCs were cultured for 18 hours in the presence or absence of an IgE cross-linking antibody (rabbit anti-human IgE, 1 μ g/mL; Bethyl Laboratories, Montgomery, Tex) or control rabbit IgG antibody (1 μ g/mL, Bethyl Laboratories). It is important to note that the IgE cross-linking antibody used in these *in vitro* assays differs from omalizumab because it binds and cross-links IgE on cell-surface Fc ϵ R1 α receptors (unlike omalizumab, which only binds to free IgE). After 18 hours, the PBMC conditions were stimulated

with RV-A16 (10^6 plaque-forming units/mL; a gift from Wai-Ming Lee and Yury Bochkov, University of Wisconsin–Madison) for 24 hours. PBMC supernatants were stored at -80°C , and IFN- α concentrations were subsequently measured by means of ELISA (MabTech, Cincinnati, Ohio).

Outcomes

The primary outcome was an asthma exacerbation defined by a worsening of asthma control requiring systemic corticosteroids or hospitalization¹⁷ in the 90-day period beginning on the first day of each participant's school year. The planned analysis also included 11 prespecified, nonmechanistic secondary outcomes (see the [full protocol](#) in this article's Online Repository at [www.jacionline.org](#)). The protocol was monitored by a National Institute of Allergy and Infectious Diseases (NIAID) Data and Safety Monitoring Board and an NIAID Medical Monitor.

Statistical analysis

The primary outcome was analyzed as a dichotomous variable (occurrence or absence of exacerbations during the 90-day outcome period). Analysis was conducted by using a logistic regression model, adjusting for site, dosing schedule, and treatment step. The analysis of continuous secondary outcomes measured longitudinally was conducted by using a similarly adjusted linear mixed-effect model with random intercept (to account for the within-subject correlation). These analyses were performed on data from the modified intention-to-treat (mITT) population (ie, participants who were randomized, began study treatment, and had ≥ 1 study contact during the 90-day outcome period). Sensitivity analyses to assess the effect of missing data on the results are reported in [Table E2](#) in this article's Online Repository at [www.jacionline.org](#). Eleven prespecified subgroup analyses were conducted to assess heterogeneity of treatment effects with a statistical test for interaction.¹⁸ All analyses were done with SAS (version 9.3; SAS Institute, Cary, NC) and R 3.2.0 (Vienna, Austria) software.

TABLE I. Characteristics of the mITT participants at randomization*

Characteristic	Overall (n = 478)	Treatment steps 2-5			Treatment steps 2-4		
		Placebo (n = 89)	Omalizumab (n = 259)	P value	ICS boost (n = 130)	Omalizumab (n = 121)	P value
Study cohort, no. (%)							
2012	229 (47.9)	43 (48.3)	127 (49.0)	.99	59 (45.4)	56 (46.3)	.99
2013	249 (52.1)	46 (51.7)	132 (51.0)		71 (54.6)	65 (53.7)	
Demographics							
Age (y)	10.2 (2.93)	10.1 (3.06)	10.3 (2.99)	.60	9.84 (2.70)	10.4 (3.11)	.13
Male sex, no. (%)	303 (63.4)	59 (66.3)	174 (67.2)	.98	70 (53.8)	78 (64.5)	.11
Clinical							
Duration of asthma (y)	7.40 (3.50)	7.24 (3.56)	7.72 (3.56)	.28	6.87 (3.28)	7.62 (3.80)	.10
Asthma control†							
C-ACT score in previous month, age 4-11 y	21.6 (3.63)	21.3 (3.52)	21.3 (3.70)	.91	22.4 (3.47)	22.3 (3.84)	.91
ACT score in previous month, age ≥12 y	21.5 (3.18)	21.2 (3.87)	21.4 (3.05)	.84	22.0 (2.96)	22.2 (2.62)	.80
Asthma-related symptoms, days in prior 2 wk‡	2.34 (3.13)	2.56 (2.95)	2.51 (3.25)	.89	1.85 (2.97)	1.83 (2.87)	.96
Wheezing	1.79 (2.65)	1.98 (2.37)	1.89 (2.70)	.77	1.46 (2.71)	1.33 (2.35)	.68
Interference with activity	1.39 (2.61)	1.72 (2.82)	1.56 (2.84)	.65	0.82 (1.76)	0.98 (2.02)	.48
Nighttime sleep disruption	0.77 (1.80)	0.90 (1.98)	0.88 (1.84)	.93	0.48 (1.54)	0.52 (1.59)	.86
Lung function							
FEV ₁ , (% predicted)	90.1 (16.6)	89.3 (21.2)	88.7 (15.4)	.80	93.7 (15.0)	91.3 (14.1)	.20
FEV ₁ /FVC × 100	77.8 (9.49)	76.6 (10.9)	77.2 (9.53)	.68	79.8 (8.05)	79.0 (8.53)	.46
Medication, no. (%)§							
Treatment steps 2-4	294 (61.5)	43 (48.3)	121 (46.7)	.89	130 (100)	121 (100)	
Treatment step 5	184 (38.5)	46 (51.7)	138 (53.3)				
Asthma-related health care use during run-in phase, no. (%)							
≥1 Asthma exacerbation	168 (35.1)	35 (39.3)	106 (40.9)	.89	27 (20.8)	26 (21.5)	.99

*Values are counts (percentages) or means (SDs).

†Scores on the Childhood Asthma Control Test (C-ACT) and the Asthma Control Test (ACT) were measured on scales of 0 to 27 and 5 to 25, respectively. A score of 19 or less on either test indicates that asthma is not well controlled. The minimally important difference for ACT equals 3 points; for the C-ACT, a 3-point increase suggests a clinically relevant improvement in asthma control, whereas a 2-point decrease suggests a clinically relevant worsening.

‡The number of days with symptoms was calculated as the largest of the following variables during the previous 2 weeks: number of days with wheezing, chest tightness, or cough; number of nights of sleep disturbance; and number of days when activities were affected. This symptom scale ranges from 0 to 14 days per 2-week period.

§Six treatment steps were established, which is consistent with report 3 of the National Asthma Education and Prevention Program guidelines to standardize prescribing patterns according to levels of asthma severity; these steps are provided in full in Table E1, B, and are summarized here. Steps 1 and 2 apply to mild asthma, step 3 to moderate asthma, and steps 4 through 5 to severe asthma. At step 0, the recommendation is for no asthma control medication or albuterol as needed; at step 1, the recommendation is for 50 µg of fluticasone twice a day; at step 2, the recommendation is for 100 µg of fluticasone twice a day; at step 3, the recommendation is for 250 µg of fluticasone twice a day; at step 4, the recommendation is for 250 µg of fluticasone and 50 µg of salmeterol twice a day (Advair, GlaxoSmithKline); and at step 5, the recommendation is for 500 µg of fluticasone and 50 µg of salmeterol twice a day (Advair, GlaxoSmithKline).

IgE cross-linking effects on rhinovirus-induced IFN-α levels were determined by normalizing the rhinovirus-induced IFN-α produced in the presence of *ex vivo* IgE cross-linking to the rhinovirus-induced IFN-α produced in the absence of IgE cross-linking. The subgroups with high (above median) and low (below median) IFN-α level increases were then evaluated in relation to the rates of asthma exacerbation during the 90-day outcome period; odds ratios (ORs) for each subgroup were calculated.

Sample size calculation

We determined that enrollment of 453 participants (223 in the omalizumab arm, 155 in the ICS boost arm, and 75 in the placebo arm [52 in steps 2-4 and 23 in step 5]) would provide greater than 90% power to compare the omalizumab and placebo arms (11.8% vs 35.9% estimated effect) and 80% power to compare the omalizumab and ICS boost arms (12.9% vs 25.8% estimated effect).

Role of the funding source

This study was funded by the NIAID and an unrestricted grant from Novartis (Basel, Switzerland). Omalizumab and fluticasone propionate were

administered in the intervention under a Food and Drug Administration Investigational New Drug Application (no. 100,210) sponsored by the NIAID. Omalizumab and matching placebo were donated by Novartis. The ICS boost and matching placebo were donated by GlaxoSmithKline. Both companies had the opportunity to comment on the study design, but they had no role in the trial's performance, data analysis, manuscript preparation, or decision to submit the manuscript for publication. Epinephrine autoinjectors (EpiPens) were donated by Mylan (Canonsburg, Pa).

The ICAC Steering Committee designed the study. The individual study sites collected the data. Rho Federal Systems Division (Chapel Hill, NC) vouches for the data and their analysis. The corresponding author had final responsibility for the decision to submit for publication.

RESULTS

Participant enrollment characteristics

Before the fall seasons of 2012 and 2013, 345 and 382 participants, respectively, were enrolled in the 4- to 9-month run-in phase of our protocol. Of these 727 participants, 513 were subsequently randomized at the end of the run-in phase into the 3

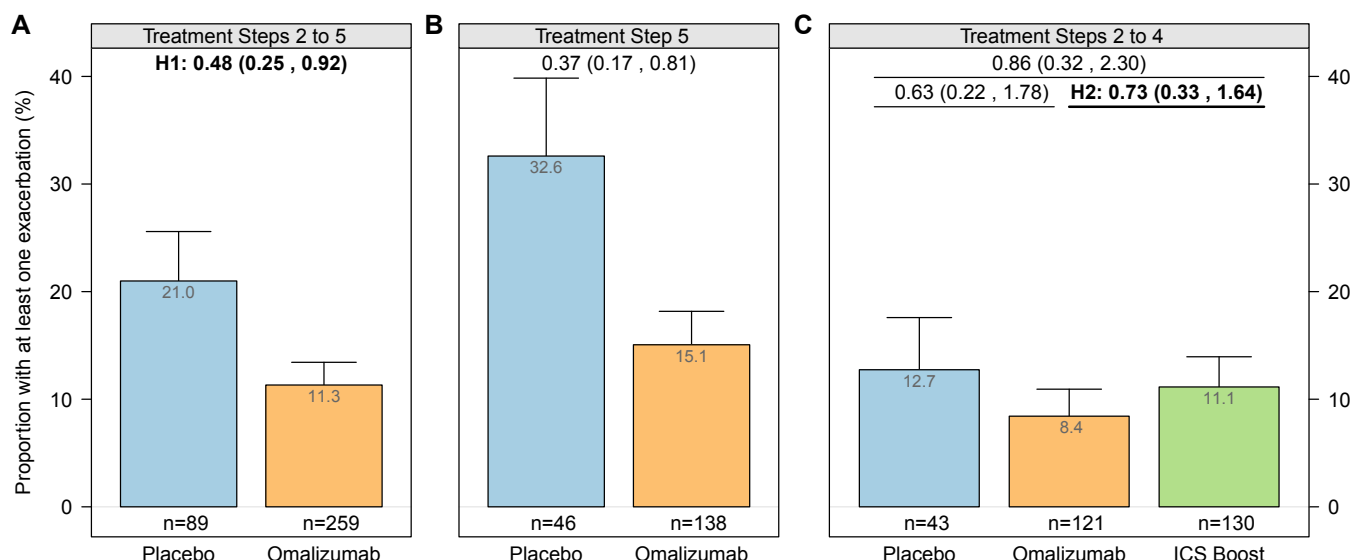


FIG 2. Proportion of participants by treatment arm with at least 1 exacerbation (*bar*) plus 1 SE (*whisker*) during the fall outcome period in the placebo and omalizumab arms randomized at steps 2 to 5 (**A**), in the placebo and omalizumab arms randomized at step 5 (**B**), and in the placebo, omalizumab, and ICS arms randomized at steps 2 to 4 (**C**). Values at the top of each panel are ORs (95% CIs). All values are adjusted for site, dosing group, and treatment step. H1, Primary hypothesis 1; H2, primary hypothesis 2.

treatment arms, and 478 were included in the mITT population (Fig 1). Characteristics of the mITT participants are provided in Table 1 and Table E3 in this article's Online Repository at www.jacionline.org. Median adherence to asthma medications after randomization was high, as measured based on self-report for guidelines-directed care (92.1%; interquartile range [IQR], 82.2% to 97.9%), inhaler counter information for ICS boost (82.4%; IQR, 51.6% to 115.4%), and study records for injections (100%; IQR, 88.9% to 100%).

Effect of run-in treatment on asthma control

The EPR3-based treatment algorithm used during the run-in phase significantly improved asthma control, as reflected by decreasing the mean number of symptom days reported over the 2 weeks before each assessment visit (4.5 [SD, 4.4] days at study entry to 2.3 [SD, 3.1] days before randomization, a difference of 2.1 days; 95% CI, 1.7-2.6 days; see Table E4 in this article's Online Repository at www.jacionline.org). At randomization, 62% of the mITT participants were at treatment steps 2 to 4 and 38% were at step 5. Of those at steps 2 to 4 at randomization, 21.8% had experienced 1 or more asthma exacerbations during the run-in phase compared with 56.5% among those at step 5 ($P < .001$). After randomization, in the placebo arm the frequency of exacerbations continued to be significantly higher in step 5 participants versus that in step 2 to 4 participants (32.6% vs 12.7%, $P = .03$).

Effects of study interventions on the frequency of fall exacerbations

For the first of our primary hypotheses, the odds of participants at all step care levels (2-5) having at least 1 exacerbation during the 90-day outcome period were significantly lower in the omalizumab versus placebo arms (11.3% vs 21.0%; OR, 0.48;

95% CI, 0.25-0.92; Fig 2, A). Stratifying by treatment step, the effect of omalizumab was still found in those receiving step 5 care (Fig 2, B). For the second primary hypothesis, in which participants at steps 2 to 4 were used, we did not observe a difference between omalizumab and the ICS boost (8.4% vs 11.1%; OR, 0.73; 95% CI, 0.33-1.64; Fig 2, C).

Effects of an exacerbation during the run-in phase on responses to study treatments in the outcome period

As previously described,⁶ an exacerbation during the run-in phase significantly increased the odds of an exacerbation during the outcome period (23.2% in participants with ≥ 1 exacerbation vs 11.9% in those without an exacerbation; OR, 2.23; 95% CI, 1.36-3.67) in participants who received placebo. Comparison of the effect of our interventions in this subgroup was one of our predetermined subgroup analyses. At all treatment steps (steps 2-5), omalizumab was strikingly more efficacious than placebo in preventing exacerbations among participants who had experienced an exacerbation during the run-in phase (6.4% vs 36.3%; OR, 0.12; 95% CI, 0.02-0.64; Fig 3, A). In addition, at steps 2 to 4 and in this subgroup of participants, omalizumab was more efficacious than an ICS boost in preventing exacerbations during the outcome period (2.0% vs 27.8%; OR, 0.05; 95% CI, 0.003-0.98; Fig 3, B). In contrast, no effect of omalizumab compared with placebo was found in participants who had not experienced an asthma exacerbations during the run-in phase (steps 2-5: 12.2% vs 13.6%; OR, 0.88; 95% CI, 0.35-2.18; steps 2-4: 11.6% vs 8.9%; OR, 1.34; 95% CI, 0.56-3.25). Notably, even in the step 5 subjects, no effect of omalizumab was detected among participants who did not experience an exacerbation during the run-in phase. Among the other predetermined subgroups, no effects with similar consistency were detected (see Table E5 in this article's Online Repository at www.jacionline.org).

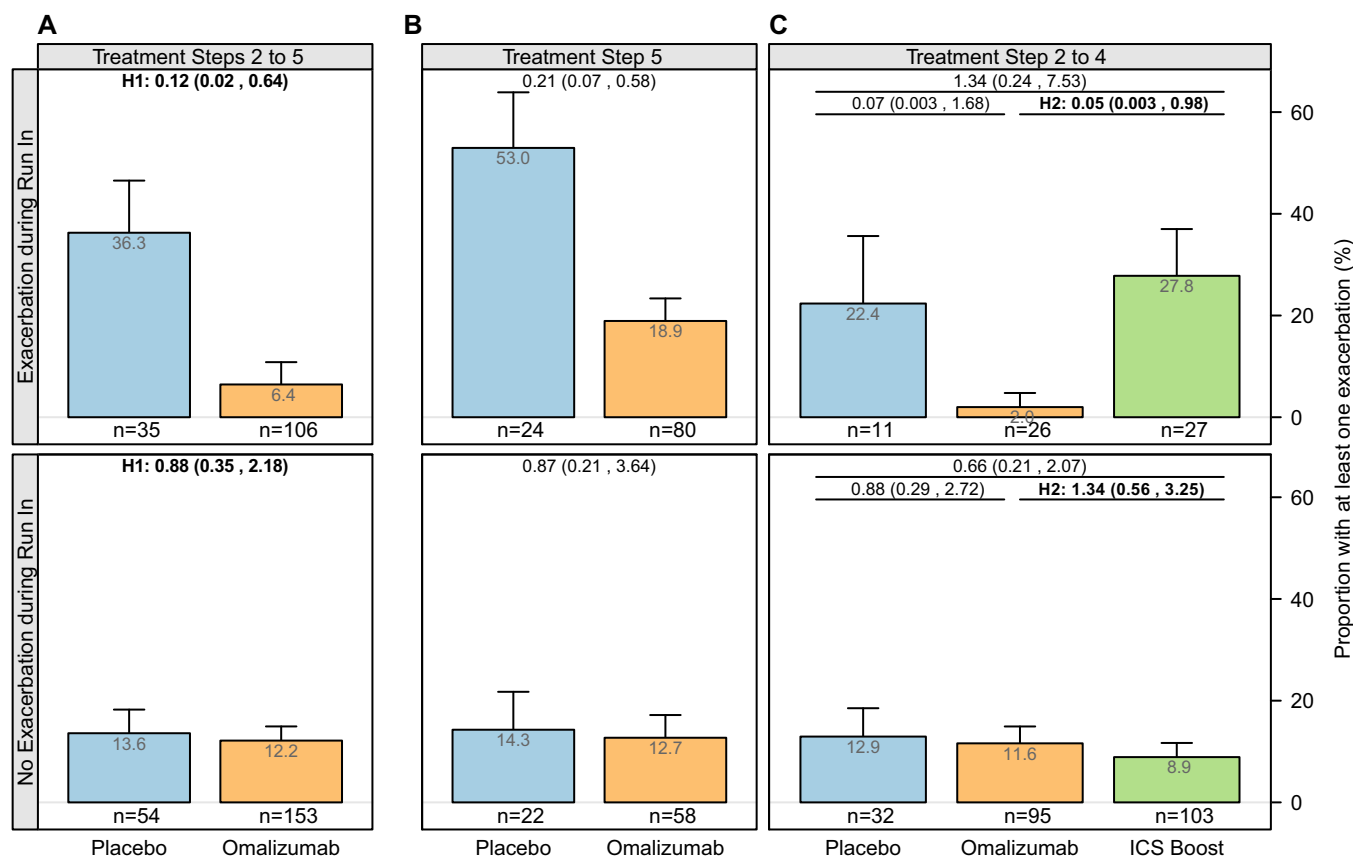


FIG 3. Proportion of participants by treatment arm with at least 1 exacerbation (bar) plus 1 SE (whisker) during the fall outcome period stratified by exacerbation status during the run-in phase among participants in the placebo and omalizumab arms randomized at steps 2 to 5 (**A**), in the placebo and omalizumab arms randomized at step 5 (**B**), and in the placebo, omalizumab, and ICS arms randomized at steps 2 to 4 (**C**). Values at the top of each panel are ORs (95% CIs). All values are adjusted for site, dosing group, and treatment step. H1, Primary hypothesis 1; H2, primary hypothesis 2. For H1 and H2, there was a significant interaction between subgroups ($P < .05$).

Participants who experienced an exacerbation during the run-in phase compared with those without an exacerbation had evidence of higher levels of allergic inflammation. At the time of randomization, those with an exacerbation during the run-in phase had higher peripheral blood eosinophil counts of 350 cells/ μ L (IQR, 210–520 cells/ μ L) and fraction of exhaled nitric oxide (FENO) levels of 29.0 ppb (IQR, 15.5–51.2 ppb) versus respective values in those without an exacerbation during the run-in phase: 280 cells/ μ L (IQR, 170–430 cells/ μ L; $P < .01$) and 19.0 ppb (IQR, 11.4–39.0 ppb; $P < .01$), respectively.

Effect of treatment interventions on asthma symptoms

Compared with placebo, omalizumab significantly decreased mean days with symptoms reported by participants in the 2 weeks before each assessment. Compared with ICS boost at steps 2 to 4, omalizumab did not significantly decrease symptom days (see Table E6 in this article's Online Repository at www.jacionline.org).

Respiratory tract virus detection in association with exacerbations

Of the 86 recorded exacerbations, 75 had 1 or more nasal samples obtained within 7 days of the exacerbation. Of these 75

exacerbations, 67 (89%) had a respiratory tract virus detected, most commonly rhinovirus (61/75 [81%]). When all nasal samples were considered, rhinoviruses were found more often in samples temporally related to exacerbations (97/171 [57%]) than in samples not related to exacerbations (2150/5959 [36%]; OR, 2.32; 95% CI, 1.71–3.16). Compared with placebo, omalizumab treatment was associated with a trend toward a lower odds of a respiratory virus-associated exacerbation (OR, 0.52; 95% CI, 0.24–1.13); this effect was statistically significant for step 5 participants (OR, 0.35; 95% CI, 0.15–0.85; see Fig E1 in this article's Online Repository at www.jacionline.org). There were too few exacerbations ($n = 8$) not associated with a virus to determine the effect of treatment on this group.

Effect of omalizumab treatment on PBMC generation of IFN- α on rhinovirus challenge and frequency of exacerbations

Before randomization, IgE receptor cross-linking in PBMCs significantly suppressed rhinovirus-induced IFN- α responses in both the placebo- and omalizumab-treated groups (Fig 4, A, left panel; $P < .001$). When the same assessments were repeated during the intervention phase, IFN- α responses to rhinovirus were significantly increased in the omalizumab-treated group

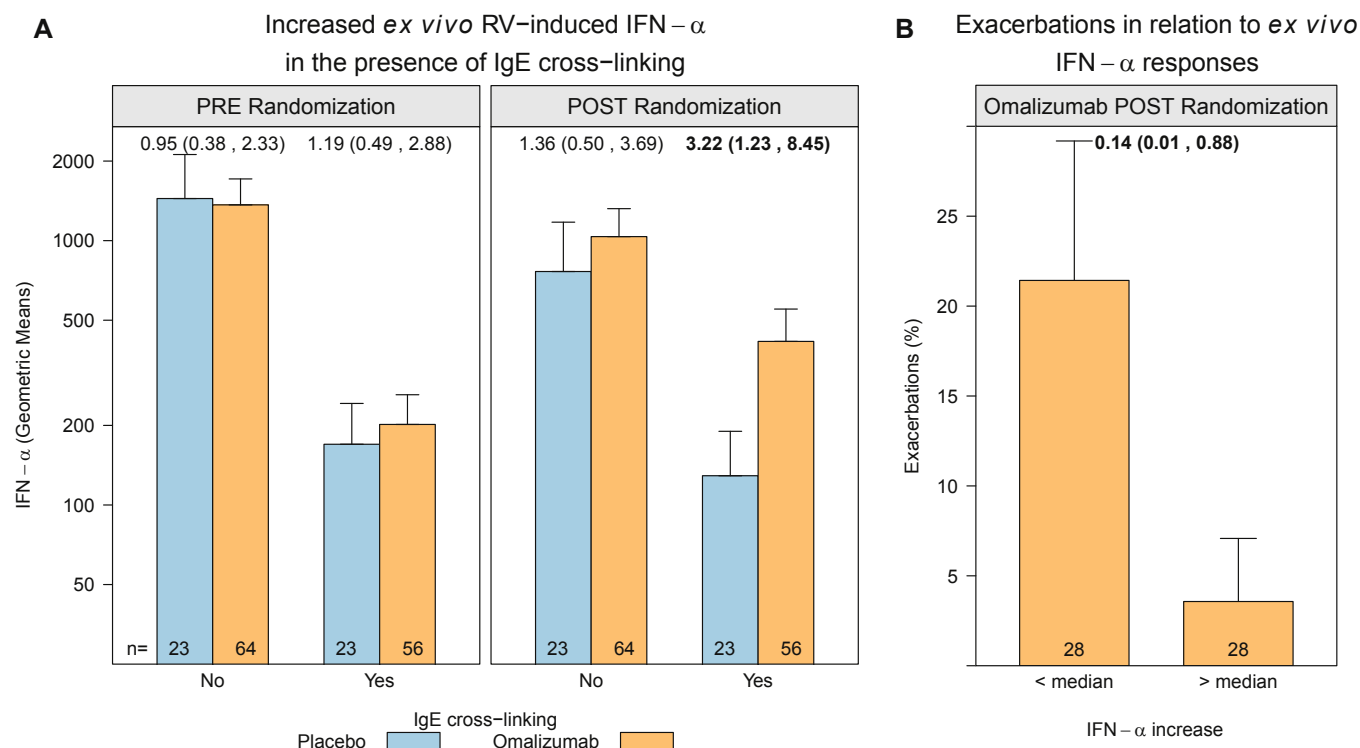


FIG 4. Enhanced *ex vivo* IFN- α responses to rhinovirus (RV) in the omalizumab group and relationship to exacerbation rates. PBMCs were incubated *ex vivo* with rhinovirus in the presence or absence of an IgE cross-linking antibody, and IFN- α levels were measured in culture supernatants. Rhinovirus-induced IFN- α was significantly reduced by IgE cross-linking; the IFN- α response was significantly increased in the omalizumab group during the intervention phase of the study. **A**, A 3.22-fold increase in omalizumab versus placebo in the postrandomization phase ($P = .03$). **B**, Among participants treated with omalizumab, those with the greatest increase in *ex vivo* IFN- α responses in the presence of IgE cross-linking were less likely to have an asthma exacerbation during the outcome period. Values at the top of each panel are ORs (95% CIs).

(Fig 4, A, right panel; $P = .03$). Notably, among the omalizumab-treated group, participants with increases in *ex vivo* IFN- α responses to rhinovirus to greater than the median value had a significantly lower rate of exacerbations during the outcome period (Fig 4, B; OR, 0.14; 95% CI, 0.01-0.88).

AEs

One or more AEs were reported by 54.5% of participants in the omalizumab arm and 54.8% of participants in the placebo arm ($P > .99$, steps 2-5) during the intervention phase. One or more AEs were reported by 43.5% of participants in the ICS boost arm and 53.3% of participants in the placebo arm ($P = .30$, steps 2-4; Table II). Three cases of grade 1 anaphylaxis occurred in the ICS boost, 2 in the placebo, and 3 in the omalizumab arms. Two serious AEs occurred during the intervention period, one each in the placebo (seventh nerve palsy) and ICS boost (anaphylaxis) arms. There were no deaths and no non-asthma-related hospitalizations during the intervention phase.

DISCUSSION

In the PROSE study we showed, in the context of our first primary objective, that a 4-month targeted treatment strategy with the addition of omalizumab beginning 4 to 6 weeks before the start of a school year to ongoing guidelines-based management significantly reduced asthma exacerbations during the fall season

among at-risk inner-city youth (Fig 2, A). This seasonal approach in treatment adjustment represents a first-time report of this novel strategy aiming to more effectively prevent exacerbations during what is referred to as the September epidemic of asthma.⁷ Our seasonal strategy in the PROSE study was as effective in reducing fall exacerbations as year-round treatment with omalizumab³ and also indicates that the protective onset of omalizumab begins well within 4 to 6 weeks of initiating this intervention. Moreover, through predetermined subgroup analysis, we found that children with exacerbations during the run-in phase were highly benefited by a seasonal addition of omalizumab, with a greater than 80% protection from fall exacerbations; in the absence of a run-in exacerbation, omalizumab was not beneficial (Fig 3).

Our second primary objective was to compare the addition of omalizumab with an ICS boost in preventing fall exacerbations. Per the study design, this comparison was only available in participants randomized at steps 2 to 4 (<1000 μ g of fluticasone propionate equivalent daily). We limited the ICS boost to not exceed 1000 μ g/d fluticasone propionate equivalence because larger doses over an extended time period provide minimal benefit in preventing exacerbations¹⁴ and increase the risk for systemic adverse effects.¹⁵ We found no significant difference in exacerbation rates between omalizumab and ICS boost (Fig 2, C) or between any of these 2 interventions and placebo, which might relate to the overall low rate of fall exacerbations in patients at steps 2 to 4.

TABLE II. Number of AEs (safety population)*

System organ class	Treatment steps 2-5			Treatment steps 2-4		
	Placebo (n = 93)	Omalizumab (n = 268)	P value†	Placebo (n = 45)	ICS boost (n = 131)	P value†
Blood and lymphatic system disorders	1 (1)	1 (1)	.45	0 (0)	1 (1)	1.00
Ear and labyrinth disorders	1 (1)	4 (4)	1.00	0 (0)	4 (3)	.57
Eye disorders	0 (0)	2 (2)	1.00	0 (0)	7 (6)	.34
Gastrointestinal disorders	10 (7)	19 (17)	.64	5 (4)	3 (3)	.07
General disorders and administration-site conditions	10 (6)	63 (41)	.03	6 (3)	18 (11)	1.00
Immune system disorders	2 (2)	5 (5)	1.00	0 (0)	3 (3)	.57
Infections and infestations	22 (17)	63 (50)	1.00	13 (10)	26 (23)	.51
Injury, poisoning, and procedural complications	7 (6)	32 (28)	.31	4 (4)	10 (9)	.74
Investigations	2 (2)	1 (1)	.16	0 (0)	2 (2)	1.00
Musculoskeletal and connective tissue disorders	1 (1)	8 (8)	.46	0 (0)	1 (1)	1.00
Neoplasms: benign, malignant, and unspecified	0 (0)	1 (1)	1.00	0 (0)	0 (0)	
Nervous system disorders	9 (8)	21 (20)	.82	4 (4)	7 (6)	.28
Pregnancy, puerperium, and perinatal conditions	0 (0)	1 (1)	1.00	0 (0)	0 (0)	
Psychiatric disorders	2 (2)	7 (6)	1.00	0 (0)	1 (1)	1.00
Reproductive system and breast disorders	1 (1)	1 (1)	.45	1 (1)	2 (2)	1.00
Respiratory, thoracic, and mediastinal disorders	11 (8)	29 (24)	1.00	5 (4)	13 (11)	1.00
Skin and subcutaneous tissue disorders	18 (14)	41 (36)	.73	10 (8)	20 (19)	.63
Surgical and medical procedures	0 (0)	0 (0)		0 (0)	1 (1)	1.00
Vascular disorders	0 (0)	1 (1)	1.00	0 (0)	0 (0)	
Total	97 (51)	300 (146)	1.00	48 (24)	119 (57)	.30

*In each case the reported data are the total number of combined serious and nonserious AEs. Numbers in parentheses are numbers of unique patients reporting such events. Only AEs during the treatment period are considered; these include AEs that occurred between randomization and 30 days after the end of the fall outcome period in participants who received at least 1 dose of study medication. Two serious AEs occurred after initiation of the intervention: Bell palsy in a participant receiving placebo and grade 1 anaphylaxis in a participant receiving an ICS boost.

†The Fisher exact test was used to compare the number of participants with at least 1 AE between groups.

In contrast, among participants in the step 2 to 4 group who experienced an exacerbation during the run-in phase, the addition of omalizumab was more efficacious than the ICS boost in preventing fall exacerbations (Fig 3, B, upper panel). In those who experienced an exacerbation during the run-in phase, peripheral blood eosinophil counts and FENO values were greater than in those who did not experience an exacerbation. This might reflect higher levels of inflammation despite guidelines-directed treatment, which could have resulted from the recent exacerbation together with an incomplete response to the standard use of systemic corticosteroids. These greater levels of inflammation might have enhanced the susceptibility for a subsequent exacerbation at the time of a respiratory tract infection.

From our results in the PROSE study, 2 asthma groups or phenotypes emerge as candidates who will benefit from the seasonal addition of omalizumab. First, patients with severe asthma, as reflected by the need for step 5 care, benefited from omalizumab over the 4-month treatment period (Fig 2, A). In our previous study, the Inner-City Anti-IgE Therapy for Asthma Study (ICATA),³ patients with asthma of all severities had a reduced frequency of exacerbations with omalizumab treatment administered over a 1-year period. This difference with the study reflects the shorter double-blind period (90 days) in the PROSE study, which resulted in a lower number of exacerbations among participants receiving step 2 to 4, thus reducing the statistical power to find a difference. In addition, a novel observation in the PROSE study was the striking benefit of seasonal omalizumab in patients with a recent exacerbation; in this setting the preventative efficacy of omalizumab was noted across all levels of disease severity (Fig 3). Without this additional prespecified analysis and based only on data from Fig 2, it might have been concluded that a seasonal benefit of omalizumab is restricted to

only those with the most severe disease. This conclusion would lead to both seasonal undertreatment and overtreatment with omalizumab to prevent fall exacerbations. Undertreatment would occur in patients with low severity and a recent exacerbation, whereas overtreatment would occur among patients with high severity without a recent exacerbations.

The rationale for our design of comparing omalizumab with an ICS boost was based on our previous work in which we found greater suppression of seasonal exacerbations in children and adolescents who received higher ICS doses as year-round treatment.² The addition of the ICS boost arm in the PROSE study was also meant to contribute to addressing the question of whether the risk for an asthma exacerbation might represent undertreatment with ICS.^{2,3} Other approaches to reduce asthma exacerbations, especially during the fall, have had little success, including adding montelukast to existing treatment at the start of school,¹⁹ increasing ICSs at the beginning of an exacerbation,²⁰ or prescribing clarithromycin in adults²¹ and azithromycin in children.²²

The mechanisms underlying fall asthma exacerbations are complex²³ and include viral respiratory tract infections (predominantly with rhinoviruses),⁸ allergic sensitization,²⁴ allergen exposure,²⁵ and diminished generation of type I and III interferons.⁹ It is likely that IgE plays an important role in the promotion of rhinovirus infections progressing to exacerbations by generating an inflammatory milieu. Omalizumab removes free circulating IgE, resulting in less IgE bound to mast cells and basophils, as well as suppression of allergic reactions and type 2 inflammation.²⁶ In our study evidence for this effect is provided by the reduction in eosinophilic cationic protein levels in nasal secretions (see Table E6). Most interestingly, *in vitro* IgE receptor activation decreases the generation of IFN- α from

plasmacytoid dendritic cells^{11,12}; the possibility that this mechanism occurs *in vivo* has not been previously tested. Our data provide support to this hypothesis and raise the possibility that restoration of virus-induced IFN- α responses might be a mechanism for the preventative effects of omalizumab on respiratory virus-associated exacerbations (Fig 4).

A challenge to the use of biologic agents in asthmatic patients is to select the patients most likely to respond to these treatments. Our findings in the PROSE study might help clarify patient selection for omalizumab. We recently published observations related to factors associated with seasonal asthma exacerbations.⁶ In particular, we noted that patients' characteristics associated with an increased risk for a fall exacerbation include an exacerbation during the prior season. This finding was replicated in the PROSE study, in which we also found that an exacerbation in the run-in phase was a major predictor of efficacy for seasonal administration of omalizumab (ie, >80% reduction in fall exacerbations). Not only did the results in the PROSE study confirm that recent exacerbations are a risk factor for a subsequent event but also our findings point to possible explanations for a recurrent exacerbation in the outcome period. The increased peripheral blood eosinophil counts and FENO values found at randomization in the participants who had an exacerbation during the preceding 4 to 9 months of the run-in phase might reflect increased airway inflammation, perhaps resulting from the recent exacerbation with incomplete resolution despite systemic corticosteroids, which in turn led to greater susceptibility to a subsequent exacerbation. These findings parallel observations by Hanania et al,²⁷ who found increases in these 2 biomarkers predicting greater future risk for an exacerbation and greater likelihood to benefit with omalizumab. Furthermore, the persistence of increased peripheral blood eosinophil counts and FENO values, despite a higher treatment dose of ICS (ie, step 5 care), parallels findings with mepolizumab and might represent biomarkers earmarking a risk for exacerbations, which cannot be prevented by conventional therapy but might require alternative treatment approaches, such as type 2-directed biologic agents.^{28,29}

Interpretation of the PROSE study requires several considerations. First, our results are derived from a largely minority low-income population. However, year-round omalizumab reduces exacerbations to a similar degree in other groups.^{3,30,31}

Second, our study population was limited to allergen-sensitized participants eligible for omalizumab therapy. Consequently, 36.0% of our screened patients were ineligible for enrollment because of negative skin test results or unsuitable weight/IgE measurements (Fig 1).¹³

Finally, the cost of omalizumab is a limitation, but our findings help identify populations most likely to respond to preseasonal treatment. For those patients, the reduced cost of treatment for only the fall season to prevent an exacerbation compared with a full year of treatment might be justifiable.

Our findings that an effective preventative strategy for fall exacerbations can be achieved with targeted seasonal treatment suggest a paradigm shift for managing high-risk patients, although further research is needed to refine the subgroups of asthmatic patients most likely to benefit from seasonal treatment with omalizumab. In addition, we need to identify more effective treatment strategies for those patients who have exacerbations despite the addition of omalizumab therapy. An early step to personalized or precision medicine is recognition of the correct phenotype to guide treatment selection. The results of the PROSE

study are a step toward an effective and time-limited treatment approach for a specific exacerbation-prone asthmatic phenotype.

Clinical implications: Inner-city children might benefit from the addition of omalizumab to ongoing guidelines-based therapy before the fall season to prevent exacerbations if they have severe disease and particularly if they have a history of a recent exacerbation, irrespective of disease severity.

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Pre-seasonal treatment with either omalizumab or an inhaled corticosteroid boost to prevent fall asthma exacerbations

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Supplemental Table 1A: Omalizumab Dosing Table

		Milligrams of Omalizumab Required per Dose									
		Body Weight (kg)									
Dosing Interval	Baseline IgE (IU/mL)	20-25	>25-30	>30-40	>40-50	>50-60	>60-70	>70-80	>80-90	>90-125	>125-150
q4wks	≥ 30-100	75	75	75	150	150	150	150	150	300	300
	>100-200	150	150	150	300	300	300	300	300	225	300
	>200-300	150	150	225	300	300	225	225	225	300	375
	>300-400	225	225	300	225	225	225	300	300	Do Not Dose/Not Eligible	
	>400-500	225	300	225	225	300	300	375	375		
	>500-600	300	300	225	300	300	375	Do Not Dose/Not Eligible			
	>600-700	300	225	225	300	375	Do Not Dose/Not Eligible				
q2wks	>700-800	225	225	300	375	Do Not Dose/Not Eligible					
	>800-900	225	225	300	375						
	>900-1000	225	300	375							
	>1000-1100	225	300	375							
	>1100-1200	300	300								
	>1200-1300	300	375								

Supplemental Table 1B: Treatment Adjustment Based on Control Levels and Adherence

Control Level	Treatment Algorithm for Participants with Unacceptable Adherence	Treatment Algorithm for Participants with Acceptable Adherence
1	Continue same controller regimen	If on Step 0, maintain at Step 0 If on Steps 1-5, decrease controller regimen by 1 step
2	Continue same controller regimen or place on Step 2 therapy, whichever is higher	Increase controller regimen by 1 step, or continue Step 5 therapy if already on Step 5
3	Continue same controller regimen or place on Step 2 therapy, whichever is higher	No systemic glucocorticosteroid since the last E&M visit* If on steps 0-4 increase controller regimen by 1 step If on step 5 continue step 5 or treat with step 5 <u>and</u> a 4 day burst of prednisone or equivalent; ≥1 course(s) of systemic glucocorticosteroids since the last E&M visit* If on steps 0-3 increase controller regimen by 2 steps If on treatment step 4 increase controller regimen to step 5 or treat with step 5 <u>and</u> a 4 day burst of prednisone or equivalent If on treatment step 5 continue step 5 or treat with step 5 <u>and</u> a 4 day burst of prednisone or equivalent
4	Continue same controller regimen or place on Step 3 therapy, whichever is higher OR Treat with 4-day prednisone burst and continue same controller regimen or place on Step 3 therapy, whichever is higher	If on steps 0-3 increase controller regimen by 2 steps If on Step 4, increase to Step 5 or treat with Step 5 <u>and</u> a 4-day prednisone burst or equivalent If already on Step 5, continue on Step 5 or treat with Step 5 <u>and</u> a 4-day burst of prednisone or equivalent

*Defined as a prescription of a course of systemic glucocorticosteroid by a clinician or initiation of a course of systemic steroids by a participant to prevent a serious asthma outcome. If a participant initiates and completes a course of systemic glucocorticosteroid without clinician involvement, this course will be counted only if it meets the following minimum dosage: prednisone, prednisolone, or methylprednisolone at ≥ 20mg per day for 3 of any 5 consecutive days; or dexamethasone at ≥ 10mg per day for ≥ 1 day.

Supplemental Table 1C: Medication Treatment Steps

Step	Medication
0	No controller medication; albuterol or levalbuterol prn
1	Inhaled fluticasone propionate 50 mcg bid
2	Inhaled fluticasone propionate 100 mcg bid
3	Inhaled fluticasone propionate 250 mcg bid
4	Inhaled fluticasone propionate/salmeterol 250/50 mcg bid
5	Inhaled fluticasone propionate/salmeterol 500/50 mcg bid

Supplemental Table 1D: Control Levels of Symptoms, Bronchodilator Usage, and FEV₁ (% personal best)

Control Level	Maximum of 1) # days with asthma symptoms/ two weeks and 2) # days with rescue albuterol use/ two weeks*	Maximum of 1) # nights of sleep disruption due to asthma/ two weeks and 2) # nights use of albuterol for awakening/ two weeks*	FEV₁ (% personal best)	Courses of Systemic Glucocorticosteroids since the last E&M Visit†
1	0-3 days	0-1 night	≥ 85	0
2	4-9 days	2 nights	80-84	1
3	10-13 days	3-4 nights	70-79	-
4	14 days	5-14 nights	< 70	-

* Determined from participant recall, based on the 2-week interval directly preceding the study visit.

†Defined as a prescription of a course of systemic glucocorticosteroid by a clinician or initiation of a course of systemic glucocorticosteroid by a participant to prevent a serious asthma outcome. If a participant initiates and completes a course of systemic glucocorticosteroid without clinician involvement, this course will be counted only if it meets the following minimum dosage: prednisone, prednisolone, or methylprednisolone at ≥ 20mg per day for 3 of any 5 consecutive days; or dexamethasone at ≥ 10mg per day for ≥ 1 day.

Supplemental Table 1E: Inhaled Fluticasone Boost Dosing Table

Step Level	Medication Equivalent at Randomization	Inhaled Fluticasone Boost Added at Randomization	Total Fluticasone during Intervention.
2	Inhaled fluticasone propionate 100 mcg bid	Inhaled fluticasone propionate 100 mcg bid	Inhaled fluticasone propionate 200 mcg bid
3	Inhaled fluticasone propionate 250 mcg bid	Inhaled fluticasone propionate 250 mcg bid	Inhaled fluticasone propionate 500 mcg bid
4	Inhaled fluticasone propionate/salmeterol 250/50 mcg bid	Inhaled fluticasone propionate 250 mcg bid	Inhaled fluticasone propionate 500 mcg bid
5	Inhaled fluticasone propionate/salmeterol 500/50 mcg bid	<i>Excluded from randomization to the glucocorticosteroid boost arm but continued in the study</i>	<i>Excluded from randomization to the glucocorticosteroid boost arm but continued in the study</i>

Supplemental Table 2: Sensitivity analyses for (H1) omalizumab vs placebo randomized at Steps 2-5; (H2) omalizumab vs ICS randomized at Steps 2-4.. Models are adjusted for site, dosing group and treatment step, H1 refers to primary hypothesis 1; H2 refers to primary hypothesis 2.

	Treatment Steps 2 to 5		Treatment Steps 2 to 4	
	Omalizumab vs Placebo (H1)		Omalizumab vs ICS Boost (H2)	
Model	Odds Ratio (95% CI)	P-value	Odds Ratio (95% CI)	P-value
Intent to Treat (Primary)	0.48 (0.25, 0.92)	0.03	0.73 (0.33, 1.64)	0.45
Per Protocol	0.51 (0.25, 1.03)	0.06	0.97 (0.39, 2.43)	0.94
Complete Case	0.46 (0.24, 0.89)	0.02	0.67 (0.30, 1.50)	0.33
Best Case	0.30 (0.16, 0.55)	<0.001	0.32 (0.15, 0.66)	0.002
Worst Case	0.79 (0.43, 1.45)	0.44	1.18 (0.57, 2.45)	0.66
Multiple Imputation	0.50 (0.28, 0.89)	0.02	0.60 (0.31, 1.17)	0.13

To assess the impact of missing data on the results, five sensitivity analyses were performed for 3 comparisons: omalizumab vs. placebo, omalizumab vs. ICS boost and ICS boost vs. placebo. All analyses included indicator variables to represent the combination of the various arms (Omalizumab, ICS Boost, or Placebo), treatment step (Steps 2-4 for all arms; Step 5 for Omalizumab and Placebo only), site, and dosing schedule as fixed effects. The methods for each sensitivity analysis are described below and results are presented in Supplemental Table 6.

1. *Per-protocol analysis*: Use logistic regression to model the odds of at least one exacerbation using per-protocol population. This analysis will exclude 39/478 (8.16%) subjects.
2. *Complete case analysis*: Use logistic regression to model the odds of at least one exacerbation in subjects who exacerbated at any point during fall outcome period or subjects who did not exacerbate but completed 91 days of follow-up. This analysis will exclude 37/478 (7.74%) subjects.
3. *Best case analysis*: Use logistic regression to model the odds of at least one exacerbation but appropriately modify response for 37/478 (7.74%) subjects who did not exacerbate and did not complete 91 days of follow-up.
 - For Omalizumab vs. Placebo, 15/259 (5.79%) subjects randomized to Omalizumab and who did not exacerbate and did not complete 91 days of follow-up will be assumed to have no exacerbations during the 91 day follow-up period. 7/89 (7.87%) subjects randomized to Placebo and who did not exacerbate and did not complete 91 days of follow-up will be assumed to have at least one exacerbation during the 91 day follow-up period.
 - For Omalizumab vs. ICS Boost, 6/121 (4.96%) subjects randomized to Omalizumab with Treatment Step 2-4 and who did not exacerbate and did not complete 91 days of follow-up will be assumed to have no exacerbations during the 91 day follow-up period. 15/130 (11.54%) subjects randomized to ICS Boost with Treatment Step 2-4 and who did not exacerbate and did not complete 91 days of follow-up will be assumed to have at least one exacerbation during the 91 day follow-up period.
 - For ICS boost vs. placebo, 15/130 (11.54%) subjects randomized to ICS Boost with Treatment Step 2-4 and who did not exacerbate and did not complete 91 days of follow-up will be assumed to have no exacerbations during the 91 day follow-up period. 4/43 (9.30%) subjects randomized to Placebo with Treatment Steps 2-4 and who did not exacerbate and did not complete 91 days of follow-up will be assumed to have at least one exacerbation during the 91 day follow-up period.
4. *Worst case analysis*: Use logistic regression to model the odds of at least one exacerbation but appropriately modify response for 37/478 (7.74%) subjects who did not exacerbate and did not complete 91 days of follow-up.
 - For Omalizumab vs. Placebo, 15/259 (5.79%) subjects randomized to Omalizumab and who did not exacerbate and did not complete 91 days of follow-up will be assumed to have at least one exacerbation during the 91 day follow-up period. 7/89 (7.87%) subjects randomized to Placebo and who did not exacerbate and did not complete 91 days of follow-up will be assumed to have no exacerbations during the 91 day follow-up period.

- For Omalizumab vs. ICS Boost, 6/121 (4.96%) subjects randomized to Omalizumab with Treatment Step 2-4 and who did not exacerbate and did not complete 91 days of follow-up will be assumed to have at least one exacerbation during the 91 day follow-up period. 15/130 (11.54%) subjects randomized to ICS Boost with Treatment Steps 2-4 and who did not exacerbate and did not complete 91 days of follow-up will be assumed to have no exacerbations during the 91 day follow-up period.
 - For ICS Boost vs. Placebo, 15/130 (11.54%) subjects randomized to ICS Boost and who did not exacerbate and did not complete 91 days of follow-up will be assumed to have at least one exacerbation during the 91 day follow-up period. 4/43 (9.30%) subjects randomized to Placebo and who did not exacerbate and did not complete 91 days of follow-up will be assumed to have no exacerbations during the 91 day follow-up period.
5. Multiple imputation: A Bayesian imputation method applied to logistic regression was used for missing binary variables while a Bayesian predictive mean matching algorithm was used for missing continuous variables. The imputation model included the following variables: (1) Exacerbation status; (2) Site; (3) Arm/treatment step; (4) Injection schedule; (5) Cohort; (6) Follow-up time; (7) Gender; (8) Race; (9) BMI percentile; (10) Job status; (11) Allergic sensitization; (12) Total IgE; (13) German roach IgE; (14) American roach IgE; (15) German roach skin test; (16) American roach skin test; (17) Composite Asthma Severity Index at randomization; (18) FEV1 (% predicted) at randomization; (19) Number of days in last 2 weeks with wheezing; (20) Number of nights in last 2 weeks disturbed by asthma; (21) Exacerbation during run-in period; and (22) Blood eosinophils. Because there were missing data on several variables included in the imputation model, a fully conditional specification based on 25 iterations was used to impute multivariate missing data. A total of 100 imputations were performed.

Supplemental Table 3: Characteristics of the Modified Intention-to-Treat Participants at Randomization *

	Overall	Treatment Step 2 to 5			Treatment Step 2 to 4		
Characteristic	(n=478)	Placebo (n=89)	Omalizumab (n=259)	P-value	ICS Boost (n=130)	Omalizumab (n=121)	P-value
Injection schedule — no. (%)							
Once per 2 weeks	183 (38.3%)	36 (40.4%)	100 (38.6%)	0.86	47 (36.2%)	42 (34.7%)	0.91
Once per 4 weeks	295 (61.7%)	53 (59.6%)	159 (61.4%)		83 (63.8%)	79 (65.3%)	
Demographics							
Race or ethnic group — no. (%)							
African American	279 (58.4%)	54 (60.7%)	145 (56.0%)	0.43	80 (61.5%)	59 (48.8%)	0.08
Hispanic	161 (33.7%)	30 (33.7%)	88 (34.0%)		43 (33.1%)	49 (40.5%)	
White, mixed or other	38 (7.9%)	5 (5.6%)	26 (10.0%)		7 (5.38%)	13 (10.7%)	
Caretaker completed high school — no. (%)	340 (71.3%)	55 (61.8%)	188 (72.9%)	0.07	97 (74.6%)	88 (72.7%)	0.84
≥1 household member employed — no. (%)	330 (69.0%)	59 (66.3%)	175 (67.6%)	0.93	96 (73.8%)	87 (71.9%)	0.84
Annual household income <\$15,000 — no. (%)	262 (55.4%)	51 (58.6%)	145 (56.6%)	0.84	66 (50.8%)	69 (57.5%)	0.35

* Values are count (percent)

Supplemental Table 4: Clinical Characteristics of the Modified Intention-to-Treat Participants (n=478) during the Run-in period.*

Variable	Screening	Randomization	Difference (95% CI)	P-value
Asthma-related symptoms — no. of days in 2 wk.‡	4.5 (4.4)	2.3 (3.1)	-2.1 (-2.6, -1.7)	<0.001
Wheezing	3.6 (3.9)	1.8 (2.6)	-1.8 (-2.2, -1.4)	<0.001
Interference with activity	2.6 (3.6)	1.4 (2.6)	-1.2 (-1.5, -0.9)	<0.001
Nighttime sleep disruption	1.9 (3.1)	0.8 (1.8)	-1.2 (-1.5, -0.9)	<0.001
Asthma control†				
C-ACT score in the previous month, age 4 to 11 yr.	18.9 (4.1)	21.6 (3.6)	2.6 (2.2, 3.1)	<0.001
ACT score in the previous month, age 12 yr. or older	19.1 (4.1)	21.5 (3.2)	2.4 (1.6, 3.1)	<0.001
Lung function				
FEV1 — % of predicted value	90.5 (17.2)	90.2 (16.6)	-0.4 (-1.7, 0.9)	0.58
FEV1:FVC ×100	77.5 (10.2)	77.8 (9.5)	0.3 (-0.4, 1.1)	0.37

* Values are mean (standard deviation). P values for the comparison of means and percentages were calculated with the use of the Wilcoxon rank-sum test for continuous variables and the chi-square test for categorical variables. FEV1 denotes forced expiratory volume in one second, and FVC forced vital capacity.

† Scores on the Childhood Asthma Control Test (C-ACT) and the Asthma Control Test (ACT) were measured on scales of 0 to 27 and 5 to 25, respectively. A score of 19 or less on either test indicates that asthma is not well controlled. The minimally important difference for ACT equals 3 points; that for Childhood ACT is not defined.

‡ The number of days with symptoms was calculated as the largest of the following variables during the previous 2 weeks: number of days with wheezing, chest tightness, or cough; number of nights of sleep disturbance; and number of days when activities were affected. This symptom scale ranges from 0 to 14 days per 2-week period.

Supplemental Table 5: Subgroup Analyses on Exacerbations using Different a-priori Characteristics*

Characteristic		Treatment Steps 2 to 5		Treatment Step 5		Treatment Steps 2 to 4					
		Omalizumab vs. Placebo	P-value	Omalizumab vs. Placebo	P-value	Omalizumab vs. Placebo	P-value	Omalizumab vs. ICS Boost	P-value	ICS Boost vs. Placebo	P-value
Exacerbation during Run In	No	0.88 (0.35, 2.18)	0.041	0.87 (0.21, 3.64)	0.111	0.88 (0.29, 2.72)	0.141	1.34 (0.56, 3.25)	0.038	0.66 (0.21, 2.07)	0.502
	Yes	0.12 (0.02, 0.64)		0.21 (0.07, 0.58)		0.07 (0.00, 1.68)		0.05 (0.00, 0.98)		1.34 (0.24, 7.53)	
EOS counts $\geq$ 320 cells/ μ L	No	1.08 (0.27, 4.30)	0.128	0.88 (0.20, 3.83)	0.137	1.32 (0.13, 13.75)	0.402	0.24 (0.06, 0.93)	0.026	5.57 (0.65, 47.66)	0.014
	Yes	0.31 (0.14, 0.70)		0.22 (0.08, 0.62)		0.42 (0.12, 1.50)		1.78 (0.59, 5.39)		0.24 (0.06, 0.87)	
Total IgE $\geq$ 255 kU/L	No	1.11 (0.31, 4.02)	0.133	0.57 (0.15, 2.14)	0.440	2.17 (0.24, 19.81)	0.198	1.43 (0.42, 4.94)	0.206	1.51 (0.16, 14.53)	0.639
	Yes	0.34 (0.14, 0.80)		0.29 (0.10, 0.84)		0.40 (0.10, 1.53)		0.48 (0.15, 1.53)		0.83 (0.26, 2.63)	
German Roach SIgE $\geq$ 0.175 KUA/l	No	0.75 (0.32, 1.73)	0.166	0.53 (0.18, 1.53)	0.481	1.05 (0.28, 3.94)	0.231	0.95 (0.36, 2.47)	0.638	1.12 (0.31, 3.96)	0.401
	Yes	0.28 (0.10, 0.84)		0.29 (0.08, 1.03)		0.28 (0.05, 1.60)		0.61 (0.12, 2.97)		0.45 (0.09, 2.42)	
Age $\geq$ 10 yrs.	No	0.33 (0.14, 0.77)	0.281	0.21 (0.07, 0.61)	0.124	0.52 (0.14, 1.94)	0.846	1.27 (0.46, 3.56)	0.116	0.41 (0.11, 1.50)	0.132
	Yes	0.73 (0.23, 2.33)		0.82 (0.21, 3.14)		0.66 (0.10, 4.34)		0.31 (0.08, 1.28)		2.09 (0.39, 11.05)	
FeNO $\geq$ 23.5 ppb	No	0.75 (0.28, 2.03)	0.283	0.84 (0.21, 3.37)	0.133	0.67 (0.16, 2.77)	0.870	1.68 (0.47, 6.00)	0.091	0.40 (0.09, 1.71)	0.226
	Yes	0.36 (0.14, 0.91)		0.22 (0.08, 0.63)		0.56 (0.12, 2.75)		0.39 (0.13, 1.19)		1.44 (0.33, 6.35)	
FEV1 percent predicted $\geq$ 90.8%	No	0.63 (0.23, 1.74)	0.309	0.44 (0.16, 1.17)	0.348	0.91 (0.16, 5.36)	0.573	1.18 (0.32, 4.29)	0.408	0.78 (0.13, 4.73)	0.943
	Yes	0.30 (0.11, 0.81)		0.19 (0.05, 0.80)		0.48 (0.13, 1.82)		0.58 (0.19, 1.71)		0.84 (0.25, 2.82)	
BMI percentile $\geq$ 85%	No	0.58 (0.25, 1.39)	0.446	0.53 (0.17, 1.72)	0.387	0.64 (0.18, 2.28)	0.736	3.31 (0.95, 11.58)	0.002	0.19 (0.04, 0.84)	0.011
	Yes	0.33 (0.10, 1.07)		0.26 (0.09, 0.79)		0.42 (0.05, 3.29)		0.13 (0.03, 0.61)		3.31 (0.66, 16.69)	
Hispanic	No	0.46 (0.21, 1.00)	0.801	0.31 (0.12, 0.82)	0.524	0.67 (0.19, 2.32)	0.867	0.66 (0.25, 1.71)	0.569	1.02 (0.32, 3.22)	0.53
	Yes	0.55 (0.17, 1.77)		0.54 (0.13, 2.19)		0.55 (0.08, 3.66)		1.12 (0.23, 5.56)		0.49 (0.07, 3.56)	
African American	No	0.53 (0.17, 1.65)	0.846	0.53 (0.14, 1.96)	0.486	0.53 (0.08, 3.41)	0.783	0.60 (0.15, 2.44)	0.675	0.89 (0.15, 5.46)	0.962
	Yes	0.46 (0.21, 1.03)		0.29 (0.11, 0.80)		0.73 (0.21, 2.56)		0.86 (0.32, 2.33)		0.85 (0.26, 2.75)	
Female	No	0.47 (0.22, 1.00)	0.884	0.31 (0.12, 0.85)	0.590	0.70 (0.22, 2.23)	0.878	1.44 (0.50, 4.15)	0.056	0.49 (0.14, 1.66)	0.195
	Yes	0.53 (0.13, 2.20)		0.50 (0.13, 1.87)		0.56 (0.04, 7.07)		0.22 (0.04, 1.10)		2.55 (0.28, 22.92)	

* All subgroup analyses were pre-specified before examination of the data (Protocol Sections 2.2 and 3.2 and Statistical Analysis Plan Section 5) and are presented in their entirety in this table. Continuous subgroup variables were dichotomized according to their median value. We employed the recommended statistical method for assessing the heterogeneity of the effect among the subgroups using a statistical test for interaction, adjusting for the pre specified baseline characteristics described in the protocol. Because they were exploratory, subgroup analyses do not include adjustment for multiple comparisons.

Supplemental Table 6: Adjusted Treatment Effect on Exacerbations, Asthma Symptoms, Lung Function, and Treatment Step for the Fall Outcome Period.*

Variable	Adjusted outcome levels during fall outcome period							Treatment Effects				
	Treatment Step 2 to 5		Treatment Step 2 to 4			Treatment Step 5		Treatment Step 2 to 5	Treatment Step 2 to 4			Treatment Step 5
	Placebo	Omalizumab	Placebo	Omalizumab	ICS Boost	Placebo	Omalizumab	Omalizumab v Placebo	Omalizumab v Placebo	Omalizumab v ICS Boost	ICS Boost v Placebo	Omalizumab v Placebo
	Adjusted Risk (SE)							OR (95% CI)				
Exacerbations (mITT)	21.0 (4.59)	11.3 (2.11)	12.7 (4.85)	8.4 (2.51)	11.1 (2.80)	32.6 (7.24)	15.1 (3.11)	0.48 (0.25,0.92)	0.63 (0.22,1.78)	0.73 (0.33,1.64)	0.86 (0.32,2.30)	0.37 (0.17,0.81)
Exacerbations (PP)	18.9 (4.94)	10.6 (2.38)	11.3 (5.00)	7.6 (2.58)	7.8 (2.62)	29.9 (7.76)	14.6 (3.55)	0.51 (0.25,1.03)	0.64 (0.21,1.98)	0.97 (0.39,2.43)	0.66 (0.21,2.05)	0.40 (0.17,0.96)
	Adjusted Geometric Means (SE)							Geometric Mean Ratio (95% CI)				
Eosinophilic Cationic Protein (ECP, mcg/L) †	816.2 (41.28)	621.4 (18.54)	883.1 (64.53)	613.1 (26.60)	846.3 (35.09)	754.6 (52.40)	629.8 (25.23)	0.76 (0.59,0.99)	0.69 (0.47,1.02)	0.72 (0.56,0.94)	0.96 (0.66,1.40)	0.83 (0.58,1.20)
	Adjusted Mean (SE)							Difference (95% CI)				
Asthma-related symptoms	1.8 (0.16)	1.2 (0.09)	1.7 (0.23)	1.0 (0.14)	1.3 (0.13)	1.9 (0.22)	1.4 (0.13)	-0.59 (-0.96,-0.23)	-0.66 (-1.18,-0.13)	-0.30 (-0.67, 0.07)	-0.36 (-0.88, 0.16)	-0.53 (-1.03,-0.04)
Wheezing	1.6 (0.15)	1.1 (0.09)	1.5 (0.21)	0.9 (0.13)	1.1 (0.12)	1.7 (0.20)	1.2 (0.12)	-0.56 (-0.88,-0.23)	-0.66 (-1.14,-0.19)	-0.25 (-0.58, 0.09)	-0.41 (-0.88, 0.06)	-0.45 (-0.90, 0.00)
Interference with activity	0.9 (0.11)	0.6 (0.07)	0.8 (0.16)	0.4 (0.10)	0.7 (0.10)	1.0 (0.16)	0.8 (0.09)	-0.28 (-0.54,-0.02)	-0.34 (-0.72, 0.03)	-0.26 (-0.53, 0.00)	-0.08 (-0.45, 0.29)	-0.22 (-0.57, 0.14)
Nighttime sleep disruption	0.6 (0.07)	0.3 (0.04)	0.4 (0.11)	0.2 (0.06)	0.3 (0.06)	0.7 (0.10)	0.4 (0.06)	-0.24 (-0.41,-0.07)	-0.16 (-0.40, 0.08)	-0.12 (-0.29, 0.05)	-0.04 (-0.28, 0.20)	-0.33 (-0.56,-0.10)
School Days Missed (%) †	1.6 (0.47)	1.2 (0.20)	0.8 (0.39)	0.9 (0.25)	2.0 (0.63)	3.2 (0.99)	1.4 (0.31)	0.72 (0.39,1.35)	1.15 (0.42,3.16)	0.48 (0.23,1.02)	2.39 (0.83,6.88)	0.45 (0.22,0.95)
ACT (previous month) ‡	21.8 (0.35)	22.9 (0.19)	22.0 (0.47)	23.0 (0.26)	22.9 (0.32)	21.6 (0.54)	22.8 (0.29)	1.11 (0.32, 1.90)	0.94 (-0.12, 2.01)	0.05 (-0.76, 0.86)	0.89 (-0.23, 2.01)	1.28 (0.08, 2.48)
C-ACT (previous month) ‡	22.5 (0.31)	23.2 (0.19)	23.0 (0.46)	23.7 (0.29)	23.1 (0.26)	22.0 (0.42)	22.7 (0.25)	0.71 (0.00, 1.41)	0.73 (-0.33, 1.79)	0.58 (-0.15, 1.30)	0.15 (-0.88, 1.18)	0.68 (-0.26, 1.62)
FEV1 — % of predicted value	92.5 (1.38)	92.2 (0.79)	92.8 (2.02)	93.2 (1.15)	90.8 (1.16)	92.2 (1.91)	91.1 (1.07)	-0.32 (-3.42,2.78)	0.47 (-4.04,4.98)	2.37 (-0.76,5.51)	-1.90 (-6.40,2.59)	-1.11 (-5.39,3.16)
FEV1:FVC ×100	78.4 (0.78)	78.6 (0.44)	77.3 (1.12)	79.1 (0.64)	77.9 (0.65)	79.5 (1.08)	78.2 (0.60)	0.25 (-1.49,1.99)	1.81 (-0.70,4.32)	1.15 (-0.61,2.91)	0.66 (-1.85,3.17)	-1.31 (-3.72,1.11)
Treatment Step level equal	3.7 (0.11)	3.6 (0.07)	2.9 (0.16)	2.7 (0.09)	2.7 (0.09)	4.5 (0.15)	4.5 (0.09)	-0.09 (-0.34,0.16)	-0.16 (-0.53,0.20)	0.05 (-0.21,0.30)	-0.21 (-0.57,0.15)	-0.02 (-0.37,0.33)

* All analyses included indicator variables to represent the combination of arm (Omalizumab, ICS Boost, or Placebo), treatment step (Step 2-4 for all arms; Step 5 for Omalizumab and Placebo only), site, and dosing schedule as fixed effects.

† Comparisons between groups for ECP and school days missed are ratios.

‡ C-ACT was measured for 358 participants between 4 and 11 years old. ACT was measured for 119 participants age 12 and older.

Supplemental Figure 1 A-C: Proportion of participants by treatment arm with at least one viral-associated exacerbation (bar) plus one standard error (whisker) during the fall outcome period (A) in the placebo and omalizumab arms randomized at Steps 2-5; (B) in the placebo and omalizumab arms randomized at Steps 5 and (C) in the placebo, omalizumab, and ICS arms randomized at Steps 2-4. Values at the top of each panel are odds ratios (95% confidence interval). All values are adjusted for site, dosing group and treatment step. H1 refers to primary hypothesis 1; H2 refers to primary hypothesis 2.

**Pre-seasonal treatment with either omalizumab or an inhaled corticosteroid boost to prevent fall
asthma exacerbations**

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Table E1A: Omalizumab Dosing Table

		Milligrams of Omalizumab Required per Dose																								
		Body Weight (kg)																								
Dosing Interval	Baseline IgE (IU/mL)	20-25	>25-30	>30–40	>40–50	>50–60	>60–70	>70–80	>80–90	>90-125	>125-150															
q4wks	≥ 30–100	75	75	75	150	150	150	150	150	300	300															
	>100–200	150	150	150	300	300	300	300	300	225	300															
	>200–300	150	150	225	300	300	225	225	225	300	375															
	>300–400	225	225	300	225	225	225	300	300	Do Not Dose/Not Eligible																
	>400–500	225	300	225	225	300	300	375	375																	
	>500–600	300	300	225	300	300	375	Do Not Dose/Not Eligible																		
	>600–700	300	225	225	300	375	Do Not Dose/Not Eligible																			
q2wks	>700–800	225	225	300	375	Do Not Dose/Not Eligible																				
	>800–900	225	225	300	375																					
	>900–1000	225	300	375	Do Not Dose/Not Eligible																					
	>1000–1100	225	300	375																						
	>1100–1200	300	300	Do Not Dose/Not Eligible																						
	>1200–1300	300	375																							

Table E1B: Treatment Adjustment Based on Control Levels and Adherence

Control Level	Treatment Algorithm for Participants with Unacceptable Adherence	Treatment Algorithm for Participants with Acceptable Adherence
1	Continue same controller regimen	If on Step 0, maintain at Step 0 If on Steps 1-5, decrease controller regimen by 1 step
2	Continue same controller regimen or place on Step 2 therapy, whichever is higher	Increase controller regimen by 1 step, or continue Step 5 therapy if already on Step 5
3	Continue same controller regimen or place on Step 2 therapy, whichever is higher	No systemic glucocorticosteroid since the last E&M visit* If on steps 0-4 increase controller regimen by 1 step If on step 5 continue step 5 or treat with step 5 <u>and</u> a 4 day burst of prednisone or equivalent; ≥1 course(s) of systemic glucocorticosteroids since the last E&M visit* If on steps 0-3 increase controller regimen by 2 steps If on treatment step 4 increase controller regimen to step 5 or treat with step 5 <u>and</u> a 4 day burst of prednisone or equivalent If on treatment step 5 continue step 5 or treat with step 5 <u>and</u> a 4 day burst of prednisone or equivalent
4	Continue same controller regimen or place on Step 3 therapy, whichever is higher OR Treat with 4-day prednisone burst and continue same controller regimen or place on Step 3 therapy, whichever is higher	If on steps 0-3 increase controller regimen by 2 steps If on Step 4, increase to Step 5 or treat with Step 5 <u>and</u> a 4-day prednisone burst or equivalent If already on Step 5, continue on Step 5 or treat with Step 5 <u>and</u> a 4-day burst of prednisone or equivalent

*Defined as a prescription of a course of systemic glucocorticosteroid by a clinician or initiation of a course of systemic steroids by a participant to prevent a serious asthma outcome. If a participant initiates and completes a course of systemic glucocorticosteroid without clinician involvement, this course will be counted only if it meets the following minimum dosage: prednisone, prednisolone, or methylprednisolone at ≥ 20mg per day for 3 of any 5 consecutive days; or dexamethasone at ≥ 10mg per day for ≥ 1 day.

Table E1C: Medication Treatment Steps

Step	Medication
0	No controller medication; albuterol or levalbuterol prn
1	Inhaled fluticasone propionate 50 mcg bid
2	Inhaled fluticasone propionate 100 mcg bid
3	Inhaled fluticasone propionate 250 mcg bid
4	Inhaled fluticasone propionate/salmeterol 250/50 mcg bid
5	Inhaled fluticasone propionate/salmeterol 500/50 mcg bid

Table E1D: Control Levels of Symptoms, Bronchodilator Usage, and FEV₁ (% personal best)

Control Level	Maximum of 1) # days with asthma symptoms/ two weeks and 2) # days with rescue albuterol use/ two weeks*	Maximum of 1) # nights of sleep disruption due to asthma/ two weeks and 2) # nights use of albuterol for awakening/ two weeks*	FEV₁ (% personal best)	Courses of Systemic Glucocorticosteroids since the last E&M Visit†
1	0-3 days	0-1 night	≥ 85	0
2	4-9 days	2 nights	80-84	1
3	10-13 days	3-4 nights	70-79	-
4	14 days	5-14 nights	< 70	-

* Determined from participant recall, based on the 2-week interval directly preceding the study visit.

†Defined as a prescription of a course of systemic glucocorticosteroid by a clinician or initiation of a course of systemic glucocorticosteroid by a participant to prevent a serious asthma outcome. If a participant initiates and completes a course of systemic glucocorticosteroid without clinician involvement, this course will be counted only if it meets the following minimum dosage: prednisone, prednisolone, or methylprednisolone at ≥ 20mg per day for 3 of any 5 consecutive days; or dexamethasone at ≥ 10mg per day for ≥ 1 day.

Table E1E: Inhaled Fluticasone Boost Dosing Table

Step Level	Medication Equivalent at Randomization	Inhaled Fluticasone Boost Added at Randomization	Total Fluticasone during Intervention.
2	Inhaled fluticasone propionate 100 mcg bid	Inhaled fluticasone propionate 100 mcg bid	Inhaled fluticasone propionate 200 mcg bid
3	Inhaled fluticasone propionate 250 mcg bid	Inhaled fluticasone propionate 250 mcg bid	Inhaled fluticasone propionate 500 mcg bid
4	Inhaled fluticasone propionate/salmeterol 250/50 mcg bid	Inhaled fluticasone propionate 250 mcg bid	Inhaled fluticasone propionate 500 mcg bid
5	Inhaled fluticasone propionate/salmeterol 500/50 mcg bid	<i>Excluded from randomization to the glucocorticosteroid boost arm but continued in the study</i>	<i>Excluded from randomization to the glucocorticosteroid boost arm but continued in the study</i>

Table E2: Sensitivity analyses for (H1) omalizumab vs placebo randomized at Steps 2-5; (H2) omalizumab vs ICS randomized at Steps 2-4.. Models are adjusted for site, dosing group and treatment step, H1 refers to primary hypothesis 1; H2 refers to primary hypothesis 2.

	Treatment Steps 2 to 5		Treatment Steps 2 to 4	
	Omalizumab vs Placebo (H1)		Omalizumab vs ICS Boost (H2)	
Model	Odds Ratio (95% CI)	P-value	Odds Ratio (95% CI)	P-value
Intent to Treat (Primary)	0.48 (0.25, 0.92)	0.03	0.73 (0.33, 1.64)	0.45
Per Protocol	0.51 (0.25, 1.03)	0.06	0.97 (0.39, 2.43)	0.94
Complete Case	0.46 (0.24, 0.89)	0.02	0.67 (0.30, 1.50)	0.33
Best Case	0.30 (0.16, 0.55)	<0.001	0.32 (0.15, 0.66)	0.002
Worst Case	0.79 (0.43, 1.45)	0.44	1.18 (0.57, 2.45)	0.66
Multiple Imputation	0.50 (0.28, 0.89)	0.02	0.60 (0.31, 1.17)	0.13

To assess the impact of missing data on the results, five sensitivity analyses were performed for 3 comparisons: omalizumab vs. placebo, omalizumab vs. ICS boost and ICS boost vs. placebo. All analyses included indicator variables to represent the combination of the various arms (Omalizumab, ICS Boost, or Placebo), treatment step (Steps 2-4 for all arms; Step 5 for Omalizumab and Placebo only), site, and dosing schedule as fixed effects. The methods for each sensitivity analysis are described below and results are presented in Supplemental Table 6.

1. *Per-protocol analysis*: Use logistic regression to model the odds of at least one exacerbation using per-protocol population. This analysis will exclude 39/478 (8.16%) subjects.
2. *Complete case analysis*: Use logistic regression to model the odds of at least one exacerbation in subjects who exacerbated at any point during fall outcome period or subjects who did not exacerbate but completed 91 days of follow-up. This analysis will exclude 37/478 (7.74%) subjects.
3. *Best case analysis*: Use logistic regression to model the odds of at least one exacerbation but appropriately modify response for 37/478 (7.74%) subjects who did not exacerbate and did not complete 91 days of follow-up.
 - For Omalizumab vs. Placebo, 15/259 (5.79%) subjects randomized to Omalizumab and who did not exacerbate and did not complete 91 days of follow-up will be assumed to have no exacerbations during the 91 day follow-up period. 7/89 (7.87%) subjects randomized to Placebo and who did not exacerbate and did not complete 91 days of follow-up will be assumed to have at least one exacerbation during the 91 day follow-up period.
 - For Omalizumab vs. ICS Boost, 6/121 (4.96%) subjects randomized to Omalizumab with Treatment Step 2-4 and who did not exacerbate and did not complete 91 days of follow-up will be assumed to have no exacerbations during the 91 day follow-up period. 15/130 (11.54%) subjects randomized to ICS Boost with Treatment Step 2-4 and who did not exacerbate and did not complete 91 days of follow-up will be assumed to have at least one exacerbation during the 91 day follow-up period.
 - For ICS boost vs. placebo, 15/130 (11.54%) subjects randomized to ICS Boost with Treatment Step 2-4 and who did not exacerbate and did not complete 91 days of follow-up will be assumed to have no exacerbations during the 91 day follow-up period. 4/43 (9.30%) subjects randomized to Placebo with Treatment Steps 2-4 and who did not exacerbate and did not complete 91 days of follow-up will be assumed to have at least one exacerbation during the 91 day follow-up period.
4. *Worst case analysis*: Use logistic regression to model the odds of at least one exacerbation but appropriately modify response for 37/478 (7.74%) subjects who did not exacerbate and did not complete 91 days of follow-up.
 - For Omalizumab vs. Placebo, 15/259 (5.79%) subjects randomized to Omalizumab and who did not exacerbate and did not complete 91 days of follow-up will be assumed to have at least one exacerbation during the 91 day follow-up period. 7/89 (7.87%) subjects randomized to Placebo and who did not exacerbate and did not complete 91 days of follow-up will be assumed to have no exacerbations during the 91 day follow-up period.

- For Omalizumab vs. ICS Boost, 6/121 (4.96%) subjects randomized to Omalizumab with Treatment Step 2-4 and who did not exacerbate and did not complete 91 days of follow-up will be assumed to have at least one exacerbation during the 91 day follow-up period. 15/130 (11.54%) subjects randomized to ICS Boost with Treatment Steps 2-4 and who did not exacerbate and did not complete 91 days of follow-up will be assumed to have no exacerbations during the 91 day follow-up period.
 - For ICS Boost vs. Placebo, 15/130 (11.54%) subjects randomized to ICS Boost and who did not exacerbate and did not complete 91 days of follow-up will be assumed to have at least one exacerbation during the 91 day follow-up period. 4/43 (9.30%) subjects randomized to Placebo and who did not exacerbate and did not complete 91 days of follow-up will be assumed to have no exacerbations during the 91 day follow-up period.
5. Multiple imputation: A Bayesian imputation method applied to logistic regression was used for missing binary variables while a Bayesian predictive mean matching algorithm was used for missing continuous variables. The imputation model included the following variables: (1) Exacerbation status; (2) Site; (3) Arm/treatment step; (4) Injection schedule; (5) Cohort; (6) Follow-up time; (7) Gender; (8) Race; (9) BMI percentile; (10) Job status; (11) Allergic sensitization; (12) Total IgE; (13) German roach IgE; (14) American roach IgE; (15) German roach skin test; (16) American roach skin test; (17) Composite Asthma Severity Index at randomization; (18) FEV1 (% predicted) at randomization; (19) Number of days in last 2 weeks with wheezing; (20) Number of nights in last 2 weeks disturbed by asthma; (21) Exacerbation during run-in period; and (22) Blood eosinophils. Because there were missing data on several variables included in the imputation model, a fully conditional specification based on 25 iterations was used to impute multivariate missing data. A total of 100 imputations were performed.

Table E3: Characteristics of the Modified Intention-to-Treat Participants at Randomization *

	Overall	Treatment Step 2 to 5			Treatment Step 2 to 4		
Characteristic	(n=478)	Placebo (n=89)	Omalizumab (n=259)	P-value	ICS Boost (n=130)	Omalizumab (n=121)	P-value
Injection schedule — no. (%)							
Once per 2 weeks	183 (38.3%)	36 (40.4%)	100 (38.6%)	0.86	47 (36.2%)	42 (34.7%)	0.91
Once per 4 weeks	295 (61.7%)	53 (59.6%)	159 (61.4%)		83 (63.8%)	79 (65.3%)	
Demographics							
Race or ethnic group — no. (%)							
African American	279 (58.4%)	54 (60.7%)	145 (56.0%)	0.43	80 (61.5%)	59 (48.8%)	0.08
Hispanic	161 (33.7%)	30 (33.7%)	88 (34.0%)		43 (33.1%)	49 (40.5%)	
White, mixed or other	38 (7.9%)	5 (5.6%)	26 (10.0%)		7 (5.38%)	13 (10.7%)	
Caretaker completed high school — no. (%)	340 (71.3%)	55 (61.8%)	188 (72.9%)	0.07	97 (74.6%)	88 (72.7%)	0.84
≥1 household member employed — no. (%)	330 (69.0%)	59 (66.3%)	175 (67.6%)	0.93	96 (73.8%)	87 (71.9%)	0.84
Annual household income <\$15,000 — no. (%)	262 (55.4%)	51 (58.6%)	145 (56.6%)	0.84	66 (50.8%)	69 (57.5%)	0.35

* Values are count (percent)

Table E4: Clinical Characteristics of the Modified Intention-to-Treat Participants (n=478) during the Run-in period.*

Variable	Screening	Randomization	Difference (95% CI)	P-value
Asthma-related symptoms — no. of days in 2 wk.‡	4.5 (4.4)	2.3 (3.1)	-2.1 (-2.6, -1.7)	<0.001
Wheezing	3.6 (3.9)	1.8 (2.6)	-1.8 (-2.2, -1.4)	<0.001
Interference with activity	2.6 (3.6)	1.4 (2.6)	-1.2 (-1.5, -0.9)	<0.001
Nighttime sleep disruption	1.9 (3.1)	0.8 (1.8)	-1.2 (-1.5, -0.9)	<0.001
Asthma control†				
C-ACT score in the previous month, age 4 to 11 yr.	18.9 (4.1)	21.6 (3.6)	2.6 (2.2, 3.1)	<0.001
ACT score in the previous month, age 12 yr. or older	19.1 (4.1)	21.5 (3.2)	2.4 (1.6, 3.1)	<0.001
Lung function				
FEV1 — % of predicted value	90.5 (17.2)	90.2 (16.6)	-0.4 (-1.7, 0.9)	0.58
FEV1:FVC ×100	77.5 (10.2)	77.8 (9.5)	0.3 (-0.4, 1.1)	0.37

* Values are mean (standard deviation). P values for the comparison of means and percentages were calculated with the use of the Wilcoxon rank-sum test for continuous variables and the chi-square test for categorical variables. FEV1 denotes forced expiratory volume in one second, and FVC forced vital capacity.

† Scores on the Childhood Asthma Control Test (C-ACT) and the Asthma Control Test (ACT) were measured on scales of 0 to 27 and 5 to 25, respectively. A score of 19 or less on either test indicates that asthma is not well controlled. The minimally important difference for ACT equals 3 points; that for Childhood ACT is not defined.

‡ The number of days with symptoms was calculated as the largest of the following variables during the previous 2 weeks: number of days with wheezing, chest tightness, or cough; number of nights of sleep disturbance; and number of days when activities were affected. This symptom scale ranges from 0 to 14 days per 2-week period.

Table E5: Subgroup Analyses on Exacerbations using Different a-priori Characteristics*

Characteristic		Treatment Steps 2 to 5		Treatment Step 5		Treatment Steps 2 to 4					
		Omalizumab vs. Placebo	P-value	Omalizumab vs. Placebo	P-value	Omalizumab vs. Placebo	P-value	Omalizumab vs. ICS Boost	P-value	ICS Boost vs. Placebo	P-value
Exacerbation during Run In	No	0.88 (0.35, 2.18)	0.041	0.87 (0.21, 3.64)	0.111	0.88 (0.29, 2.72)	0.141	1.34 (0.56, 3.25)	0.038	0.66 (0.21, 2.07)	0.502
	Yes	0.12 (0.02, 0.64)		0.21 (0.07, 0.58)		0.07 (0.00, 1.68)		0.05 (0.00, 0.98)		1.34 (0.24, 7.53)	
EOS counts $\geq$ 320 cells/ μ L	No	1.08 (0.27, 4.30)	0.128	0.88 (0.20, 3.83)	0.137	1.32 (0.13, 13.75)	0.402	0.24 (0.06, 0.93)	0.026	5.57 (0.65, 47.66)	0.014
	Yes	0.31 (0.14, 0.70)		0.22 (0.08, 0.62)		0.42 (0.12, 1.50)		1.78 (0.59, 5.39)		0.24 (0.06, 0.87)	
Total IgE $\geq$ 255 kU/L	No	1.11 (0.31, 4.02)	0.133	0.57 (0.15, 2.14)	0.440	2.17 (0.24, 19.81)	0.198	1.43 (0.42, 4.94)	0.206	1.51 (0.16, 14.53)	0.639
	Yes	0.34 (0.14, 0.80)		0.29 (0.10, 0.84)		0.40 (0.10, 1.53)		0.48 (0.15, 1.53)		0.83 (0.26, 2.63)	
German Roach SIgE $\geq$ 0.175 KUA/l	No	0.75 (0.32, 1.73)	0.166	0.53 (0.18, 1.53)	0.481	1.05 (0.28, 3.94)	0.231	0.95 (0.36, 2.47)	0.638	1.12 (0.31, 3.96)	0.401
	Yes	0.28 (0.10, 0.84)		0.29 (0.08, 1.03)		0.28 (0.05, 1.60)		0.61 (0.12, 2.97)		0.45 (0.09, 2.42)	
Age $\geq$ 10 yrs.	No	0.33 (0.14, 0.77)	0.281	0.21 (0.07, 0.61)	0.124	0.52 (0.14, 1.94)	0.846	1.27 (0.46, 3.56)	0.116	0.41 (0.11, 1.50)	0.132
	Yes	0.73 (0.23, 2.33)		0.82 (0.21, 3.14)		0.66 (0.10, 4.34)		0.31 (0.08, 1.28)		2.09 (0.39, 11.05)	
FeNO $\geq$ 23.5 ppb	No	0.75 (0.28, 2.03)	0.283	0.84 (0.21, 3.37)	0.133	0.67 (0.16, 2.77)	0.870	1.68 (0.47, 6.00)	0.091	0.40 (0.09, 1.71)	0.226
	Yes	0.36 (0.14, 0.91)		0.22 (0.08, 0.63)		0.56 (0.12, 2.75)		0.39 (0.13, 1.19)		1.44 (0.33, 6.35)	
FEV1 percent predicted $\geq$ 90.8%	No	0.63 (0.23, 1.74)	0.309	0.44 (0.16, 1.17)	0.348	0.91 (0.16, 5.36)	0.573	1.18 (0.32, 4.29)	0.408	0.78 (0.13, 4.73)	0.943
	Yes	0.30 (0.11, 0.81)		0.19 (0.05, 0.80)		0.48 (0.13, 1.82)		0.58 (0.19, 1.71)		0.84 (0.25, 2.82)	
BMI percentile $\geq$ 85%	No	0.58 (0.25, 1.39)	0.446	0.53 (0.17, 1.72)	0.387	0.64 (0.18, 2.28)	0.736	3.31 (0.95, 11.58)	0.002	0.19 (0.04, 0.84)	0.011
	Yes	0.33 (0.10, 1.07)		0.26 (0.09, 0.79)		0.42 (0.05, 3.29)		0.13 (0.03, 0.61)		3.31 (0.66, 16.69)	
Hispanic	No	0.46 (0.21, 1.00)	0.801	0.31 (0.12, 0.82)	0.524	0.67 (0.19, 2.32)	0.867	0.66 (0.25, 1.71)	0.569	1.02 (0.32, 3.22)	0.53
	Yes	0.55 (0.17, 1.77)		0.54 (0.13, 2.19)		0.55 (0.08, 3.66)		1.12 (0.23, 5.56)		0.49 (0.07, 3.56)	
African American	No	0.53 (0.17, 1.65)	0.846	0.53 (0.14, 1.96)	0.486	0.53 (0.08, 3.41)	0.783	0.60 (0.15, 2.44)	0.675	0.89 (0.15, 5.46)	0.962
	Yes	0.46 (0.21, 1.03)		0.29 (0.11, 0.80)		0.73 (0.21, 2.56)		0.86 (0.32, 2.33)		0.85 (0.26, 2.75)	
Female	No	0.47 (0.22, 1.00)	0.884	0.31 (0.12, 0.85)	0.590	0.70 (0.22, 2.23)	0.878	1.44 (0.50, 4.15)	0.056	0.49 (0.14, 1.66)	0.195
	Yes	0.53 (0.13, 2.20)		0.50 (0.13, 1.87)		0.56 (0.04, 7.07)		0.22 (0.04, 1.10)		2.55 (0.28, 22.92)	

* All subgroup analyses were pre-specified before examination of the data (Protocol Sections 2.2 and 3.2 and Statistical Analysis Plan Section 5) and are presented in their entirety in this table. Continuous subgroup variables were dichotomized according to their median value. We employed the recommended statistical method for assessing the heterogeneity of the effect among the subgroups using a statistical test for interaction, adjusting for the pre specified baseline characteristics described in the protocol. Because they were exploratory, subgroup analyses do not include adjustment for multiple comparisons.

Table E6: Adjusted Treatment Effect on Exacerbations, Asthma Symptoms, Lung Function, and Treatment Step for the Fall Outcome Period.*

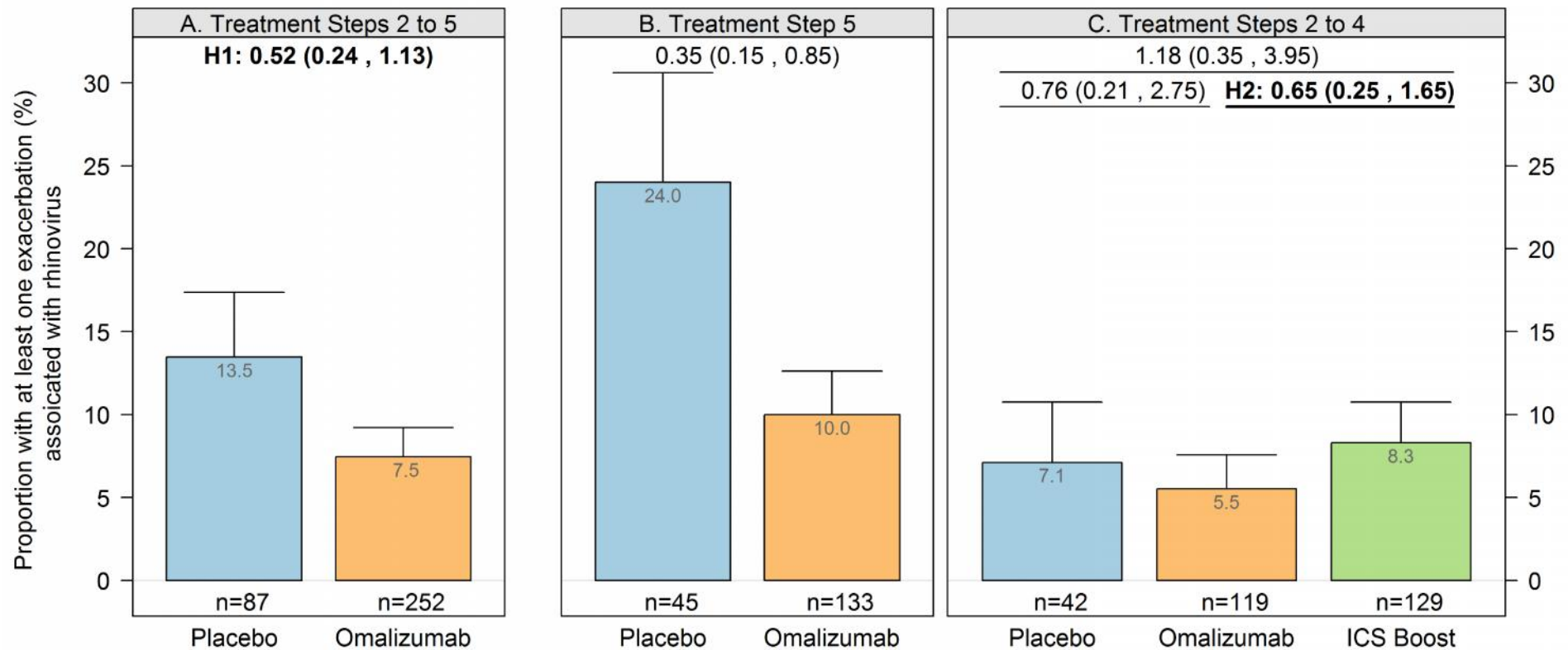
Variable	Adjusted outcome levels during fall outcome period							Treatment Effects				
	Treatment Step 2 to 5		Treatment Step 2 to 4			Treatment Step 5		Treatment Step 2 to 5	Treatment Step 2 to 4			Treatment Step 5
	Placebo	Omalizumab	Placebo	Omalizumab	ICS Boost	Placebo	Omalizumab	Omalizumab v Placebo	Omalizumab v Placebo	Omalizumab v ICS Boost	ICS Boost v Placebo	Omalizumab v Placebo
	Adjusted Risk (SE)							OR (95% CI)				
Exacerbations (mITT)	21.0 (4.59)	11.3 (2.11)	12.7 (4.85)	8.4 (2.51)	11.1 (2.80)	32.6 (7.24)	15.1 (3.11)	0.48 (0.25,0.92)	0.63 (0.22,1.78)	0.73 (0.33,1.64)	0.86 (0.32,2.30)	0.37 (0.17,0.81)
Exacerbations (PP)	18.9 (4.94)	10.6 (2.38)	11.3 (5.00)	7.6 (2.58)	7.8 (2.62)	29.9 (7.76)	14.6 (3.55)	0.51 (0.25,1.03)	0.64 (0.21,1.98)	0.97 (0.39,2.43)	0.66 (0.21,2.05)	0.40 (0.17,0.96)
	Adjusted Geometric Means (SE)							Geometric Mean Ratio (95% CI)				
Eosinophilic Cationic Protein (ECP, mcg/L) †	816.2 (41.28)	621.4 (18.54)	883.1 (64.53)	613.1 (26.60)	846.3 (35.09)	754.6 (52.40)	629.8 (25.23)	0.76 (0.59,0.99)	0.69 (0.47,1.02)	0.72 (0.56,0.94)	0.96 (0.66,1.40)	0.83 (0.58,1.20)
	Adjusted Mean (SE)							Difference (95% CI)				
Asthma-related symptoms	1.8 (0.16)	1.2 (0.09)	1.7 (0.23)	1.0 (0.14)	1.3 (0.13)	1.9 (0.22)	1.4 (0.13)	-0.59 (-0.96,-0.23)	-0.66 (-1.18,-0.13)	-0.30 (-0.67, 0.07)	-0.36 (-0.88, 0.16)	-0.53 (-1.03,-0.04)
Wheezing	1.6 (0.15)	1.1 (0.09)	1.5 (0.21)	0.9 (0.13)	1.1 (0.12)	1.7 (0.20)	1.2 (0.12)	-0.56 (-0.88,-0.23)	-0.66 (-1.14,-0.19)	-0.25 (-0.58, 0.09)	-0.41 (-0.88, 0.06)	-0.45 (-0.90, 0.00)
Interference with activity	0.9 (0.11)	0.6 (0.07)	0.8 (0.16)	0.4 (0.10)	0.7 (0.10)	1.0 (0.16)	0.8 (0.09)	-0.28 (-0.54,-0.02)	-0.34 (-0.72, 0.03)	-0.26 (-0.53, 0.00)	-0.08 (-0.45, 0.29)	-0.22 (-0.57, 0.14)
Nighttime sleep disruption	0.6 (0.07)	0.3 (0.04)	0.4 (0.11)	0.2 (0.06)	0.3 (0.06)	0.7 (0.10)	0.4 (0.06)	-0.24 (-0.41,-0.07)	-0.16 (-0.40, 0.08)	-0.12 (-0.29, 0.05)	-0.04 (-0.28, 0.20)	-0.33 (-0.56,-0.10)
School Days Missed (%) †	1.6 (0.47)	1.2 (0.20)	0.8 (0.39)	0.9 (0.25)	2.0 (0.63)	3.2 (0.99)	1.4 (0.31)	0.72 (0.39,1.35)	1.15 (0.42,3.16)	0.48 (0.23,1.02)	2.39 (0.83,6.88)	0.45 (0.22,0.95)
ACT (previous month) ‡	21.8 (0.35)	22.9 (0.19)	22.0 (0.47)	23.0 (0.26)	22.9 (0.32)	21.6 (0.54)	22.8 (0.29)	1.11 (0.32, 1.90)	0.94 (-0.12, 2.01)	0.05 (-0.76, 0.86)	0.89 (-0.23, 2.01)	1.28 (0.08, 2.48)
C-ACT (previous month) ‡	22.5 (0.31)	23.2 (0.19)	23.0 (0.46)	23.7 (0.29)	23.1 (0.26)	22.0 (0.42)	22.7 (0.25)	0.71 (0.00, 1.41)	0.73 (-0.33, 1.79)	0.58 (-0.15, 1.30)	0.15 (-0.88, 1.18)	0.68 (-0.26, 1.62)
FEV1 — % of predicted value	92.5 (1.38)	92.2 (0.79)	92.8 (2.02)	93.2 (1.15)	90.8 (1.16)	92.2 (1.91)	91.1 (1.07)	-0.32 (-3.42,2.78)	0.47 (-4.04,4.98)	2.37 (-0.76,5.51)	-1.90 (-6.40,2.59)	-1.11 (-5.39,3.16)
FEV1:FVC ×100	78.4 (0.78)	78.6 (0.44)	77.3 (1.12)	79.1 (0.64)	77.9 (0.65)	79.5 (1.08)	78.2 (0.60)	0.25 (-1.49,1.99)	1.81 (-0.70,4.32)	1.15 (-0.61,2.91)	0.66 (-1.85,3.17)	-1.31 (-3.72,1.11)
Treatment Step level equal	3.7 (0.11)	3.6 (0.07)	2.9 (0.16)	2.7 (0.09)	2.7 (0.09)	4.5 (0.15)	4.5 (0.09)	-0.09 (-0.34,0.16)	-0.16 (-0.53,0.20)	0.05 (-0.21,0.30)	-0.21 (-0.57,0.15)	-0.02 (-0.37,0.33)

* All analyses included indicator variables to represent the combination of arm (Omalizumab, ICS Boost, or Placebo), treatment step (Step 2-4 for all arms; Step 5 for Omalizumab and Placebo only), site, and dosing schedule as fixed effects.

† Comparisons between groups for ECP and school days missed are ratios.

‡ C-ACT was measured for 358 participants between 4 and 11 years old. ACT was measured for 119 participants age 12 and older.

Fig E1 A-C: Proportion of participants by treatment arm with at least one viral-associated exacerbation (bar) plus one standard error (whisker) during the fall outcome period (A) in the placebo and omalizumab arms randomized at Steps 2-5; (B) in the placebo and omalizumab arms randomized at Steps 5 and (C) in the placebo, omalizumab, and ICS arms randomized at Steps 2-4. Values at the top of each panel are odds ratios (95% confidence interval). All values are adjusted for site, dosing group and treatment step. H1 refers to primary hypothesis 1; H2 refers to primary hypothesis 2.



Preventative Omalizumab or Step-up Therapy for Severe Fall Exacerbations

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Version 3.0

16 March 2012

Statement of Compliance

This study was designed to ensure the protection of the participants according to the ethical principles of the Declaration of Helsinki and amendments concerning medical research in human subjects. This study will be conducted in compliance with the protocol, the International Conference on Harmonization Good Clinical Practice (ICH-GCP), the U.S. Code of Federal Regulations 45 CFR 46 and 21 CFR parts 50 and 56, and local legal and regulatory requirements.

Investigator Signature Page	
Protocol ICAC - 20 Title: <u>P</u> reventative <u>O</u> malizumab or <u>S</u> tep-up Therapy for Severe Fall <u>E</u> xacerbations	Version/Date: 3.0 / 16 March 2012 Protocol Chair – Stanley Szeffler, M.D.
Short Title: PROSE	
The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines. _____ Principal Investigator (Print) / Title _____ Principal Investigator (Signature) / Title _____ Research Site _____ Date	

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List of Abbreviations

AAAAI	American Academy of Allergy Asthma and Immunology
ACAAI	American College of Allergy Asthma and Immunology
ADL	Activities of Daily Living
ACE	Asthma Control Evaluation
ACT	Asthma Control Test
AE	Adverse Event/Adverse Experience
ALT	Alanine Transaminase
AoC	Assumption of Care
ATS	American Thoracic Society
BDP	Beclomethasone Dipropionate
BID	Twice daily
Bla g1	Cockroach allergen
BUN	Blood Urea Nitrogen
CACT	Childhood Asthma Control Test
Can f 1	Dog allergen
CARE	Childhood Asthma Research and Education
CFR	Code of Federal Regulations
cGCP	current Good Clinical Practice
CI	Confidence Interval
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DAIT	Division of Allergy, Immunology and Transplantation
DC	Dendritic Cells
Der f	Dermatophagoides farinae
Der p	Dermatophagoides pteronyssinus
DMS	Data Management System
DNA	Deoxyribonucleic Acid
DPI	Dry Powder Inhaler
DSMB	Data and Safety Monitoring Board
ED	Emergency Department
E&M	Evaluation and Management
EPR	Expert Panel Report
ETS	Environmental Tobacco Smoke
eNO	Exhaled Nitric Oxide
FcεRI	Fragment Crystalline Epsilon Receptor I (high-affinity IgE receptor)
FDA	Food and Drug Administration
Fel d 1	Cat allergen
FeNO	Fraction of Exhaled Nitric Oxide
FEV ₁	Forced Expiratory Volume in 1 second
Flu	Influenza Virus
FVC	Forced Vital Capacity

List of Abbreviations

GI	Gastrointestinal
GOAL	Gaining Optimal Asthma Control
GSK	GlaxoSmithKline
HCT	Hematocrit
HFA	Hydrofluoroalkane
HGB	Hemoglobin
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HMO	Health Maintenance Organization
ICAC	Inner City Asthma Consortium
ICATA	Inner City Anti-IgE Therapy of Asthma
ICH	International Conference on Harmonization
ICS	Inhaled Corticosteroid
IFN- α	Interferon-alpha
IgE	Immunoglobulin E
IND	Investigational New Drug Application
INR	International Normalized Ratio
IRB	Institutional Review Board
IRF	Interferon Regulatory Factors
ITT	Intention to Treat
IU	International Units
kg	kilograms
L	Liters
LABA	Long-acting Beta Agonist
LTRA	Leukotriene Receptor Antagonist
mcg	Microgram
MedDRA©	Medical Dictionary for Regulatory Activities
MDA	Melanoma-Differentiation-Associated Gene 5
MDI	Metered Dose Inhaler
mg/ml	Milligram per milliliter
MOP	Manual of Procedures
Mus m 1	Mouse allergen
N	Number (typically refers to participants)
NAEPP	National Asthma Education and Prevention Program
NCI	National Cancer Institute
NHLBI	National Heart, Lung, and Blood Institute
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NO	Nitric Oxide
OR	Odds Ratio
PBMC	Peripheral Blood Mononuclear Cell
PC ₂₀	Provocative Concentration that causes a 20% fall in FEV ₁

List of Abbreviations

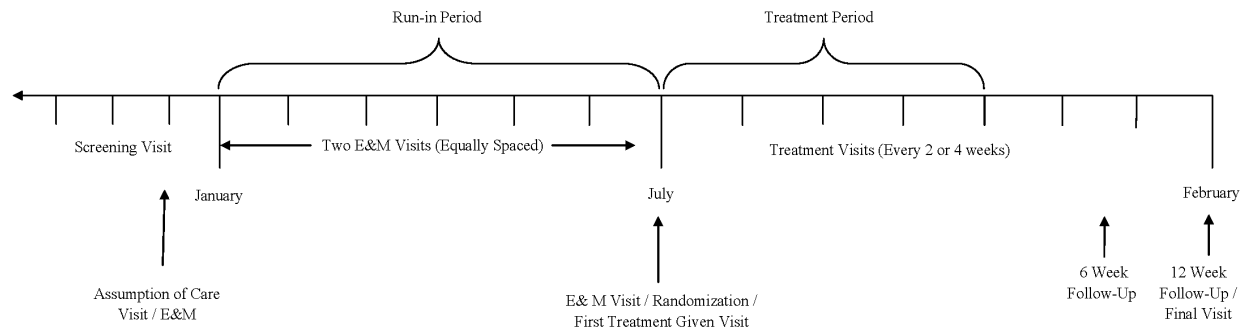
pDC	plasmacytoid Dendritic Cells
PCP	Primary Care Provider
PCR	Polymerase Chain Reaction
PEF	Peak Expiratory Flow
PI	Principal Investigator
PP	Per Protocol
QOL	Quality of Life
RACR	Registry for Asthma Characterization and Recruitment
RBC	Red Blood Cell Count
RIG-I	Retinoic Acid-Inducible Gene 1 Protein
RNA	Ribonucleic Acid
RT-PCR	Reverse Transcriptase-Polymerase Chain Reaction
RV	Rhinovirus
SACCC	Statistical and Clinical Coordinating Center
SAE	Serious Adverse Event/Serious Adverse Experience
SAR	Suspected Adverse Reaction
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SpO ₂	Saturation of Peripheral Oxygen
SQ	Subcutaneous
SUSAR	Serious and Unexpected Suspected Adverse Reaction
TLR	Toll-like receptor 9
TREXA	TReating Children to Prevent Exacerbations of Asthma
U	Units
ULN	Upper Limit of Normal
URI	Upper Respiratory Tract Infection
WBC	White Blood Cell Count

Protocol Summary

Full Title	<u>P</u> reventative <u>O</u> malizumab or <u>S</u> tep-up Therapy for Severe Fall <u>E</u> xacerbations
Short Title	PROSE
Clinical Trial Phase	IV
IND Sponsor	Division of Allergy Immunology and Transplantation National Institute of Allergy and Infectious Diseases (NIAID)
Conducted By	Inner-City Asthma Consortium
Protocol Chair	Stanley Szeffler, MD
Protocol Co-Chair	Stephen Teach, MD
Sample Size	An estimated 1,000 consented in order to have an estimated 533 eligible for the AoC visit (V1) and approximately 453 randomized.
Study Population	The study population will consist of inner-city participants 6 to 17 years of age who have persistent allergic asthma and a history of asthma exacerbations and who meet the inclusion/exclusion criteria in Section 4.1.
Accrual Period	Two cohorts will make up the entire study population. They will be accrued during fall and winter of Years 1 and 2.
Study Design	A three-armed prospective randomized double-blind placebo-controlled trial investigating the efficacy of standard care plus 4-5 months of treatment with (a) a boost of inhaled corticosteroid therapy Flovent [®] Diskus [®] (fluticasone) versus (b) Xolair [®] (omalizumab) or (c) placebo Xolair [®] (omalizumab) and placebo Flovent [®] Diskus [®] (fluticasone) in reducing the exacerbations during the fall season.
Study Duration	All participants will be enrolled in the study for a single fall season, including a run-in phase prior to randomization. Two cohorts will be enrolled over each of 2 successive years, and the entire study period will occur over 2 years.
Study Agent/Intervention Description	Xolair [®] (omalizumab) is a recombinant DNA-derived humanized IgG1κ monoclonal antibody that selectively binds to human immunoglobulin E (IgE). It is administered as a subcutaneous (SQ) injection. The composition of the placebo Xolair [®] (omalizumab) is the same as the active study drug without the Xolair [®] (omalizumab). Flovent [®] Diskus [®] (fluticasone) is an inhaled corticosteroid medication. Placebo Diskus of Flovent [®] Diskus [®] (fluticasone) contains lactose powder.

Primary Objective	The primary objective of this trial is to compare the efficacy of 4 to 5 months of 3 treatments — Xolair [®] (omalizumab), inhaled corticosteroid (ICS) therapy boost, and placebo — in reducing fall exacerbations in inner-city children and adolescents with allergic persistent asthma when initiated approximately 4 to 6 weeks prior to the first day of each participant's school year.
Secondary Objectives	To compare the efficacy of the 3 treatment strategies in reducing exacerbations and/or the duration or intensity of asthma symptoms associated with viral respiratory infection. To compare the efficacy of the Xolair[®] (omalizumab) vs. placebo in reducing exacerbations in participants taking 1000 mcg of Flovent[®] Diskus[®] (fluticasone) daily. To compare the efficacy of the 3 treatment strategies in improving asthma control (as measured by the CACT or ACT questionnaire) and in reducing asthma severity (as measured by the Composite Asthma Severity Index) during the fall season. To measure the pharmacoeconomic impact of utilizing these treatment strategies. To determine if response to each treatment strategy is associated with specific pre-randomization asthma characteristics: degree of atopy, total IgE level, allergen-specific IgE levels, dust mite sensitivity and/or exposure, cockroach sensitivity and exposure, demographic characteristics, eNO, and viral detection by RT-PCR. To identify risk factors and predictors of exacerbations. To explore the interaction of allergen sensitivity and exposure with viral illnesses as determinants of exacerbations. To determine the safety of each treatment regimen. To measure time of onset of exacerbations between groups.
Exploratory Objectives	To determine whether treatment-related reduction of allergic airway inflammation enhances antiviral responses. To determine whether Xolair[®] (omalizumab) therapy impacts pDC interferon-α responses to viral exposure (rhinovirus and influenza). To determine whether Xolair[®] (omalizumab) therapy impacts viral induced expression of genes involved in the regulation of IFN-α secretion.

Endpoints	All endpoints will be collected and analyzed for a 90-day fall outcome period beginning on the first day of each participant's school year. • Primary endpoint: The primary outcome is the occurrence of ≥ 1 asthma exacerbation defined as a prescription of a course of systemic steroids by a clinician or initiation of a course of systemic steroids by a participant or a hospitalization during the fall outcome period (90 day period beginning on the first day of the participant's school year) to prevent a serious asthma outcome. If a participant initiates and completes a course of systemic steroids without clinician involvement, this course will be counted only if it meets the following minimum dosage: prednisone, prednisolone, or methylprednisolone at $\geq 20\text{mg}$ per day for 3 of any 5 consecutive days; or dexamethasone at $\geq 10\text{mg}$ per day for ≥ 1 day. • Secondary endpoints: a. Virus-induced exacerbations as measured by an exacerbation that is associated with a virus detected using the nasal mucus samples. b. Severity of asthma symptoms (defined as the highest value among the following 3 variables: number of days with wheezing, tightness in the chest, or cough; number of nights with disturbed sleep as a result of asthma; and number of days on which the participant had to slow down or discontinue play/physical activities over a two-week period) associated with a viral infection. c. Number of exacerbations evaluated monthly with and without viral respiratory infections. d. pDC frequency in peripheral blood. e. FcεRI expression on pDC in peripheral blood. f. IFN-α response to RV, Flu, and gardiquimod stimulation in peripheral blood mononuclear cells. g. RV, Flu, and gardiquimod-induced expression of IFN-α regulatory genes in peripheral blood mononuclear cells. h. Economic outcomes. i. Spirometry measurements. j. Composite Asthma Severity Index. k. Asthma control measurements (including ACT and CACT scores). l. School absences. m. Estimates of treatment adherence. n. Safety data (adverse events and serious adverse events). o. Home allergen levels.
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Schematic of Overall Study Design:

Key Roles

Sponsor: Division of Allergy, Immunology, and Transplantation, National Institute of Allergy and Infectious Diseases (DAIT)

Institutions: Research Sites are listed in the PROSE Manual of Operations (MOP)

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1. BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

1.1 Background Information

1.1.1 The Fall Asthma Epidemic

While the increase in the prevalence of asthma has abated, levels of asthma morbidity and mortality remain near record highs. An asthma exacerbation is a major factor contributing to morbidity, and even mortality in patients with asthma. Although current approaches to treatment have reduced these risks, asthma exacerbations are major problems for inner-city patients and their families, and prevention of these events continues to be a significant challenge. In children with asthma, there are predictable seasonal epidemics of exacerbations, especially during the fall season, otherwise known as the “September epidemic.”

Current practice for childhood asthma is based on a step gradient related to the categorization of frequency and severity of symptoms (NAEPP, 2007). When an inhaled corticosteroid (ICS) alone is insufficient, a combination of a long-acting beta-agonist (LABA) and ICS is recommended with a leukotriene receptor antagonist (LTRA) as a second line alternative. Oral corticosteroids are used for management of exacerbations. Even with excellent adherence to guidelines-based asthma therapy, children and adolescents continue to have exacerbations and symptoms (Szeffler et al, 2008; Jones et al, 2007). The addition of a short-term boost of ICS or an immunomodulator, such as omalizumab, to conventional ICS therapy offers an opportunity to further reduce asthma morbidity during the fall season.

1.1.2 Observed Effect of Omalizumab in ICATA

The Inner City Anti-IgE Therapy of Asthma (IND 100210, Protocols ICAC08/09: ICATA) trial evaluated the addition of omalizumab to guidelines-based therapy. Overall, participants receiving omalizumab experienced a decrease in asthma morbidity as compared to the guidelines-based group (Busse et al, 2011). Of particular note was the almost complete elimination of the fall increase in asthma exacerbations. This finding led to the creation of a study arm to determine if short-term use of omalizumab during the fall season would have the same effect.

We will test this innovative approach to administering Xolair[®] (omalizumab) therapy prior to and during the fall season to determine if the previously observed suppression of fall exacerbations observed in our year-long treatment evaluated in ICATA is similarly effective during this critical period of fall exacerbations.

1.1.3 Observed Effect of ICS in ACE

The Asthma Control Evaluation (IND 69269, Protocols ICAC-01/02: ACE) Study was designed to evaluate the addition of a biomarker of inflammation, the Fraction of exhaled Nitric Oxide (FeNO), to guidelines-based management of asthma among inner city children (Szeffler et al, 2008). As part of the ACE study, participants were given asthma care by an asthma specialist and provided with free medications and access to an asthma counselor at each study visit to maximize asthma education and adherence. The findings of the ACE study demonstrated that the addition of FeNO monitoring did not result in better overall control as measured by the impairment domain; however, it did note a 25% reduction in the number of participants who had 1 or more exacerbations in the biomarker-supplemented arm compared to control. The addition of a biomarker to asthma management increased the amount of

ICS prescribed to the biomarker group by approximately 120 mcg of fluticasone per day. Subsequent analyses of the seasonal patterns of asthma morbidity in the ACE study found that the fall exacerbation rate was significantly reduced in the biomarker group as compared to the control group that received guidelines-based care without the addition of a biomarker (Szeffler et al, 2008; ICAC, ACE study, data on file).

1.1.4 Rationale for Studying Both Approaches in a Randomized Clinical Trial

The significant reduction of the fall asthma exacerbations with a small difference of ICS dose noted between the 2 study arms in the ACE study led to the creation of a study arm in PROSE to determine if this effect was reproducible. The minimum 200 mcg increase in fluticasone in the ICS arm of PROSE is based on this ACE finding. This dose (200 mcg per day of fluticasone propionate) will be used for those who are receiving less than 500 mcg per day fluticasone propionate equivalent at the time of PROSE randomization.

In carefully evaluating the dose selection for this steroid boost, we felt that a higher dose would be necessary in those participants who are receiving ≥ 500 mcg per day of fluticasone propionate equivalent at the time of randomization. For this group, the steroid boost will be 500 mcg per day of fluticasone propionate. However, in order to avoid increased safety risks due to ICS and to avoid exceeding the maximum ICS dose recommended by current guidelines (NAEPP, 2007), participants who are receiving 1000 mcg per day of fluticasone propionate equivalent at randomization will not be eligible for randomization to the steroid boost arm (see Table 3.1a). We believe that this decision also mirrors clinical practice in which few providers would increase total ICS dosing above 1000 mcg fluticasone propionate equivalent per day, both out of safety concerns and because of the possible “plateau” effect in clinical effectiveness when ICS is used in high dose (Szeffler et al., 2002).

The ACE trial provides some rationale for providing a higher ICS boost to patients randomized with a higher baseline requirement for ICS. Among those ACE participants randomized at ≥ 200 mcg of fluticasone at baseline (n=258), by the final study visit, patients in the intervention arm had received a mean fluticasone dose that was 178 mcg more than the placebo group while attaining a 22% relative reduction in the rate of fall exacerbations. By comparison, among those ACE participants randomized at < 200 mcg of fluticasone at baseline (n=237), by the final study visit, patients in the intervention arm had received a mean fluticasone dose that was 29 mcg more than the placebo group while attaining a 51% relative reduction in the rate of fall exacerbations. In short, substantially more fluticasone was required among those with a higher baseline ICS requirement to achieve a less robust decrease in the exacerbation rate. Therefore, we will seek to determine whether a higher dose of 500 mcg (compared to 200 mcg) per day for the steroid boost as preventative therapy in those already receiving a high baseline requirement for ICS (i.e., 500 mcg per day or more fluticasone propionate) could have a greater response than the 22% reduction in fall exacerbations observed in the ACE study.

Another consideration in the design of this arm was the great cost differential between omalizumab and inhaled fluticasone propionate. If equivalent results are found between the omalizumab and fluticasone arms in the reduction of the fall exacerbation rate, the differential between the cost of the 2 agents would favor the use of inhaled fluticasone propionate.

We will compare both of these treatments to the conventional guidelines-based approach, which adjusts treatment based on an assessment of control at a visit in order to improve overall asthma control over the next treatment interval. We feel that the conventional strategy may have some limitations, as defined in our ACE study, in that it reacts to inadequate symptom control by stepping up therapy at the visit rather

than trying to take a preventative approach and stepping up therapy to prevent loss of control. Because modifications are being made in the protocols applied in ICATA and ACE by limiting the step-up therapy to visits just prior to and during the fall season, we are uncertain whether the results will be the same as that noted in those previous ICAC studies. The benefit of such an anticipatory step-up strategy could be a successful method of preventing or at least attenuating fall exacerbations in a dosing strategy rather than a continuous form of treatment.

1.1.5 Description of the Study Agent(s)/Intervention(s)

1.1.5.1 Xolair® (Omalizumab)

Xolair® (omalizumab) is a recombinant DNA-derived, humanized, IgG1κ monoclonal antibody that selectively binds to human Immunoglobulin E (IgE). The antibody has a molecular weight of approximately 149 kiloDaltons. Xolair is produced by a Chinese hamster ovary cell suspension culture in a nutrient medium containing the antibiotic gentamicin. Gentamicin is not detectable in the final product. Xolair® Solution for Injection (omalizumab) is supplied as single-use pre-filled syringes for subcutaneous (SQ) injection.

The composition of the placebo is the same as the active study drug without the Xolair® (omalizumab). Xolair® (omalizumab) and placebo Xolair® (omalizumab) are manufactured by Vetter Pharma-Fertigung on behalf of Novartis.

For additional information on the study drug (packaging, labeling, storage, handling, preparation, and administration), refer to Sections 5.1 – 5.3.

1.1.5.2 Flovent® Diskus® (Fluticasone)

Flovent® Diskus® 100 mcg (fluticasone propionate inhalation powder, 100 mcg) and Flovent® Diskus® 250 mcg (fluticasone propionate inhalation powder, 250 mcg) have been selected for use in the ICS boost arm of the protocol. Each actuation of the Diskus® device provides 94 or 229 mcg of fluticasone propionate. Each device is sealed by the manufacturer in a moisture-protective foil pouch and contains 60 blisters of fluticasone propionate inhalation powder.

Placebo Flovent® Diskus® contains a foil strip of 60 blisters, each blister contains a nominal 13mg fill of lactose powder. Flovent® Diskus® and placebo Diskus supplies are manufactured by GlaxoSmithKline (GSK).

For additional information on the study drug (packaging, labeling, storage, handling, preparation, and administration), refer to Sections 5.1 – 5.3.

1.1.6 Summary of Relevant Clinical Studies

1.1.6.1 Proof of Concept Studies

Several studies confirm the premise that reduction of serum IgE due to treatment with anti-IgE (omalizumab) results in positive changes in clinical characteristics of asthma (Busse et al, 2001; Milgrom et al, 2001; Soler et al, 2001). Treatment with omalizumab reduces both the early bronchoconstriction response, (a mast cell-related event), and the late phase inflammatory response (a T-cell orchestrated event with polymorphonuclear and eosinophil infiltration) in patients challenged with inhaled allergen. Airway hyperresponsiveness is reduced. Cellular effects include a decrease in the number of eosinophils

in sputum (related to pretreatment levels), and decreased eosinophils in the submucosal compartment (as shown by endobronchial biopsy). In fact, all of the cells involved in the sequence of pulmonary events, mast cells, basophils, neutrophils and eosinophils, are affected. The eosinophils in circulating blood are also significantly reduced.

Anti-IgE not only suppresses the serum IgE levels to 1% of pretreatment levels but also results in a downregulation of Fragment Crystalline Epsilon Receptor I (FcεRI) on basophils, suggesting that FcεRI density is regulated in some way by plasma-free IgE levels. Basophil response to *Dermatophagoides farinae* (Der f) stimulation is reduced by ~90% (MacGlashan et al, 1997).

Studies of the clinical effects corresponding to a reduction in total serum-IgE relate significant effects upon the airway response to allergen challenge. With the reduction in serum IgE brought about by treatment with omalizumab, increasing doses of allergen are required to provoke an early asthma response with allergen inhalant challenge. This effect carries over to attenuation of the late phase response as well (Fahy et al, 1997). PC20 for methacholine after treatment was also examined and demonstrated a non-significant improvement.

These findings together with previous studies establish a major role for IgE in orchestrating airway narrowing, airway tissue eosinophilia, and the airway hyperresponsiveness of the late phase response to allergen challenge.

1.1.6.2 Clinical Trials

1.1.6.2.1 Omalizumab Treatment of Exacerbations

The general designs of the phase III clinical studies with omalizumab (Busse et al, 2001; Milgrom et al, 2001; Soler et al, 2001; Holgate et al, 2004; Lanier et al, 2009) are similar and consist of 5 sequential periods: 1) a 1 week screening period, 2) a 4-6 week ICS conversion period where all participants received the same ICS (this includes a 2 week baseline period), 3) a 7 month double blind core study period (subdivided into 2 study periods), 4) a 5 month extension period, and, lastly, 5) a 12 week follow-up visit. The core portion of the studies was designed to assess the efficacy as well as the safety of omalizumab compared with placebo. These phase III studies were submitted to the FDA in support of the omalizumab indication for maintenance therapy for prophylaxis of asthma exacerbations and control of symptoms in adults and children (12 years of age and older) with moderate to severe allergic asthma that is inadequately controlled despite the use of ICS. The definition of allergic asthma was defined as “asthma with co-existing evidence of allergy.”

The double blind 7-month core portion was then divided into 2 periods. The first period was considered a 4-month stabilization period during which patients received randomly assigned omalizumab or placebo treatment and a stable dose of beclomethasone dipropionate (BDP). (Conceptually, this would be considered as omalizumab used as add-on therapy.) This period was then followed by 3-month steroid dose reduction phase. (This would be considered as omalizumab used as “steroid-sparing.”) During the first 8 weeks of this phase, the participants continued study treatment and the BDP dose was reduced by 25% of the baseline dose every 2 weeks (a visit every 2 weeks) until total elimination of ICS or development of uncontrolled asthma was determined. At this point the stable, lowest tolerated BDP dose was maintained for the last 4 weeks.

During these core double-blind treatment periods, patients were not allowed to take any other asthma medication except for the fixed dose of BDP, rescue beta-2 agonists, and treatment for asthma exacerbations.

The 5-month extension period was primarily designed to assess the long-term safety of omalizumab. However, secondary assessments included the effects of omalizumab on asthma exacerbations, corticosteroid usage, and Quality of Life (QOL). Patients continued receiving the double-blind treatment as in the 7-month core study, but in the extension phase they were allowed to be treated with other asthma medications if necessary for asthma control at the investigators' discretion. These medications included LABA and ICS other than BDP. A single visit at 12 weeks after the final visit took place for post-treatment clinical evaluation and blood sampling to evaluate serum total IgE and anti-omalizumab antibody levels.

Four placebo-controlled studies using subcutaneously administered omalizumab have been published (Busse et al, 2001; Milgrom et al, 2001; Soler et al, 2001; Holgate et al, 2004). All 4 studies included patients with at least 1 positive skin test to a perennial allergen, with increased serum IgE levels, with asthma for at least 1 year, and requiring daily ICS medication. Three studies included patients with an age range of 12 -75 years (Busse et al, 2001; Soler et al, 2001; Holgate et al, 2004) and 2 pediatric studies included children of 6-12 years of age (Busse et al, 2010; Milgrom et al, 2001). Two of the studies included patients with moderate to severe asthma (Busse et al, 2001; Soler et al, 2001) and 1 included patients with defined severe asthma (Holgate et al, 2004). Marked reductions in free serum IgE were noted in all studies. Significant clinical effects related to exacerbations, reductions in ICS requirement, complete withdrawal of ICS requirement, reduced rescue medication use, and improved QOL were observed as well as an excellent safety record. In the Holgate (2004) study of severe asthma, there were no significant effects on either incidence or frequency of exacerbations in either treatment phase of the study, and in the pediatric study of Milgrom (2001), a significant reduction in exacerbations was noted only during the ICS dose reduction phase. Overall, there were significant increases in the number of patients who were able to reduce their ICS dose by over 50%, completely withdrew their daily steroid intake, and were less likely to suffer an asthma exacerbation with treatment as an adjunct to ICS or as an ICS tapering agent.

In the NIAID ICAC ICATA study (discussed above) (Busse et al, 2011), among the 419 randomized participants aged 6 – 20 years, omalizumab treatment resulted in a 25% reduction of asthma symptoms (0.48 days per 2 weeks, $p < 0.001$) and a 30% reduction in exacerbations (37.2% vs. 53.6%, $p = 0.001$). While the control group experienced more than 100% increase in exacerbations from summer to fall, only a small, non-significant increase occurred in the omalizumab group. These improvements were obtained despite significant reductions in both ICS and LABA in the omalizumab group. Participants sensitized and exposed to German cockroach, compared to all others receiving omalizumab, had greater reductions in symptom days per 2 weeks [1.1 (95% CI 0.4 – 1.8) vs. 0.4 (95% CI 0.1 – 0.7)], ICS use [268 mcg (95% CI 109 – 427) vs. 93 mcg (95% CI 19 – 166)], and lower exacerbation rates [3% (95% CI 0.8% - 5.2%) vs. 9.4% (95% CI 3.3% - 15.5%)].

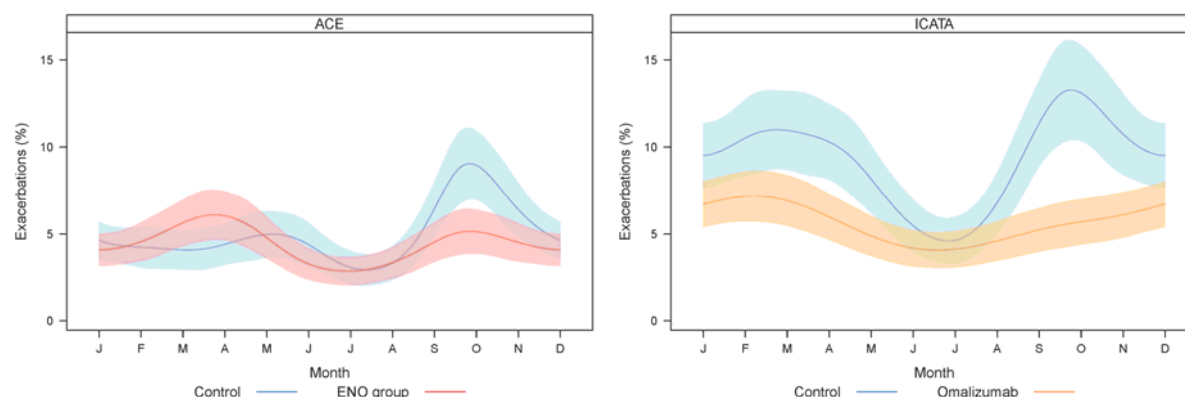
Another recent publication, by Lanier et al (2009), reported on a randomized, double-blind, placebo-controlled trial of omalizumab among children 6 to 11 years with perennial allergen sensitivity and history of exacerbations and asthma symptoms despite at least-medium dose ICS. The study was conducted over a 52 week period (24-week fixed-steroid phase followed by a 28-week adjustable steroid phase). A total of 627 patients (omalizumab, $n = 421$; placebo, $n = 192$) were randomized, with efficacy analyzed in 576 (omalizumab, $n = 384$; placebo, $n = 192$). Over the 24-week fixed-steroid phase, omalizumab reduced the rate of clinically significant asthma exacerbations (defined by symptoms requiring doubling of baseline ICS dose and/or systemic steroids) by 31% versus placebo (0.45 vs 0.64; rate ratio, 0.69; $p = .007$). Over a period of 52 weeks, the exacerbation rate was reduced by 43% versus placebo ($p < .001$). Omalizumab significantly reduced severe exacerbations. In addition, over a period of 52 weeks, omalizumab had an acceptable incidence of adverse events. Therefore, the investigators concluded that add-on omalizumab is effective and well tolerated as maintenance therapy in children (6 to

<12 years) with moderate-to-severe persistent allergic asthma whose symptoms are inadequately controlled despite medium to high doses of ICS.

A Cochrane analysis in 2006, which evaluated the effectiveness of omalizumab in chronic asthma, including 14 trials across all age groups, similarly concluded that treatment with omalizumab led to a significant reduction in exacerbations and a significant reduction in the need for ICS. (Walker et al, 2006)

In the ICATA trial, we observed significant suppression of the seasonal exacerbation with omalizumab therapy. The figure below shows the seasonality of asthma exacerbations in ACE and ICATA by study group. In ICATA, during the fall season asthma exacerbations were significantly reduced by more than 50% in the omalizumab group (38% Controls vs. 18% treatment group) odds ratio of 2.9 (95% CI 1.8 - 4.7). In ACE, during the fall season asthma exacerbations were reduced by 30% in the FeNO-guided group who received approximately 120 mcg more fluticasone per day.

Figure 1.1.6.2.1a: Exacerbations seasonal variation during ACE and ICATA by study group, bands show 95% CIs.



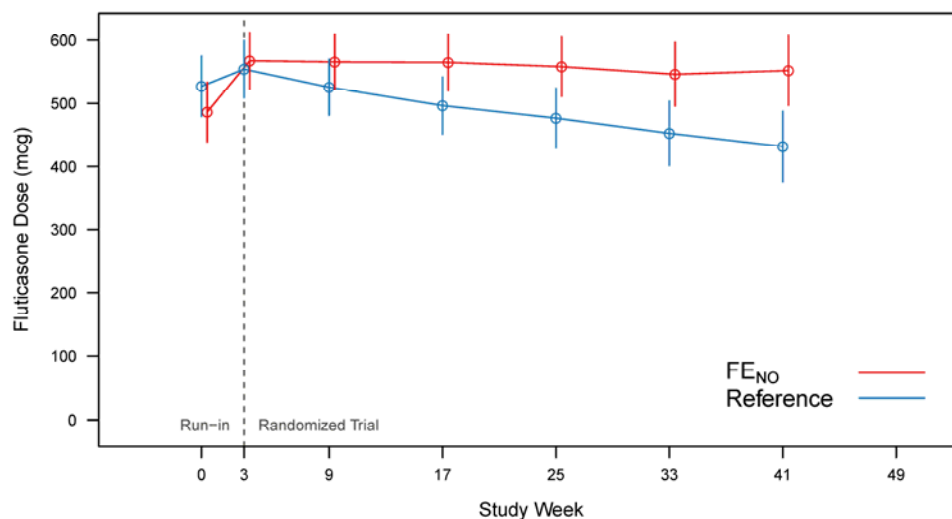
1.1.6.2.2 Non-Omalizumab Treatment to Prevent Exacerbations

Several studies have been conducted in young children in an attempt to prevent an asthma exacerbation by administering treatment at the first sign of a respiratory illness in young children. Recently, Bacharier et al (2008) reported on such a study conducted in the National Heart Lung and Blood Institute (NHLBI) Childhood Asthma Research and Education (CARE) Network. This study concluded that episodic use of budesonide or montelukast administered at the earliest signs of a respiratory tract illness does not increase the proportion of episode free days or decrease oral corticosteroid use over a 12-month period, but does decrease symptom severity during acute respiratory tract illnesses.

Kelly and Busse (2008) and Sears (2008) have summarized the impact of treatment on reducing asthma exacerbations. Corticosteroids are the preferred treatment for persistent asthma as defined by the asthma guidelines (NAEPP, 2007). As indicated by the results of the NHLBI Childhood Asthma Management Program (2000), ICS reduced asthma exacerbations by approximately 50% as compared to as needed beta-adrenergic agonist, albuterol, therapy among children with persistent asthma. However, ICS did not eliminate exacerbations even under conditions of close monitoring and long-term treatment. A summary of available studies indicates that although corticosteroids are effective in asthma and diminish the frequency of wheezing with a cold, the effects are not uniform (Kelly and Busse, 2008). Clinical observations suggest that although components of the immune response to viruses that promote asthma are sensitive to the corticosteroid effects, other aspects of the response to viruses are not modulated by

this treatment (Kelly and Busse, 2008). **Furthermore, no trial to date has attempted to increase the dose of ICS prior to the fall season to determine if this strategy can reduce fall exacerbations.**

Figure 1.1.6.2a



Based on the results of the ACE study, we feel that an increase in ICS dose of approximately 120 mcg per day equivalent of fluticasone propionate, could reduce the risk of an exacerbation but likely not completely remove the risk of such an exacerbation. This is the premise for the boost ICS arm in the PROSE protocol as previously discussed in Section 1.1.4.

Studies with LTRA suggest that respiratory viral provocation of asthma involves the generation of leukotriene products. Furthermore, blockade of leukotrienes by LTRA can reduce the increase in asthma symptoms triggered by a cold (Kelly and Busse, 2008). In a cohort of predominantly school-aged children, the addition of montelukast to usual therapy during the “September asthma epidemic” significantly reduced the number of days of increased asthma symptoms by about 50% and events requiring a visit to a clinician or ED or use of oral corticosteroid therapy by 78% (Johnston et al, 2007).

In young children, the use of montelukast over the course of a year reduced the number of exacerbations by ~30% but did not reduce the use of oral corticosteroids prescribed for severe exacerbations (Bisgaard et al, 2005). In children with a history of virus-induced asthma symptoms, short courses of montelukast initiated at the first indications of a cold or asthma symptoms significantly lowered the use of health care visits and symptom scores, but did not change the need for oral corticosteroids or rescue inhaler medication (Robertson et al, 2007). Therefore, LTRA may mildly ameliorate, but likely do not eliminate asthma exacerbations in children.

The Back to School asthma study was designed to determine the effectiveness of montelukast therapy in reducing the asthma burden in children when initiated prophylactically on school return, in children with asthma aged 6-14 years. Montelukast 5 mg chewable tablets (n=580) or matching placebo (n=582) was taken the night before the first day of school and nightly thereafter for 8 weeks. The primary endpoint was the percentage of days with worsening asthma. The reduction in the percentage of days with worsening asthma with montelukast-use versus placebo was not significant (24.3% as 27.2%, p = 0.07) (Weiss et al 2010).

Several recent studies have focused on the use of combination ICS and long-acting β -adrenergic agonist therapy in reducing exacerbations. The Gaining Optimal Asthma Control (GOAL) study showed that exacerbations could be reduced, and well-controlled asthma achieved in the majority of patients, by escalating daily doses of ICS with LABA until the patient was symptom-free (Bateman et al, 2004). This approach is somewhat similar to that used in the ICAC ACE study that was previously described. Both studies reduced but did not eliminate asthma exacerbations (Szeffler et al, 2008; Bateman et al, 2004). One potential reason for this limited effect in GOAL and ACE is that treatment steps were adjusted based on inadequate control and a step-up approach was not used to prevent symptoms in the presence of otherwise controlled asthma. In PROSE, we will be stepping up treatment with either omalizumab or a steroid boost in an effort to prevent exacerbations in comparison to those managed conventionally with a guidelines-based approach.

A series of studies using formoterol combined with budesonide either as maintenance therapy, or as both maintenance and reliever therapy, have shown promise for use of combination therapy as a strategy to reduce asthma exacerbations (O'Byrne et al, 2005; Rabe et al, 2006; Kuna et al, 2007). Other studies have evaluated the effect of low and high dose budesonide alone and in combination with formoterol (O'Byrne et al, 2001; Pauwels et al, 1997). Formoterol added to low dose ICS was more effective than doubling the dose of ICS (O'Byrne et al, 2001). However, it appears that the most effective maintenance treatment in reducing the risk of exacerbations is the combination of high dose budesonide (400 mcg twice daily) and formoterol (Pauwels et al, 1997). The use of combined ICS and LABA as reliever therapy permits the reduction of maintenance ICS and LABA therapy (O'Byrne et al, 2005; O'Byrne, 2007). However, the use of combination ICS maintenance and LABA reliever therapy is not approved in the United States and likely will not be approved. In the PROSE study, all participants will receive maintenance ICS therapy with adjustments of ICS and addition of LABA based on the guidelines-approach to management.

Another approach to reducing exacerbations has been the application of biomarkers, such as FeNO and sputum eosinophils, as well as airway hyperresponsiveness to adjust therapy (Sont et al, 1999; Green et al, 2002; Smith et al, 2005). Our study with FeNO showed a marginal reduction in exacerbations, approximately 25% of those with one or more exacerbations (Szeffler et al, 2008). However, studies utilizing airway hyperresponsiveness and sputum eosinophils to adjust therapy showed a reduction by 50% or more (Sont et al, 1999; Green et al, 2002). The latter measures are somewhat impractical and can be obtained only periodically in specialized settings. Therefore, they may be used to adjust therapy but are likely not good at anticipating an asthma exacerbation. We did observe that the use of FeNO monitoring actually resulted in sustaining a higher dose of ICS by preventing medication reduction. As previously noted, the resulting difference in ICS dose was approximately 120 mcg per day higher after 1 year of management in the FeNO plus guidelines-based approach as compared to the guidelines alone approach. As described in Section 1.1.4, this observation prompted our assessment of inhaled steroid boost therapy as a preventative step in reducing the risk of a fall asthma exacerbation.

Another strategy for managing an impending exacerbation is to increase the ICS dose. It has become clear that doubling the dose of ICS at the time of an exacerbation is ineffective and it may require a higher dose, such as using 4 times the baseline dose, to prevent further loss of asthma control associated with an impending asthma exacerbation (FitzGerald and Gibson, 2006).

It has also been suggested that disease management programs could be effective in improving asthma control and reducing asthma exacerbations. However, Galbreath et al. (2008) recently reported that 2 previously successful disease management programs, one employing a telephone reminder system and another augmented with home visits, were no more successful than traditional therapy in decreasing health care utilization or improving clinical outcomes in an underserved asthma population.

1.2 Rationale

Two previous ICAC studies provide findings that guided the development of this protocol. The first was the Asthma Control Evaluation (ACE) Study, which was designed to evaluate the addition of a biomarker FeNO to guidelines-based management of asthma among inner city children (Szeffler et al, 2008). The addition of a biomarker to asthma management tended to increase the amount of inhaled corticosteroids prescribed to the biomarker group by a mean of 120 mcg of fluticasone per day with little increase in overall control in the impairment domain. Subsequent analyses of the seasonal patterns of asthma morbidity in the ACE data found that the fall exacerbation rate was significantly reduced in the biomarker group as compared to the control group that received guidelines-based care without the addition of a biomarker. The second was the Inner City Anti-IgE Therapy of Asthma (ICATA), which evaluated the addition of omalizumab to guidelines-based therapy. Overall, the omalizumab group experienced a decrease in asthma morbidity as compared to the guidelines-based group. Of particular note was the almost complete elimination of the fall increase in asthma exacerbations.

Therefore, based on observations from our 2 recent NIAID Inner City Asthma Consortium studies, ACE and ICATA, we hypothesize that step-up therapy, either as omalizumab therapy or step-up with ICS therapy, administered prior to the period of anticipated fall exacerbations, can prevent a severe asthma exacerbation as compared to current guidelines-based treatment. Of note in these 2 studies, the effect of omalizumab appears to be greater on reducing the risk of a fall exacerbation than that seen with the biomarker-based approach from the ACE study. The significant reduction of the fall asthma exacerbation rate with a small boost of ICS led to the creation of a study to determine if this effect was reproducible in another study. However, in order to avoid increased safety risks due to inhaled corticosteroids and to avoid exceeding the maximum ICS dose recommended by current guidelines (NAEPP, 2007), participants who are receiving 1000 mcg per day of fluticasone propionate equivalent at randomization will not be eligible for randomization to the steroid boost arm. If equivalent results are found between the omalizumab and fluticasone arms in the reduction of the fall exacerbation rate, fluticasone may be more cost effective.

In addition to studying the impact of additional therapies on reducing the fall exacerbation rate, the PROSE study offers the opportunity to better understand a number of previously reported risk factors for exacerbations.

1.2.1 Viral Infections and Asthma Exacerbations

In children, 9 to 11 years, 80% to 85% of asthma exacerbations resulting in reduction of peak expiratory flow (PEF) and wheezing were associated with upper respiratory viral infections (Johnston et al, 1995). Rhinovirus (RV) has been the most commonly detected infectious agent in these studies (Friedlander and Busse, 2005; Khetsuriani et al, 2007). Among children 2 to 17 years old with exacerbations, compared with controls, RV was the most prevalent (60% among cases, 18% among controls) and the only virus significantly associated with exacerbations (odds ratio [OR], 6.8; 95% CI, 3.2-14.5) (Khetsuriani et al, 2007).

1.2.2 Predisposing Factors for an Asthma Exacerbation

Johnston et al (2005) sought to determine the underlying cause of the marked increase in exacerbations in children in September by conducting a case control study in EDs by examining children (cases) who presented during the September epidemic and comparing findings with children from the same community (controls) with equally severe asthma not requiring an ED visit. Of interest, although many

features were similar between the 2 groups, cases were 50% less likely to have been prescribed a regular anti-inflammatory therapy, and were more likely to have had multiple ED visits in the past. The prevalence of viral infection, predominantly RV, was 61% in cases and 40% in controls (Johnston et al, 2005). It was thought that the lower use of anti-inflammatory therapy was a key factor in predisposing to viral-associated asthma worsening. A similar study was conducted by Murray et al (2006) with some similar findings. They also reported that the combination of virus detection and sensitization with a high allergen exposure increased the risk of admission to a hospital (OR, 19.4; 95% CI, 3.7-101.5, $p < .001$).

Kling et al (2005), based on a study of children age 4 to 12 years admitted to an ED with a severe asthma exacerbation, reported that those children with detectable RV after 6 weeks had more severe persistent asthma with lower peak expiratory flow, and a slower recovery than those in whom it was absent at 6 weeks, suggesting a link of more severe RV infection with prolonged recovery. Of note, human metapneumovirus has been associated with asthma exacerbations (Williams et al, 2005). Also, there is an increased risk for asthma admission with allergen sensitization and exposure (Murray et al, 2004; Green et al, 2002).

1.2.3 Predictors of Asthma Exacerbations

Covar et al (2008) sought to determine factors associated with exacerbations in children with persistent asthma by analyzing data collected during the 48-week CARE Network's Pediatric Asthma Controller Trial (PACT) study (Sorkness et al, 2007). Regression modeling was used to identify historical, phenotypic, treatment, and time-dependent factors associated with the occurrence of exacerbations, defined by the need for oral corticosteroids or emergency or hospital care. Children age 6 to 14 years with mild to moderate persistent asthma were randomized to either: fluticasone propionate 100 mcg twice daily, montelukast 5 mg once daily, or fluticasone propionate 100 mcg in AM and salmeterol twice daily. A total of 285 participants were randomized and 48% had 231 exacerbations. Using a multivariate analysis, only a history of an asthma exacerbation requiring a systemic corticosteroid in the past year (OR, 2.10; $p < .001$) was associated with a subsequent exacerbation.

Univariate analysis for factors linked to asthma exacerbations revealed significant associations for treatment with montelukast versus fluticasone propionate monotherapy (OR, 2.00; $p = .005$), season (spring, fall or winter vs summer; $p \leq .001$), and average seasonal reduction in AM peak expiratory flow of 5% or more (OR, 1.21; $p = .01$). Worsening symptoms, increasing β -agonist rescue use, and low peak expiratory flow track together before an exacerbation, but have poor positive predictive value of an exacerbation.

This study concluded that children with mild-to-moderate persistent asthma with previous exacerbations are more likely to have a repeat exacerbation despite controller treatment. Inhaled corticosteroids are superior to montelukast at modifying this exacerbation risk. Also, the investigators reported that available physiologic measures and biomarkers and diary card tracking are not reliable predictors of asthma exacerbations.

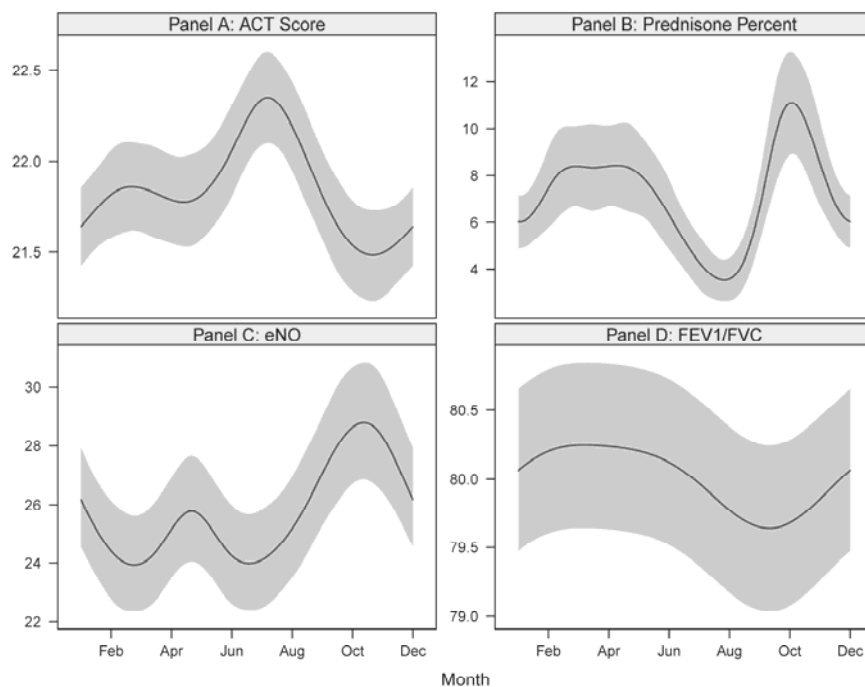
1.2.4 ACE Study Observations

The ACE study provided the opportunity to assess patterns of control in over 546 participants (Szeffler et al, 2008). In this study, treatment was adjusted to achieve control. Because FeNO did not have a significant effect on improving asthma control, the 2 study arms were evaluated as one dataset. There is marked variability within individual participants in the ability to attain and maintain control. In review of the patterns of asthma control, the majority of participants (67%) reached a level of well-controlled by the

randomization visit with only 3% of participants failing to reach a well-controlled level throughout the study. For those who eventually did reach control (97%), approximately 30% lost control at a later visit.

Evaluating the control data based on calendar month of the year revealed several patterns of interest. Assessment of mean data identified a seasonal pattern of increased symptoms (as reflected by a lower ACT score) and prednisone courses during the spring and especially the fall season (Figure 1.2.4a, panel A and B). The fall season was also associated with an increase in FeNO and a decrease in FEV₁/FVC (Figure 1.2.4a, panel C and D). Treatment with controller regimen steps was also increased during the fall season.

Figure 1.2.4a



Summary data obtained from the ICAC ACE study (from Szeffler et al, 2008) combining the total number of participants (N=565) and analyzed by calendar month to show seasonal variation in (a) Asthma control Test score; (b) percent of study population receiving a prednisone course; (c) exhaled nitric oxide (ppb); and FEV₁/FVC ratio as a percent

Features of ACE participants who had a fall exacerbation include a higher total blood eosinophil count; a positive allergen skin test to German cockroach; higher total IgE; higher specific IgE to cockroach as well as house dust mite and cat; and greater exposure to cockroach (Bla g1) allergen (Table 1.2.4a). Therefore, higher sensitivity and exposure to cockroach were prominent features associated with the occurrence of a fall exacerbation.

Table 1.2.4a Allergen sensitivity and exposure characteristics of the ICAC ACE study participants (from Szeffler et al., 2008) who did not versus those who did have a fall exacerbation.* [NIAID, ICAC, ACE study, data on file]

	No Fall Exacerbation		Fall Exacerbation	P-value
	N	(N=410)	(N=136)	
German Roach Wheal >= Saline Wheal + 3 mm	531	44% (176)	58% (75)	0.006
Roach Mix Wheal >= Saline Wheal + 3 mm	531	56% (224)	68% (89)	0.011
Skin Test Positive to One or More Rodent allergen	531	36% (143)	46% (60)	0.032
Skin Test Positive to One or More Roach allergen	531	58% (234)	70% (91)	0.018
Specific IgE Dust Mite (Der p) (IU/mL)	534	0.247 (0.050-1.889)	0.619 (0.050-7.795)	0.003
Specific IgE Dust Mite (Der f) (IU/mL)	533	0.223 (0.050-1.879)	0.660 (0.050-9.752)	0.001
Specific IgE Cat (IU/mL)	533	0.228 (0.050-5.457)	1.058 (0.050-10.084)	0.018
Specific IgE Cockroach (IU/mL)	534	0.171 (0.050-2.779)	1.362 (0.050-9.543)	0.001
Indoor specific IgE total (Der p + Der f + cat + roach) (IU/mL)	533	4.572 (0.309-33.850)	18.523 (3.137/56.951)	<0.001
Total IgE	534	218.39 (89.94-626.54)	362.61 (143.66-783.40)	0.007
Numeric Exposure Bla g 1 - U/g	518	0.50 (0.50-1.57)	0.50 (0.50-3.90)	0.012
Total Blood Eosinophil (Visit 2)	533	202.25 (116.85-344.17)	242.00 (130.40-425.25)	0.021

*Interquartile range is provided in parentheses with medians. N is the number of non-missing values. Numbers after percents are frequencies. There was no significance detected for the two groups for the following (1) allergen skin test reactions to dog, dust mite (der p, der f), rat, cat, mouse, *Alternaria tenuis*, *aspergillus* mix, ragweed mix, *cladosporium*, *penicillium notatum*, timothy grass; (2) skin test positive to one or more dust mite allergens or mold allergens; (3) Specific IgE to *Alternaria*; (4) Numeric exposure to fel d1, can f1, der f1, der p1, mus m1; (5) per cent white blood cells; (6) methacholine PC20.

A similar analysis was conducted for springtime exacerbations but neither allergen sensitivity nor exposure was significantly related to the risk of exacerbation. Unfortunately no testing was performed for springtime outdoor allergens such as trees.

The unique features of this study included the evaluation of inner-city children, who had a high percentage of allergen sensitivity and high exposure, the design of the protocol utilizing a medication adjusted algorithm to achieve control, and precautions to avoid medication reduction prior to fall, even if well controlled. Despite guidelines-based controller therapy and good adherence, approximately 25% had a fall exacerbation requiring at least a 100 mg course of a systemic corticosteroid. A key risk factor appeared to be cockroach sensitivity (skin test, specific IgE) and exposure and other indicators included increased total IgE and blood eosinophilia.

The ACE study suggests that an increase in daily ICS use can reduce the rate of exacerbations. In this study, it was shown that fall exacerbations were significantly reduced in the FeNO arm as compared to the guidelines-based arm alone (Figure 1.1.6.2.1a). In the FeNO-arm of the study, ICS treatment was increased for participants who had elevated FeNO readings and poor control and was not reduced for participants with elevated FeNO and good control. As a result, FeNO-arm participants received an average of 120 additional mcg of ICS per day compared to participants in the placebo group. We hypothesize that this difference in ICS therapy reduced the number of the fall exacerbations in the treatment group. It is not known whether targeted stepping up of treatment prior to the fall season would have a similar effect on preventing asthma exacerbations in the fall season as observed with the year-long increase in treatment in ACE. The implication of these findings is that there are distinct patterns for seasonal loss of control that occur despite ongoing long-term control therapy adjusted based on a guidelines approach. Sensitivity and exposure to indoor allergens, especially cockroach, appear to be associated with greater likelihood of exacerbations during the fall season. Because fall exacerbations of asthma are strongly associated with infections with RV and other respiratory viruses, these findings are consistent with the hypothesis that there are synergistic interactions between respiratory allergy and viral infection to increase the risk of asthma exacerbation. Therefore, steps to reduce allergic airway

inflammation and possibly allergen exposure prior to the fall season could be effective strategies to prevent fall exacerbations.

1.2.5 Clinical Implications

The overall conclusions from these studies include the following. First, an exacerbation in the previous year increases the risk for exacerbation in the following year. Second, available measures are poorly predictive of an emerging exacerbation. Third, the best strategy may be preventive strategies initiated prior to the fall season that effectively reduce allergic inflammation and consequent asthma exacerbations.

1.2.6 Opportunities for Intervention with Conventional Therapies

It appears that the easiest and most convenient management approach would be step up therapy with an increase in ICS dose, plus addition of LABA and LTRA, so-called “triple therapy.” This treatment strategy has not been previously tested. The advantage is that it combines ICS/LABA and LTRA that are both found to reduce exacerbations by approximately 50%. The step-up approach involves increased use of asthma controllers only during a limited period of time and thus provides potential safety benefits over a more extended escalation in therapy. However, this approach was utilized in the ACE protocol where symptoms and pulmonary function, as well as FeNO, directed treatment. As described in the background information, this guidelines-directed strategy did not cause an overall reduction in exacerbations in the cohort as a whole; however, we did see some reduction of exacerbations in the FeNO treatment arm only, where participants retained a higher ICS treatment regimen than the guidelines-based arm.

There are several other alternatives that could be considered. For example, one strategy that has received attention in countries other than the United States is combination ICS administered as maintenance and LABAs as an as needed therapy (O’Byrne et al, 2005). However, this strategy will likely not receive FDA approval due to the black-box warning associated with LABA therapy in asthma.

Another alternative is to substitute a short acting β -adrenergic agonist, specifically albuterol, for LABA in the combination therapy administered as needed. The results of the CARE Network study, called TREXA, were presented at the 2010 American Thoracic Society meeting and were published in Lancet (Martinez et al, 2011). In a 44-week, randomized, double-blind, placebo-controlled, 4-arm trial, 288 children with mild persistent asthma well controlled on ICS were randomized to receive: daily beclomethasone with rescue beclomethasone (combined); daily beclomethasone with rescue placebo (daily); daily placebo with rescue beclomethasone (rescue); or daily placebo with rescue placebo (placebo). Daily therapy was one puff of beclomethasone-HFA (40 mcg/puff) or placebo twice a day; rescue therapy was 2 puffs of beclomethasone-HFA (40 mcg/puff) or placebo concurrent with 2 puffs of albuterol. The primary outcome was time to first exacerbation requiring oral corticosteroids.

Exacerbation incidence was 49% in the placebo arm. After adjusting for multiple comparisons, the exacerbation incidence was significantly lower for the daily arm and lower for the combined and rescue arms. Lung function and proportion of asthma control days did not differ between arms; FeNO was lower in the combined and daily arms than in the rescue and placebo arms.

The CARE Network investigators concluded that discontinuing ICS results in an increase in exacerbations in children with mild persistent asthma. Daily ICS is the most effective treatment for preventing exacerbations; adding rescue ICS does not add benefit to daily ICS. However, rescue ICS with albuterol demonstrated benefits over albuterol alone and avoids daily ICS administration. Using ICS as rescue medication may be an effective step-down strategy for children with well-controlled mild asthma.

Therefore, this strategy of adding as needed albuterol and ICS does not further reduce exacerbations above maintenance ICS therapy alone.

Other considerations could include the application of low-dose theophylline therapy since it has potential bronchodilator and anti-inflammatory therapy. However, theophylline has well documented adverse effects, a low therapeutic index necessitating blood concentration monitoring and prevention or management of multiple drug interactions. Oral corticosteroids at the time of onset of upper respiratory viral infections to prevent a hospitalization is another approach to consider but multiple courses could be associated with adverse effects.

1.2.7 An Alternative Strategy Directed at Respiratory Allergy

There is convincing evidence that respiratory allergy is a risk factor for RV wheezing. In studies conducted in ED, risk factors for wheezing included detection of RV, allergen-specific IgE, and blood or airway eosinophilia (Rakes et al, 1999). Furthermore, the risk of hospitalization among virus-infected individuals is increased in patients who are both sensitized and exposed to respiratory allergens (Green, 2002). In the ACE study, urban children with a fall exacerbation were more likely to be sensitized to cockroach, cat, or dust mite (see Table 1.2.4a).

There is also evidence that allergic inflammation inhibits innate antiviral responses of plasmacytoid dendritic cells (pDC), which are important sources of IFN- α . Plasmacytoid dendritic cells express high-affinity IgE receptors (Fc ϵ R1), which are increased in cells from allergic donors. Cross-linking Fc ϵ R1 reduced TLR9-induced IFN- α secretion, and conversely, TLR9 activation down-regulated Fc ϵ R1 expression (Schroeder et al, 2005). Furthermore, mononuclear cells from allergic individuals had 6-fold lower CpG-induced IFN- α , and the IFN- α responses were inversely correlated with pDC Fc ϵ R1 expression (Tversky et al, 2008). These results suggest that allergic airway inflammation could inhibit IFN- α , and thus promote more severe RV infections.

We have, therefore, decided to focus our attention on pre-fall season therapy that targets allergic inflammation, such as omalizumab or intensified use of ICS asthma controllers. In analysis of the ICAC ICATA study, we found that participants treated with omalizumab over the course of a year experienced a significant reduction in fall exacerbations (66% as compared to placebo) and we now seek to determine whether a pre-fall season initiated omalizumab regimen for at least 4 months will be similarly effective in reducing these seasonal exacerbations.

Investigational agents will be initiated approximately 4-6 weeks in advance of the start of a participant's school year. The ICATA study data have shown that maximal impact of omalizumab occurs within 4 weeks of initiation. This pattern was replicated with both exacerbations and maximum days of asthma symptoms as shown by the figure below. Furthermore, an analysis by dosing group (every 2 or 4 week injection schedule) showed comparable effects.

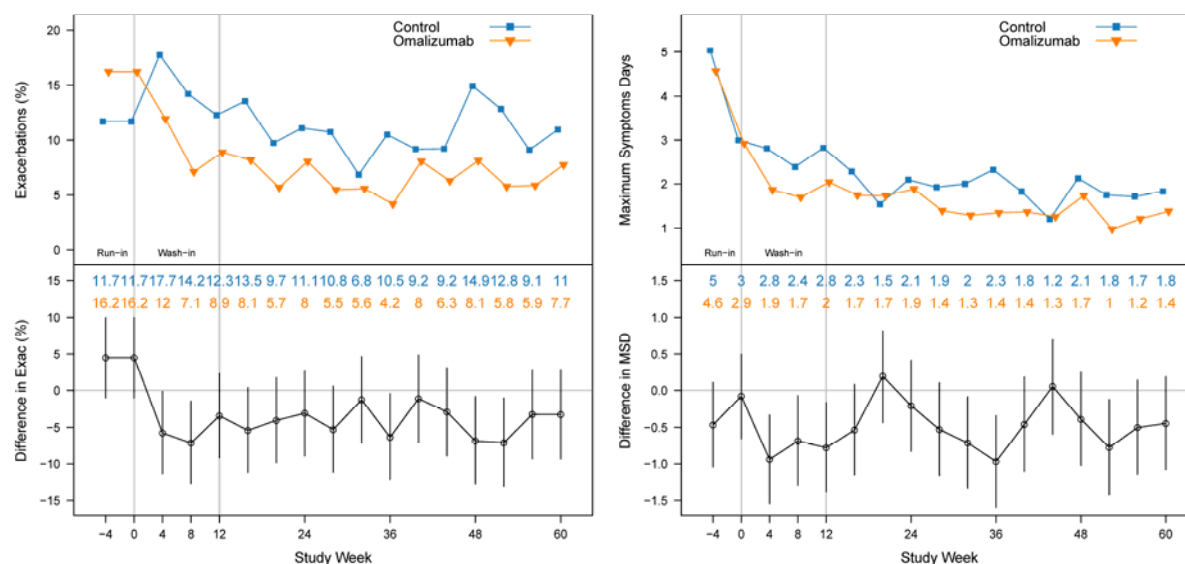
Figure 1.2.7a: Time for omalizumab to become effective (Exacerbations and Symptoms)

Figure 1.2.7a illustrates the maximal impact on exacerbations and symptoms occurring within a month of the first omalizumab injection. Therefore, we feel that a course of treatment that begins at least 4 weeks before the fall season could be effective in reducing the allergen-induced airway inflammation that predisposes the airway to an enhanced response in the presence of a viral infection. This strategy could not only reduce asthma morbidity but could reduce the need to escalate therapy with other medications.

Furthermore, omalizumab treatment also results in substantial improvements in nasal symptoms, QOL and rescue antihistamine use compared with placebo or specific immunotherapy (Adelroth et al, 2000; Price et al, 2005; Casale et al, 2001). Therefore, although omalizumab is not approved for the treatment of allergic rhinitis, it may provide some additional benefits in management for patients with exacerbation of nasal symptoms in the fall season, perhaps due to a combination of allergy and viral infection.

Our focus in this trial will be on children and adolescents, 6 to 17 years of age. Although omalizumab is not approved for use in children less than 12 years of age, available studies have shown its effectiveness in reducing asthma exacerbations by as much as 50% in children, as well as reducing the need for ICS (Milgrom et al, 2001). In an associated preliminary study, it was found that treatment with omalizumab may inhibit airway inflammation during corticosteroid reduction in children with allergic asthma. The degree of inhibition of FENO was similar to that seen for ICS alone (Silkoff et al, 2004). As noted in our unpublished data from the ACE study (Figure 1.2.4a), there is a fall season increase in FENO that is associated with a decrease in FEV₁/FVC, a decrease in Asthma Control Test (ACT) score, and an increased risk for exacerbations. Thus, omalizumab could play a role in blunting this allergic airway inflammation and the risk of viral-induced asthma exacerbations during the fall season in particular. In addition, our own experience in the NIAID ICATA trial supports efficacy of omalizumab in children as young as 6 years of age (Busse et al, 2011).

We therefore propose a strategy focused on stepping up treatment with omalizumab beginning just prior to and continuing through the fall season, in an attempt to determine if this focused and short course of treatment could be effective in preventing fall exacerbations as compared to a guidelines-based approach,

as well as an approach that seeks to boost ICS therapy prior to the fall and continuing during the fall season.

1.2.8 Rationale for Dendritic Cell Studies

Evidence of counter regulation between TLR-mediated and antiviral responses and the FcεRI pathway in DCs is emerging. Crosslinking of IgE with anti-IgE (omalizumab) has been shown to abrogate TLR-9 mediated interferon-α responses in plasmacytoid dendritic cells (pDC) (Schroeder 2005) as well as interferon-α (IFN-α) production (likely TLR-7 mediated) after exposure to respiratory viruses including influenza (Gill 2010) and RV. The finding that IgE crosslinking on pDC exposed to anti-IgE *in vitro* results in diminished antiviral responses raises the possibility that IgE crosslinking after allergen exposure *in vivo* could result in similar dampening of pDC responses to viruses such as RV. Data indicate that *in vitro* exposure of pDC isolated from dust-mite sensitive patients to dust mite antigen results in interference of the IFN-α response upon viral exposure (Gill 2010). Such allergen-driven interference with RV-induced pDC IFN-α production could in part account for the association between allergic sensitization and increased RV-induced asthma exacerbations. By reducing the number of FcεRI receptors available for IgE occupancy and subsequent allergen-induced IgE crosslinking, antiviral responses to RV may be improved after omalizumab therapy. The resulting increased capacity for RV-exposed pDC to secrete IFN-α may result in decreased frequency of asthma exacerbations following RV infections.

In this trial, we will examine whether omalizumab therapy impacts pDC interferon-α responses to viral exposure (RV and influenza) and whether omalizumab therapy impacts viral induced expression of genes involved in the regulation of IFN-α secretion.

1.2.9 Rationale for Selection of Study Population

The trial will study a group of 6-17 year old children and adolescents with persistent allergic asthma who are living in urban poverty as defined by their primary place of residence, and who are also at risk for an asthma exacerbation in the coming year based on a history of an exacerbation in the year prior to enrollment. The criteria used to select this group are expected to enroll a population of children and adolescents who are predominantly self-identified African-Americans or Hispanic Americans.

Inner-city children and adolescents with allergic asthma have the potential to benefit from Xolair® (omalizumab) therapy, or perhaps more so than from boost ICS therapy, because prior studies have shown that they face substantial barriers to adherence to standard therapies. Because medical personnel administer Xolair® (omalizumab) every 2 or 4 weeks, it is anticipated that it will be an easier regimen to follow and will decrease symptoms more than standardized specialist care alone. These children are also known to have multiple aeroallergen sensitivities and ongoing exposures to these allergens. On the other hand, omalizumab is expensive and has the burden of injections and travel to a health care facility for administration.

In summary, we will compare treatment with Xolair® (omalizumab) to the conventional guidelines-based approach as well as an approach based on increasing ICS-dose prior to and during the fall season. We will not only determine which of the 3 treatments is more efficacious in preventing fall exacerbations but also will determine whether one of the treatments has particular efficacy in achieving overall optimal control. A pharmacoeconomic analysis will also be conducted to determine the cost-effectiveness of each of these 3 treatment strategies.

1.2.10 Selection of Investigational Agents

In choosing investigational agents to investigate alternative strategies to diminish fall-related exacerbations in atopic inner-city children and adolescents, we have deliberately selected the same agents employed in the ACE (Szeffler et al, 2008) and ICATA studies (Busse et al, 2011).

1.2.10.1 Xolair® (Omalizumab)

In the ICATA trial, Xolair® (omalizumab) was associated with a significant overall decrease in the rate of asthma exacerbations and an almost complete obliteration of the fall peak in exacerbations among atopic inner-city children and adolescents (Busse et al, 2011). The beneficial effect of Xolair on asthma exacerbations was observed within one month from treatment initiation. In the ICATA trial, Xolair® (omalizumab) was administered for 60 weeks. This clinical trial is designed to address the question whether Xolair® (omalizumab), administered only for 4-5 months (beginning approximately 4-6 weeks prior to the start of a participant's school year and continuing through fall), will be effective in preventing asthma exacerbations. To date, no clinical trial has specifically sought to determine if targeted use of Xolair® (omalizumab) could be effective in preventing fall asthma exacerbations when added to conventional guidelines-driven therapy.

1.2.10.2 Flovent® Diskus® (Fluticasone)

The ACE study conducted by ICAC (Szeffler et al, 2008) raised the possibility that a moderately increased dose of ICS (fluticasone being the primary ICS used in that study), may suppress the increase rate of fall asthma exacerbations in children with asthma (see Figures 1.1.6.2.1a and 1.1.6.2.2a). To directly test this hypothesis, we are proposing to use a pre-season boost of 200 or 500 mcg per day (dependent on ICS dose at randomization) of Flovent® Diskus® (fluticasone), added to ongoing guidelines-based therapy and continued throughout the fall season. To date, no trial of such a step-up ICS dosing to prevent the increase in fall asthma exacerbations has been reported.

1.3 Potential Risks and Benefits

1.3.1 Potential Risks

1.3.1.1 Xolair® (Omalizumab)

Participants may experience adverse reactions from Xolair® (omalizumab). Injection site reactions, including bruising, redness, warmth, burning, stinging, itching, hive formation, pain, indurations, mass, and inflammation of the skin around the injection site, are common. The majority of injection site reactions have occurred within 1 hour post-injection. Other common side effects include viral infections, upper respiratory tract infection (URI), sinusitis, headache, and pharyngitis. These events were observed at similar rates in Xolair® (omalizumab)-treated participants and control participants in clinical trials.

The most serious adverse reactions occurring in clinical studies with Xolair® (omalizumab) were malignancies and anaphylaxis. These events were rare. In studies, 0.5% of participants receiving Xolair® (omalizumab) developed cancer, as compared to 0.2% receiving placebo. Several different types of cancer were seen, thus causality is unlikely. In pre-marketing clinical trials, the frequency of anaphylaxis attributed to Xolair® (omalizumab) use was estimated to be 0.1%. Based on post-marketing spontaneous reports from approximately 57,300 patients from June 2003 through December 2006, anaphylaxis following Xolair® (omalizumab) treatment occurred in at least 0.2% of treated people without other identifiable allergic triggers. Symptoms and signs of anaphylaxis in the reported cases included

bronchospasm, hypotension, syncope, hives, swelling of the throat or tongue, dyspnea, cough, chest tightness and cutaneous angioedema. While most anaphylactic reactions occurred within 2 hours of the injection, some occurred up to 4 days after administration. Anaphylaxis may occur after any dose of Xolair[®] (omalizumab), even if past doses were well tolerated. Anaphylaxis has occurred as early as after the first dose of Xolair[®] (omalizumab), but also has occurred beyond 1 year after beginning regularly scheduled treatment. Participants in the PROSE study will be observed after each injection, for time periods consistent with AAAAI/ACAAI guidelines (Cox et al, 2007). Following administration of the first 3 injections, the participant will be observed for 2 hours. Following subsequent injections, the participant will be observed for 30 minutes before being released. A medical provider trained in treating anaphylaxis will be available to provide immediate treatment in the event that a participant experiences an allergic reaction. Participants and caretakers will be educated on the signs and symptoms of anaphylaxis and will be trained on the proper use of epinephrine auto-injectors for treatment of anaphylactic reactions. Participants will also be provided with epinephrine auto-injectors and an antihistamine free of charge.

Other side effects have been reported post-marketing. Severe idiopathic thrombocytopenia was reported in 1 patient and rare cases of hair loss have been reported (less than 0.1%). In a one year clinical trial conducted in Brazil, there was an increase in the percentage of high risk patients infected with geohelminth parasites in the Xolair[®] (omalizumab)-treated group compared to the placebo group.

The safety data from the initial 12 month trial has been published (Berger et al, 2003), with a summary of safety data for the 202 children who were treated with Xolair[®] (omalizumab) for 52 weeks. Most of the AEs reported were rated as mild or moderate and were not considered treatment-related. About 7% of children experienced an AE suspected to be caused by Xolair[®] (omalizumab) and 1 of these events was considered serious (urticaria). The most common AEs reported were similar for the 52 week evaluation compared with the 28 week double-blind phase and included URI (47.1%), headache (42.7%), pharyngitis (34.7%), and viral infection (31.6%). Urticaria occurred in 11 patients (4.9% of 225) throughout the 52 week evaluation, but only 1 child required corticosteroid therapy. One participant did discontinue therapy because of hives, which occurred after the seventh and eighth injections, but the reaction resolved completely with the administration of an antihistamine. Overall, AEs were similar not only during the double-blind treatment phase and in the open-label extension but also between Xolair[®] (omalizumab) and placebo-treated groups. There were no clinically significant changes from baseline in vital signs, laboratory parameters, or temperature. The authors concluded that not only was Xolair[®] (omalizumab) safe for use in children 6-12 years old but long-term (1 year) efficacy was maintained and the steroid-sparing effects experienced in the first 28 weeks continued in the latter 24 weeks.

The overall safety profile of Xolair[®] (omalizumab) in the 6–20 year old participants of ICATA was very reassuring (Busse et al, 2011). One or more adverse events were reported by 47.4% of the control group and 39.4% of the Xolair[®] (omalizumab) group ($p=0.05$); SAE (>1) were reported by 13.7% of the control group and 6.3% of the Xolair[®] (omalizumab) group ($p<0.001$). The majority of the serious adverse events were asthma hospitalizations, more frequent in the control group. Comparison across the major AE categories identified three areas of difference. The treatment group experienced a higher level of gastrointestinal disorders (4.8% vs. 0.9%, $p=0.02$). The control group experienced both a higher level of hematology disorders (5.7% vs. 0.5%, $p=0.002$) and a borderline increase in respiratory signs and symptoms (22.3% vs. 16.3%, $p=0.06$). No participant met the pre-specified criteria for stopping study drug secondary to a decrease in platelets. Seven episodes of hypersensitivity reaction or anaphylaxis occurred among 7 participants. Only 1 of those participants was in the Xolair[®] (omalizumab) group, who experienced mild cough and throat pruritus after receiving the last study dose of Xolair[®] (omalizumab).

For complete information regarding the risks associated with administration of Xolair[®] (omalizumab), refer to Novartis' Investigator's Brochure for Xolair[®] (omalizumab).

1.3.1.2 Flovent® Diskus® (Fluticasone)

Most common adverse reactions (incidence >3% in US controlled clinical trials) include upper respiratory tract infection, throat irritation, sinusitis/sinus infection, upper respiratory inflammation, rhinitis, oral candidiasis, nausea and vomiting, gastrointestinal discomfort, viral gastrointestinal infection, non-specific fever, viral infection, viral respiratory infection, cough, bronchitis, headache, muscle injury, musculoskeletal pain, and injury.

ICS have also been associated with modest growth effects, which should be minimized by the short duration of boost therapy. Height will be monitored throughout PROSE, by calibrated stadiometers.

Adverse effects will be minimized by instructing participants on good administration technique and mouth rinsing after each use. For complete information regarding the risks associated with Flovent® Diskus® (fluticasone), refer to the Flovent® Diskus® Package Insert in the PROSE MOP.

1.3.2 Potential Benefits

All participants will receive standardized asthma care. The participant may benefit by receiving frequent asthma assessments and care from a study clinician, as well as asthma education including select environmental control measures. The participant's asthma may or may not improve while in this study.

2. STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this trial is to compare the efficacy of 4 to 5 months of 3 treatments — Xolair® (omalizumab), inhaled corticosteroid (ICS) therapy boost, and placebo — in reducing fall exacerbations in inner-city children and adolescents with allergic persistent asthma when initiated approximately 4-6 weeks prior to the first day of each participant's school year.

2.2 Secondary Objectives

Secondary objectives include the following:

- To compare the efficacy of the 3 treatment strategies in reducing exacerbations and/or the duration or intensity of asthma symptoms associated with viral respiratory infection.
- To compare the efficacy of the Xolair® (omalizumab) vs. placebo in reducing exacerbations in participants taking 1000 mcg of Flovent® Diskus® (fluticasone) daily.
- To compare the efficacy of the 3 treatment strategies in improving asthma control (as measured by the CACT or ACT questionnaire) and in reducing asthma severity (as measured by the Composite Asthma Severity Index) during the fall season.
- To measure the pharmacoeconomic impact of utilizing these treatment strategies.
- To determine if response to each treatment strategy is associated with specific pre-randomization asthma characteristics: degree of atopy, total IgE level, allergen-specific IgE levels, dust mite sensitivity and/or exposure, cockroach sensitivity and exposure, demographic characteristics, eNO, and viral detection by RT-PCR.
- To identify risk factors and predictors of exacerbations.
- To explore the interaction of allergen sensitivity and exposure with viral illnesses as determinants of exacerbations.

- To determine the safety of each treatment regimen.
- To measure time of onset of exacerbations between groups.

2.3 Exploratory Objectives

Accompanying mechanistic studies will be performed to:

- Determine whether treatment-related reduction of allergic airway inflammation enhances antiviral responses.
- Determine whether Xolair[®] (omalizumab) therapy impacts pDC interferon- α responses to viral exposure (RV and influenza).
- Determine whether Xolair[®] (omalizumab) therapy impacts viral induced expression of genes involved in the regulation of IFN- α secretion.

Details regarding these studies are outlined in the PROSE MOP.

3. STUDY DESIGN

3.1 Description of the Study Design

The PROSE clinical protocol (ICAC-20) is a 3-armed prospective randomized double-blind placebo-controlled trial investigating the efficacy of standard care plus 4–5 months of treatment with (a) a boost of ICS therapy versus (b) Xolair[®] (omalizumab) or (c) placebo in reducing exacerbations during the fall season in inner-city children and adolescents with persistent allergic asthma. Approximately 453 inner-city children and adolescents aged 6–17 years with allergic persistent asthma will be randomized and receive standardized specialist asthma care, with (a) approximately 155 participants receiving additional ICS steroid boost therapy, (b) approximately 223 participants receiving additional treatment with Xolair[®] (omalizumab), and (c) approximately 75 participants serving as controls. In order to randomize the 453 participants needed for adequate power, participants will be enrolled in 2 cohorts. The second cohort will begin their Screening Visits a year after screening and enrollment of the first cohort.

Participants will be followed using a guidelines-approach algorithm to assess asthma control, need for supplementary medication, and the frequency of any asthma exacerbations during the fall of their treatment year.

Following a Screening Visit (V0) to determine eligibility, participants' asthma care will be directed by PROSE study clinicians (see Section 5.5) during a run-in phase to begin at their Assumption of Care (AoC) (V1) visit and continuing through Visits 2 and 3. At Visit 4, each participant will then be randomized to either (a) the ICS boost arm for 4–5 months equivalent to 100 mcg bid or 250 mcg bid of Flovent[®] Diskus[®] (fluticasone) dependent upon their ICS dose at randomization, (b) the subcutaneous Xolair[®] (omalizumab) arm for 4–5 months receiving injections once every 2 or 4 weeks based on body weight and IgE, or (c) placebo for 4–5 months. The first treatment will occur approximately 4 to 6 weeks prior to the start of each participant's school year due to the viral illness and "September epidemic" association with the start of the school calendar.

Participants will be randomized to one of the 3 arms. Participants in the (a) ICS boost arm will receive active ICS and placebo injections instead of Xolair[®]. Each participant in the ICS boost arm will receive Flovent[®] Diskus[®] (fluticasone) inhalers sufficient to deliver the required 200 mcg or 500 mcg daily boost of Flovent[®] Diskus[®] (fluticasone) (Table 3.1a). Participants randomized to the (b) Xolair[®] (omalizumab)

arm will receive active Xolair[®] (omalizumab) injections and a placebo inhaler instead of Flovent[®] Diskus[®]. Each participant in the Xolair[®] (omalizumab) arm will receive Xolair[®] (omalizumab) SQ injections at a minimum dose of 0.016 mg/kg/IgE [IU/mL] every 2 or 4 weeks during the treatment period. Participants in the (c) placebo arm will receive placebos of both Xolair[®] and Flovent[®] Diskus[®]. The placebo injection and placebo ICS control groups are necessary to evaluate the efficacy of the therapy beyond the effect of the attention that the every 2 or 4 week injections and the additional inhaler will bring.

As shown in Table 3.1a, participants assigned less than 200 mcg of fluticasone propionate equivalent at the point of randomization will be discontinued from the study prior to randomization because it is not appropriate for participants requiring such a low dose to receive Xolair[®] (omalizumab). Participants assigned 1000 mcg of fluticasone propionate equivalent at the point of randomization will not be eligible for randomization to the steroid boost arm because the addition of the boost to an already high ICS dose may increase risks associated with exceeding the maximum dose of ICS permitted by current NAEPP guidelines (NAEPP, 2007). These participants will continue in the study and will be randomized to either the Xolair[®] (omalizumab) or the placebo arm only. Therefore, all of these participants will receive the placebo ICS.

Table 3.1a Boost Based on ICS Requirement at Randomization

Step Level (see 5.5.1)	Medication Equivalent at Randomization	ICS Boost
0	No controller medication; albuterol or levalbuterol prn	<i>Excluded from randomization</i>
1	Flovent [®] Diskus [®] (fluticasone) 50 mcg bid	<i>Excluded from randomization</i>
2	Flovent [®] Diskus [®] (fluticasone) 100 mcg bid	Flovent [®] Diskus [®] (fluticasone) 100 mcg bid
3	Flovent [®] Diskus [®] (fluticasone) 250 mcg bid	Flovent [®] Diskus [®] (fluticasone) 250 mcg bid
4	Advair [™] Diskus [®] 250/50 mcg bid	Flovent [®] Diskus [®] (fluticasone) 250 mcg bid
5	Advair [™] Diskus [®] 500/50 mcg bid	<i>Excluded from randomization to the steroid boost arm but continued in the study</i>

Adherence to all study medications will be strictly monitored and reinforced at every Evaluation and Management Visit (E&M) and monthly Injection Visit. E&M visits are discussed further below and in Section 7.4. Participants will be required to bring the ICS boost medications to every monthly visit, in order to estimate adherence by Diskus[®] counter device.

In addition, participants will receive standardized specialist care and be prescribed asthma step therapy in accordance with NAEPP 2007 guidelines (<http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm>). Basic asthma education will be provided by the study teams.

Two E&M visits (V2 and V3), approximately equally spaced, will be performed during the run-in phase and will include spirometry, adherence review, and clinical assessment that will consist of “step-up” and “step-down” therapy according to a treatment algorithm based on NAEPP guidelines (see Section 5.5.2). Study drug will not be administered during the asthma stabilization phase.

At the Randomization Visit (V4), participants will receive their final adjustment to their asthma step therapy, and they will continue this treatment throughout the Treatment Period while study drugs are

administered. Participants who qualify will be randomized at the end of this visit. This visit may occur up to 75 days prior to the start of a participant's school year; however, it must occur no later than 4 weeks prior to the start of a participant's school year because the Visit 4 activities and randomization must be complete prior to the first treatment.

Participants will receive treatment with study drug and/or placebo(s) for 4-5 months, beginning with the first Treatment Visit (V4t). Visit 4 and Visit 4t may be combined into one visit when the visit windows for the two visits overlap. Visit 4t must be initiated approximately 4-6 weeks prior to the start of each participant's school year. For exact visit windows and details on combining these visits, refer to the PROSE MOP.

The primary efficacy analysis will focus on all exacerbations requiring initiation of systemic corticosteroids or hospitalization during the 90 day period beginning on the first day of each participant's school year. Two key principles will therefore underlie treatment with Xolair® (omalizumab), the Flovent® Diskus® (fluticasone) boost, and their placebos:

- Each participant must receive their first Xolair® (omalizumab)/placebo injection and begin their Flovent® Diskus® (fluticasone)/placebo boost at least 4 weeks before the start of the participant's school year.
- Each participant must continue to receive their Xolair® (omalizumab)/placebo injections and their Flovent® Diskus® (fluticasone)/placebo boosts for 90 days beginning on the first day of each participant's school year.

Figure 3.1b demonstrates an approximate visit schedule for a participant screened in October and receiving injections every 4 weeks. Participants screened later will have a shorter run-in period but will be randomized during the timeframe described above. Participants receiving injections every 2 weeks will have additional visits during the treatment period. A table summarizing visits and activities for participants receiving injections every 4 weeks is in Appendix 2. A similar table for participants receiving injections every 2 weeks is included in the PROSE MOP. Exact windows for all visits are described in the PROSE MOP.

Figure 3.1b Sample Study Visit Schedule for Participants Receiving Injections Every 4 Weeks

Screening Visit	Assumption of Care Visit	Run-In	Treatment Period		Follow - Up
Screening Visit	E&M Visit	E&M Visits	Randomization / E&M Visit	Injection Visits	E&M Visits
Oct	Nov	Jan, Apr	Jun – Jul	Jul – Nov	Dec, Feb
Visit 0	Visit 1	Visits 2, 3	Visit 4	Visits 4t*, 5, 6, 7, 8, 8b	Visits 9, 10

*Visit 4t may be combined with Visit 4, according to the rules described in the PROSE MOP.

After completion of the 4–5 month treatment period, all participants will be observed for 12 weeks and have 2 additional E&M visits (V9 and V10); the first at approximately 6 weeks after treatment and the final visit at approximately 12 weeks after treatment ends.

A final post-treatment evaluation will be conducted approximately 12 weeks following the final injection and the completion of the ICS boost treatment. In order to accomplish the goals of the 12 week post-treatment evaluation, the consent process will clearly indicate that Xolair® (omalizumab) and the ICS boost will not be available to participants at study conclusion. In addition, the 12 week run-out phase will

allow the study clinicians to evaluate the participants following 12 weeks off Xolair[®] (omalizumab) or ICS boost so that they can re-establish appropriate asthma controller regimens for participants to continue on in the potential absence of Xolair[®] (omalizumab) therapy or the ICS boost.

3.2 Study Endpoints

3.2.1 Primary Endpoint

The primary outcome is the occurrence of ≥ 1 asthma exacerbation defined as a prescription of a course of systemic steroids by a clinician or initiation of a course of systemic steroids by a participant or a hospitalization during the fall outcome period (90 day period beginning on the first day of each participant's school year) to prevent a serious asthma outcome. If a participant initiates and completes a course of systemic steroids without clinician involvement, this course will be counted only if it meets the following minimum dosage: prednisone, prednisolone, or methylprednisolone at $\geq 20\text{mg}$ per day for 3 of any 5 consecutive days; or dexamethasone at $\geq 10\text{mg}$ per day for ≥ 1 day.

3.2.2 Secondary Endpoints

The secondary endpoints assessed during the treatment period will include:

- Virus-induced exacerbations as measured by an exacerbation that is associated with a virus detected using nasal mucus samples.
- Severity of asthma symptoms (defined as the highest value among the following 3 variables: number of days with wheezing, tightness in the chest, or cough; number of nights with disturbed sleep as a result of asthma; and number of days on which the participant had to slow down or discontinue play/physical activities over a 2-week period) associated with a viral infection.
- Number of exacerbations evaluated monthly with and without viral respiratory infections.
- pDC frequencies in peripheral blood.
- FcεRI expression on pDC in peripheral blood.
- IFN-α response to RV, Flu, and gardiquimod stimulation in peripheral blood mononuclear cells.
- RV, Flu, and gardiquimod-induced expression of IFN-α regulatory genes in peripheral blood mononuclear cells.
- Economic outcomes.
- Spirometry measurements.
- Composite Asthma Severity Index.
- Asthma control measurements (including ACT and CACT scores).
- School absences.
- Estimates of treatment adherence.
- Safety data (adverse events and serious adverse events).
- Home allergen levels.

4. STUDY POPULATION

The study population will consist of inner-city residents 6 to 17 years of age who have persistent allergic asthma requiring ICS therapy and a history of asthma exacerbations and who meet the inclusion/exclusion criteria in Section 4.1.

4.1 Description of the Study Population

4.1.1 Participant Inclusion Criteria

Participants who meet *all* of the following criteria are eligible for assumption of care. Participants may be reassessed if not initially eligible.

1. Males and females ages 6 – 17 years, inclusive, at Screening (V0).
2. With combined body weight (as measured at the Screening visit [V0]) and total serum IgE level (as measured within 3 months of the Screening Visit [V0]) suitable for Xolair[®] (omalizumab) dosing.
3. Who have had a diagnosis of asthma by a clinician made > 1 year prior to recruitment; participants who received an asthma diagnosis by a clinician ≤ 1 year prior to recruitment must report that their respiratory symptoms were present for more than 1 year prior to recruitment.
4. Who have a requirement for at least Step Level 2 therapy (defined in Table 5.5.1b) at the Assumption of Care Visit (V1) and who meet at least one of the following criteria:
 - i. One or more asthma-related exacerbations, separated by at least 2 weeks, requiring treatment with a systemic corticosteroid course, which occurred on or after September 1, 2010, for the first cohort or on or after September 1, 2011, for the second cohort.
 - ii. One or more asthma-related overnight hospitalizations, which occurred on or after September 1, 2010, for the first cohort or on or after September 1, 2011, for the second cohort.
5. With a positive prick skin-test to at least 1 perennial allergen (as outlined in the PROSE MOP) documented at the Screening Visit (V0) or at any ICAC study visit within 12 months of the Screening Visit (V0).
6. Whose primary place of residence is in one of the pre-selected recruitment census tracts as outlined in the PROSE MOP.
7. Who are able to perform spirometry at the Assumption of Care Visit (V1).
8. Who are willing to sign the written Informed Consent or whose parent or legal guardian is willing to sign the written Informed Consent (age appropriate) prior to *initiation* of any study procedure.
9. Who are willing to sign the assent form, if age appropriate.
10. Who have a self-reported history of clinical varicella or administration of varicella vaccine.
11. Who have some form of insurance that covers costs of medications at the Screening Visit (V0).

4.1.2 Participant Exclusion Criteria

Participants who meet any of the following criteria are not eligible for assumption of care but may be reassessed.

1. Who are assigned a treatment step level < 2 at AoC (V1).
2. Who are pregnant or lactating. Females of child-bearing potential (post-menarche) must be abstinent or use a medically acceptable birth control method throughout the study (e.g. oral, subcutaneous, mechanical, or surgical contraception).

3. With clinically significant laboratory abnormalities (not associated with the study indication) at the Screening Visit (V0).
4. With platelet counts $< 100 \times 10^9/L$ at the Screening Visit (V0).
5. Who are currently participating in another asthma-related pharmaceutical study or intervention study or who have participated in another asthma-related pharmaceutical study or intervention study in the month prior to Recruitment.
6. Who live with a foster parent; not applicable if participant is able to provide consent.
7. Who do not have access to a phone (needed for scheduling appointments).
8. Who plan to move from the area during the study period.
9. Who have previously been treated with Xolair[®] (omalizumab) therapy within 1 year of Recruitment.
10. Who are currently receiving or have received hyposensitization therapy to any allergen in the past year prior to Recruitment.
11. Who have received hyposensitization therapy to dust mite, Alternaria or cockroach for ≥ 6 months in the past 3 years prior to Recruitment.
12. Who have had a life-threatening asthma exacerbation in the last 2 years requiring intubation, mechanical ventilation, or resulting in a hypoxic seizure.
13. Who are home-schooled or are in year round school.
14. Who are currently taking or who have taken any of the following medications within 4 weeks of the Screening Visit (V0): Monoamine oxidase inhibitors (phenelzine, tranylcypromine); Tricyclic and tetracyclic antidepressants; beta adrenergic blocker drugs (both oral and topical); Anticonvulsants (carbamazepine, phenobarbital, phenytoin, mephobarbital, primidone, ethosuximide, methsuximide, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate, valproic acid, divalproex sodium, zonisamide); Protease inhibitors (ritonavir, indinavir, nelfinavir); Calcium channel blockers (verapamil, diltiazem); Modafinil; Tamoxifen; non-nucleoside reverse transcriptase inhibitors; Macrolide antibiotics* (erythromycin, clarithromycin, dirithromycin, troleandomycin); chloramphenicol; nefazodone; aprepitant; St Johns Wort; Rifampin*; Azole antifungals* (ketoconazole, fluconazole, itraconazole); Sibutramine*; bergamottin* (constituent of grapefruit juice).

*may be rescreened if this therapy is short-lived
15. Who will not allow the study clinician, an asthma specialist, to manage their disease for the duration of the study or who are not willing to change their asthma medications to follow the protocol.

Participants who meet any of the following criteria are not eligible for assumption of care and may not be reassessed except where noted.

16. Who have a current severe hypersensitivity to milk.
17. Who were enrolled in the previous ICAC trial, Inner-City Anti-IgE Therapy for Asthma (ICATA, ICAC-08/09).

18. Who have any medical illnesses that in the opinion of the investigators would a) increase the risk the subject would incur by participating in the study, b) interfere with the measured outcomes of the study, or c) interfere with the performance of the study procedures. Examples of such diseases are: phenylketonuria, cystic fibrosis, bronchiectasis, Type I diabetes, hemophilia, Von Willebrand's disease, sickle cell disease, cerebral palsy, rheumatoid arthritis, lupus, psoriasis, hyperimmunoglobulin E syndrome, parasite infections, Wiskott-Aldrich Syndrome or allergic bronchopulmonary aspergillosis.
19. Who have known hypersensitivity to any ingredients, including excipients (arginine hydrochloride, histidine, polysorbate 20) of the study medication or drugs related to Xolair[®] (omalizumab) (e.g. monoclonal antibodies, polyclonal gamma globulin) or Flovent[®] Diskus[®] (fluticasone).
20. Who currently have diagnosed cancer, are currently being investigated for possible cancer, or who have a history of cancer.
21. Who do not primarily speak English or Spanish at centers with Spanish speaking staff.
22. Whose caretaker does not primarily speak English or Spanish at centers with Spanish speaking staff; not applicable if participant is able to provide consent.
23. Who have a history of severe (grade 3) anaphylactoid or anaphylactic reaction(s).

4.1.2.1 Co-enrollment Guidelines

Participants who were previously enrolled in the RACR study will have the opportunity to enroll in PROSE once eligibility is established. RACR is a registry study for the purpose of eligibility screening and enrollment in other ICAC studies. Participants may be eligible to enroll in PROSE that were previously included in other ICAC studies based on the discretion of ICAC study investigators unless noted otherwise in the eligibility criteria.

4.2 Strategies for Recruitment and Retention

Participants will be identified for recruitment based on the RACR participant registry as well as site-approved recruitment sources.

Participants will be contacted between visits to remind them of upcoming events. They will also be reimbursed for their time and transportation costs.

5. STUDY AGENT/INTERVENTIONS

5.1 Formulation, Packaging, and Labeling

5.1.1 Investigational Agent #1: Xolair[®] (Omalizumab)

Xolair[®] (omalizumab) is a recombinant DNA-derived humanized IgG1 κ monoclonal antibody that selectively binds to human IgE. Xolair[®] Solution for Injection (omalizumab) is packaged as single-use pre-filled syringes for subcutaneous (SQ) injection. Each pre-filled syringe of Xolair[®] Solution for Injection (omalizumab) contains 150 mg/mL of omalizumab (75 mg omalizumab in 0.5 mL or 150 mg omalizumab in 1.0 mL). Each syringe also contains 200 mM arginine hydrochloride, 20 mM histidine and

0.04% polysorbate 20 at pH 6.0. The 1mL long glass syringe, with staked 26 gauge x 0.5 inch needle, contains a safety device which covers the needle after use.

Xolair[®] (omalizumab) is manufactured by Vetter Pharma-Fertigung on behalf of Novartis and marketed by Novartis Pharmaceuticals Corporation. Labeled Xolair[®] (omalizumab) prefilled syringes, as clinical trials supplies, will be provided by the manufacturer. Syringes will be shipped open-label from Novartis to a central drug distributor for subsequent dissemination to the clinical sites research pharmacy (open-label). The product label will include a protocol identifier and indicate that it is limited to investigational use.

5.1.2 Investigational Agent #2: Flovent[®] Diskus[®] (Fluticasone)

Flovent[®] Diskus[®] 100 mcg (fluticasone propionate inhalation powder, 100 mcg) and Flovent[®] Diskus[®] 250 mcg (fluticasone propionate inhalation powder, 250 mcg) have been selected for use in the ICS boost arm of the protocol. Each actuation of the Diskus[®] device provides 94 or 229 mcg of fluticasone propionate. Each device is sealed by the manufacturer in a moisture-protective foil pouch and contains 60 blisters of fluticasone propionate inhalation powder.

Flovent[®] Diskus[®] (fluticasone) is manufactured and marketed by GlaxoSmithKline (Research Triangle Park, NC). It will be packaged as clinical trials supplies by the manufacturer. It will be shipped open-label from GlaxoSmithKline to a central drug distributor for labeling and subsequent dissemination to the clinical sites research pharmacy (open-label). The clinical sites research pharmacy will dispense the study drug and placebo in a blinded fashion as per the randomization schedule provided by the SACCC. The product label will include a protocol identifier and indicate that it is limited to investigational use.

5.1.3 Investigational Agent #3: Placebo Xolair[®] (Omalizumab)

The composition of the placebo Xolair[®] is the same as the active study drug without the omalizumab. The placebo Xolair[®] (omalizumab) is manufactured by Vetter Pharma-Fertigung on behalf of Novartis. It will be packaged and labeled as described above for the Xolair[®] prefilled syringes.

5.1.4 Investigational Agent #4: Placebo Flovent[®] Diskus[®] (Fluticasone)

Placebo Flovent[®] Diskus[®] (fluticasone) contains a foil strip of 60 blisters, each blister contains a nominal 13mg fill of lactose powder. The placebo Flovent[®] Diskus[®] (fluticasone) is manufactured by GlaxoSmithKline (Research Triangle Park, NC). It will be packaged as clinical trials supplies and shipped open-label from GlaxoSmithKline to a central drug distributor for labeling and subsequent dissemination to the clinical sites research pharmacy (open-label). The clinical sites research pharmacy will dispense the study drug and placebo in a blinded fashion as per the randomization schedule provided by the SACCC. The product label will include a protocol identifier and indicate that it is limited to investigational use.

5.2 Storage and Handling

5.2.1 Investigational Agent #1: Xolair[®] (Omalizumab)

Xolair[®] (omalizumab) will be shipped and stored under refrigerated conditions 2-8° C (36-46° F). It will not be frozen. It will not be used beyond the manufacturer's listed expiration date. Xolair[®] (omalizumab) is for single-use only and contains no preservatives.

5.2.2 Investigational Agent #2: Flovent[®] Diskus[®] (Fluticasone)

The storage and handling of Flovent[®] Diskus[®] (fluticasone) will follow the commercial Prescribing Information. Flovent[®] Diskus[®] (fluticasone) should be stored at room temperature (20-25° C [68-77°F]) in a dry place away from heat and sunlight. It will not be used beyond the expiration date.

5.2.3 Investigational Agent #3: Placebo Xolair[®] (Omalizumab)

Placebo Xolair[®] should be shipped and stored under controlled ambient temperature ($\leq 30^{\circ}\text{C}$ [$\leq 86^{\circ}\text{F}$]). It may be refrigerated. It will not be used beyond the manufacturer's listed expiration date. Placebo Xolair[®] is for single-use only and contains no preservatives.

5.2.4 Investigational Agent #4: Placebo Flovent[®] Diskus[®] (Fluticasone)

The storage and handling requirements for the placebo Flovent[®] Diskus[®] are the same as the active study drug.

5.3 Preparation and Administration

5.3.1 Investigational Agent #1: Xolair[®] (Omalizumab)

Study drug preparation and administration is based on manufacturer's instructions. To prepare the syringe for injection, it must be brought to ambient temperature prior to injection (20 minutes). The clinical sites research pharmacy will dispense the study drug as per the randomization schedule provided by the SACCC. The injections will be administered by unblinded study staff who will only be permitted to do other study activities that would not compromise the blind. Prior to injection, an unblinded staff member will confirm the expiration date, the dose, and randomization assignment. The product will remain blinded to blinded study staff and the participant.

Xolair[®] (omalizumab) will be administered to each participant every 2 or 4 weeks beginning with the initial Treatment Visit (V4t) and continuing for 4-5 months. The injection may take 5-10 seconds to administer. Doses (mg) and dosing frequency are determined by serum total IgE level (IU/mL), measured at Visit 2 or Visit 3, and body weight (kg). Doses of more than 150 mg are divided among more than 1 injection site to limit injections to not more than 150 mg per site. The participant's dosing regimen and number of injections are determined from Tables A1a and A1b in Appendix 1. The Dosing Table is the same as the table that was used in ICATA (ICAC-08/09), and this table is required by Novartis for use in this trial.

Before each injection, participants will be screened for evidence of an ongoing allergic reaction or worsening of asthma according to guidelines in the PROSE MOP. If a participant is unable to receive the study drug injection that day, the injection will be rescheduled according to the PROSE MOP.

After each injection of study drug is administered, the participant will be observed for time periods consistent with AAAAI/ACAAI guidelines (Cox et al, 2007). A medical provider trained in treating anaphylaxis will be available to provide immediate treatment in the event that a participant experiences an allergic reaction. Participants and caretakers will be educated on the signs and symptoms of anaphylaxis and will be trained on the proper use of epinephrine auto-injectors for treatment of anaphylactic reactions. Participants will also be provided with epinephrine auto-injectors and an antihistamine free of charge. Additional information on handling injection-related reactions is in the PROSE MOP.

5.3.2 Investigational Agent #2: Flovent[®] Diskus[®] (Fluticasone)

Flovent[®] Diskus[®] (fluticasone) is self-administered. PROSE study personnel will teach participants how to use the Diskus[®] according to instructions in the package insert and will review appropriate Diskus[®] technique at every study encounter if needed. Literature has documented the acceptance of the Diskus[®] in both pediatric and adult populations because of its ease of use. In addition, the Diskus[®] has a built-in dose counter, which will allow estimation of adherence.

Flovent[®] Diskus[®] (fluticasone) is FDA-approved for the maintenance treatment of asthma as prophylactic therapy in adults and pediatric patients 4 years of age and older. For the PROSE trial, this therapy will be recommended as the primary standard in the usual care step-up ICS treatment as well (see Section 5.5 for concomitant medication adjustments). The selection of Flovent[®] Diskus[®] will prevent confusion by both study participants and coordinators as we conduct the step-up and step-down dosing algorithms in the PROSE trial.

5.3.3 Investigational Agent #3: Placebo Xolair[®] (Omalizumab)

The preparation and administration for the placebo Xolair[®] are the same as the active study drug.

5.3.4 Investigational Agent #4: Placebo Flovent[®] Diskus[®] (Fluticasone)

The preparation and administration for the placebo Flovent[®] Diskus[®] are the same as the active study drug.

5.4 Assessment of Participant Adherence with Study Agent(s)/ Intervention(s)

Xolair[®] (omalizumab) and its placebo will be administered SQ by site personnel and thus adherence will be determined by the number of injections received over the expected number of injections based on the protocol.

Flovent[®] Diskus[®] (fluticasone) and its placebo will be administered from a device with a built in counter. Adherence will be estimated by the number of doses taken according to the counter over the expected number of doses based on the protocol. For devices not returned, adherence will be based on self-report.

5.4.1 Study Agent Accountability Procedures

Under Title 21 of the Code of Federal Regulations (21CFR §312.62) the investigator is required to maintain adequate records of the disposition of all investigational agents, including the date and quantity of the drug received, to whom the drug was dispensed (participant-by-participant accounting), and a detailed accounting of any drug accidentally or deliberately destroyed.

All records regarding the disposition of the investigational product will be available for inspection by the clinical trial monitor. At the termination of the trial, all unused trial medication will be destroyed by the sites after authorization from NIAID through the Statistical and Clinical Coordinating Center (SACCC). For more information on handling of study medication, please refer to the PROSE MOP.

5.5 Concomitant Medications and Procedures

During the study, after the initial allergy skin testing, allergy and asthma medications will be permitted along with other maintenance medications, aside from those excluded in Section 4.1.2, Participant Exclusion Criteria, and in Sections 5.6.1 and 8.4.

In addition to the injection and additional inhaled therapies, all participants will receive asthma step care according to the Guidelines for the Diagnosis and Management of Asthma (Expert Panel Report 3 [EPR-3], NAEPP, 2007). Treatment will be supervised by a study clinician. The study clinician will prescribe initial appropriate concomitant asthma therapies (see Section 5.5.1) and will provide a written asthma care plan for the participant at the AoC Visit (V1) and at all subsequent E&M Visits. The regimen will then be adjusted as necessary at E&M Visits throughout the duration of the trial based on the principles of the EPR-3 guidelines (see Table 5.5.2b, below).

The study clinician will prescribe the appropriate step controller therapy, according to the participant's insurance/HMO guidelines (Refer to PROSE MOP). The preferred controller steps and alternate equivalent medications may be modified or updated based on changes in standard clinical practice, discontinuation of current medications, or the introduction of new medications. Oral prednisone and written instructions for use will be provided by the research site for the standardized treatment of asthma exacerbations.

In order to enter this study, all participants are required to have medical insurance that will cover, at least in part, the costs of their asthma medications. It is likely, however, that some participants may lose this coverage during the time that they are in the study. In order to maintain participant safety and avoid a loss of these participants to the study, PROSE will fund the cost of these participants' asthma medications. Medications will be prescribed in the same manner using the same algorithms as all insured participants. Medications will not be handed out at the research site; instead, each site will develop plans to use local pharmacies in a cost efficient and timely manner. This design is in place to mimic the support typical insured participants receive, i.e. they receive a prescription and have to fill it at a pharmacy. To limit the time that PROSE is required to fund the cost of asthma medications for a participant who has lost coverage, each research site will develop a plan for evaluation of insurance options and referral to appropriate support systems to obtain coverage for medication costs. In addition to addressing potential insurance from employers and governmental sources, this may include free clinics and support programs available through pharmaceutical firms.

5.5.1 Initial Regimen

During the AoC Visit (V1), if it is determined that the participant meets the entry criteria, the study clinician will determine the participant's appropriate initial asthma control regimen. Each participant will then be re-evaluated at 2 subsequent visits (V2 and V3) prior to randomization (V4). The purpose of these 2 visits prior to randomization is to allow transition to protocol-driven asthma management and stabilization of clinical status.

At the AoC Visit (V1), along with the participant's medical history and physical examination results, the controller medication regimen is determined by the participant's symptoms, percent-predicted FEV₁, exacerbation history that required systemic corticosteroids, and current level of therapy.

First, the clinician will determine the highest "control level" of the participant's morbidity across the 4 categories in Table 5.5.1a. For example, if the participant has 8 days with symptoms (control level 2), 1 night with symptoms (control level 1), is at 75% predicted FEV₁ (control level 3), and had 1 systemic

corticosteroid course in the last 6 months (control level 2), then the participant is at control level 3, since that is the highest of these 4 categories.

Table 5.5.1a Asthma Symptoms for Determining Initial Asthma Medication Regimen at Visit 1

Control Level	Maximum of 1) # days with asthma symptoms/ 2 weeks and 2) # days with rescue albuterol or levalbuterol use/ 2 weeks*	Maximum of 1) # nights of sleep disruption due to asthma/ 2 weeks and 2) # nights use of albuterol or levalbuterol for awakening/ 2 weeks*	FEV ₁ (% predicted)	Courses of Systemic Corticosteroids in last 6 months**
1	0-3 days	0-1 night	≥ 85	0
2	4-9 days	2 nights	80-84	1
3	10-13 days	3-4 nights	70-79	2
4	14 days	5-14 nights	< 70	>2
* Determined from participant recall, based on the 2-week interval directly preceding the study visit. **Defined as a prescription of a course of systemic steroids by a clinician or initiation of a course of systemic steroids by a participant to prevent a serious asthma outcome. If a participant initiates and completes a course of systemic steroids without clinician involvement, this course will be counted only if it meets the following minimum dosage: prednisone, prednisolone, or methylprednisolone at ≥ 20mg per day for 3 of any 5 consecutive days; or dexamethasone at ≥ 10mg per day for ≥ 1 day.				

Note: Shading in the table corresponds to the example described in the text above.

Next the clinician will determine the current level of controller therapy that the participant is using. Table 5.5.1b shows the asthma regimens that will be used during the study. If the participant is currently on one of the therapies below, then the step level of that therapy will be noted. Otherwise, the clinician must refer to the PROSE MOP for equivalency tables of other asthma therapies. From the equivalency tables, the clinician will determine the corresponding step level of therapy that the participant is currently using. For example, if the participant is currently taking Advair™ Diskus® 250/50 mcg bid, then he/she is receiving Step 4 therapy.

Table 5.5.1b Step Medication Equivalent**

Step	Medication Equivalent
0	No controller medication; albuterol or levalbuterol prn
1	Flovent® Diskus® (fluticasone) 50 mcg bid
2	Flovent® Diskus® (fluticasone) 100 mcg bid
3	Flovent® Diskus® (fluticasone) 250 mcg bid
4	Advair™ Diskus® 250/50 mcg bid
5	Advair™ Diskus® 500/50 mcg bid

** Alternate medications listed in the PROSE MOP may be used as substitutes.

Note: Shading in the table corresponds to the example described in the text above.

Based on the participant's current control level (from Table 5.5.1a) and the participant's current step level of therapy (from Table 5.5.1b or equivalent medications listed in the PROSE MOP), the clinician will then find the corresponding row in Table 5.5.1c below that includes both the current regimen and the current control level. The last column of that row gives the corresponding regimen as a Step Level, which refers back to Table 5.5.1b. The clinician will prescribe this initial regimen. Continuing the example from above, since the participant is taking Step 4 therapy and is at control level 3, he/she would be in the row shaded below. This row shows that the regimen assigned would be Step 5 (Advair™ Diskus® 500/50 mcg bid from Table 5.5.1b).

Table 5.5.1c Algorithm for Prescribing Initial Treatment Regimen at Visit 1

The current regimen plus the current control level determine the regimen assigned at Visit 1.

Current Regimen	Current Control Level	Regimen Assigned
Regimen equivalent to step 0 (or 1-3 days/week of a regimen equivalent to step 1)	Control level 1	Step 2
	Control level 2	Step 2
	Control level 3	Step 2
	Control level 4	Step 2 (and may also need prednisone burst)
Regimen equivalent to step 1 (or 1-3 days/week of a regimen equivalent to step 2)	Control level 1	Step 2
	Control level 2	Step 2
	Control level 3	Step 2
	Control level 4	Step 3 (and may also need prednisone burst)
Regimen equivalent to step 2 (or 1-3 days/week of a regimen equivalent to step 3)	Control level 1	Step 2
	Control level 2	Step 3
	Control level 3	Step 3
	Control level 4	Step 4 (and may also need prednisone burst)
Regimen equivalent to step 3 (or 1-3 days/week of a regimen equivalent to step 4)	Control level 1	Step 3
	Control level 2	Step 4
	Control level 3	Step 4
	Control level 4	Step 5 (and may also need prednisone burst)
Regimen equivalent to step 4 (or 1-3 days/week of a regimen equivalent to step 5)	Control level 1	Step 4
	Control level 2	Step 5
	Control level 3	Step 5
	Control level 4	Step 5 (and may also need prednisone burst)
Regimen equivalent to step 5	Control level 1	Step 5
	Control level 2	Step 5
	Control level 3	Step 5 (and may also need prednisone burst)
	Control level 4	Step 5 (and may also need prednisone burst)

Note: Shading in the table corresponds to the example described in the text above.

In addition to the controller regimen assigned above, all participants will be prescribed a metered dose inhaler (MDI) beta-agonist (albuterol or levalbuterol) to be used as needed. The clinician will prescribe enough of each medication to last until the next visit. If a participant is currently taking any medicine for asthma other than that prescribed, he/she will be switched to the prescribed medications. If a participant is not eligible to continue, the study clinician may prescribe an appropriate treatment regimen based on clinical judgment.

5.5.2 Algorithm-based Treatment Adjustment

During the run in period (E&M visits V2, V3, V4) and at the first follow-up visit (V9), participants' asthma medication regimen will be adjusted based on symptoms, albuterol/levalbuterol use, FEV₁, recent

exacerbations, and their current level of therapy. The clinician will be blinded to both Xolair[®] (omalizumab) injection and boost ICS treatment status.

Participants will be stepped down from controller medications at each E&M visit for which their control level is equal to 1, (with the important exception of the Randomization Visit [V4], which occurs in the summer, a point at which it is inappropriate to reduce Step level). During the double-blind treatment phase, the lowest step that will be prescribed will be Step 2 equivalent. Therefore, if at the Randomization Visit (V4), a participant is assigned Step Level 0 or 1, then he/she will not be eligible to proceed into the double-blind treatment phase (Table 3.1a). In addition, those participants assigned Step level 5 will not be eligible to receive a steroid boost due to increased safety risks associated with exceeding the maximum dose of ICS permitted by current NAEPP guidelines (NAEPP 2007).

At each E&M visit after V1, participants will undergo pre-bronchodilator spirometry and an assessment of symptoms, rescue bronchodilator usage, recent exacerbations and medication adherence. Bronchodilator used as a preventive measure prior to exercise will not count toward the assessment of rescue bronchodilator use. Based on these data, a study clinician will determine the participant's current control level from Table 5.5.2a below. For all participants, the highest control level for days with symptoms or albuterol/levalbuterol use, nights with symptoms or albuterol/levalbuterol use, % personal best FEV₁, and exacerbation history will be determined by the study clinician. The day and night symptoms, albuterol/levalbuterol use, adherence to prescribed asthma controller medications by self-report, and exacerbation history are determined from questionnaires. The FEV₁ personal best is defined in Section 6.1.4. If the quality of the spirometry maneuver at the current visit is unacceptable according to the technician's judgment, FEV₁ will not be used in Table 5.5.2a, and the control level will be based on day and night symptoms, albuterol/levalbuterol use, and exacerbation history. For example, if a participant has 0 days with symptoms (control level 1), 4 nights with symptoms (control level 3), FEV₁ at 85% of personal best (control level 1), and 1 exacerbation (control level 2), then the participant's overall control level is 3 because that is the maximum value of control levels 1, 3, 1, and 2. The control levels originated from the published national guidelines, Guidelines for the Diagnosis and Management of Asthma (EPR-3, NAEPP, 2007).

Table 5.5.2a Control Levels of Symptoms, Bronchodilator Usage, FEV₁ (% personal best), and Exacerbations

Control Level	Maximum of 1) # days with asthma symptoms/ 2 weeks and 2) # days with rescue albuterol/levalbuterol use/ 2 weeks*	Maximum of 1) # nights of sleep disruption due to asthma/ 2 weeks and 2) # nights use of albuterol/levalbuterol for awakening/ 2 weeks*	FEV ₁ (% personal best)	Courses of Systemic Steroids since the last E&M Visit**
1	0-3 days	0-1 night	≥ 85	0
2	4-9 days	2 nights	80-84	1
3	10-13 days	3-4 nights	70-79	-
4	14 days	5-14 nights	< 70	-

* Determined from participant recall, based on the 2-week interval directly preceding the study visit.

**Defined as a prescription of a course of systemic steroids by a clinician or initiation of a course of systemic steroids by a participant to prevent a serious asthma outcome. If a participant initiates and completes a course of systemic steroids without clinician involvement, this course will be counted only if it meets the following minimum dosage: prednisone, prednisolone, or methylprednisolone at ≥ 20mg per day for 3 of any 5 consecutive days; or dexamethasone at ≥ 10mg per day for ≥ 1 day.

Note: Shading in the table corresponds to the example described in the text above.

Based on the overall control level and the participant's estimated level of adherence, the clinician will use Table 5.5.2b below to determine how the participant's current therapy should be modified. At E&M visits after V1, the study participant will be considered to have acceptable adherence if he/she reports having taken 50% or more of the prescribed doses in the last two weeks. Participants with unacceptable adherence will not be stepped up in the same way as those with acceptable adherence. Continuing with the same example, since this participant is at control level 3 and assuming he/she has acceptable adherence, the clinician would recommend a 2-step increase in therapy (or an increase to step 5 if on step 4 or maintenance on step 5 if already on step 5). In all cases, consideration would be given to a burst of prednisone according to the suggestions in the table.

Table 5.5.2b Treatment Adjustment Based on Control Levels and Adherence

Control Level	Treatment Algorithm for Participants with Unacceptable Adherence	Treatment Algorithm for Participants with Acceptable Adherence
1	Continue same controller regimen	If on Step 0, maintain at Step 0 If on Steps 1-5, decrease controller regimen by 1 step
2	Continue same controller regimen or place on Step 2 therapy, whichever is higher	Increase controller regimen by 1 step, or continue Step 5 therapy if already on Step 5
3	Continue same controller regimen or place on Step 2 therapy, whichever is higher	No systemic steroids since the last E&M visit* If on steps 0-4 increase controller regimen by 1 step If on step 5 continue step 5 or treat with step 5 <u>and</u> a 4 day burst of prednisone or equivalent; ≥1 course(s) of systemic steroids since the last E&M visit* If on steps 0-3 increase controller regimen by 2 steps If on treatment step 4 increase controller regimen to step 5 or treat with step 5 <u>and</u> a 4 day burst of prednisone or equivalent If on treatment step 5 continue step 5 or treat with step 5 <u>and</u> a 4 day burst of prednisone or equivalent
4	Continue same controller regimen or place on Step 3 therapy, whichever is higher OR Treat with 4-day prednisone burst <u>and</u> continue same controller regimen or place on Step 3 therapy, whichever is higher	If on steps 0-3 increase controller regimen by 2 steps If on Step 4, increase to Step 5 or treat with Step 5 <u>and</u> a 4-day prednisone burst or equivalent If already on Step 5, continue on Step 5 or treat with Step 5 <u>and</u> a 4-day burst of prednisone or equivalent
*Defined as a prescription of a course of systemic steroids by a clinician or initiation of a course of systemic steroids by a participant to prevent a serious asthma outcome. If a participant initiates and completes a course of systemic steroids without clinician involvement, this course will be counted only if it meets the following minimum dosage: prednisone, prednisolone, or methylprednisolone at ≥ 20mg per day for 3 of any 5 consecutive days; or dexamethasone at ≥ 10mg per day for ≥ 1 day.		

Note: Shading in the table corresponds to the example described in the text above.

Based on the participant's step level assigned at the last visit and the change in steps determined above, the new regimen will be prescribed according to Table 5.5.2b above. In the example above, if the participant were currently on Step 2 and having no problems with adherence, then the recommended new treatment step based on symptoms, albuterol/levalbuterol use, FEV₁, and exacerbations is Step 4.

5.5.3 Final Clinical Evaluation (Visit 10)

At the final study visit (V10), all study participants will be prescribed an asthma medication regimen based on symptoms, albuterol/levalbuterol use, FEV₁, exacerbations, and their current Step Level. The final treatment regimen prescribed will be up to the discretion of the study clinician who examines the participant. The asthma action plan will be reviewed and modified if necessary. A new written action plan will be provided. No Xolair® (omalizumab) injections or ICS boost inhalers will be provided to the study participant at this final visit or at the visit directly proceeding (V9).

5.5.4 Rescue Medications

Use of albuterol/levalbuterol by participants and clinicians will be guided by each participant's Asthma Action Plan (see Section 5.5.6) which will be updated and provided at each E&M visit (V1, V2, V3, V4, V9, and V10). In order to achieve as much uniformity in approach as possible across clinical sites, these plans will be pre-printed with specific albuterol dosing. This dosing or product (levalbuterol alternative) may be modified by clinicians per allowable dosing outlined in the PROSE MOP.

Prednisone or equivalent will be added if symptoms progress and meet specific criteria for starting (see Section 5.5.5). Prednisone (or equivalent) supplies will be given to each participant with specific instructions to call the ICAC center for advice on when to start should symptoms worsen.

In addition, participants will receive epinephrine auto-injectors during the first Treatment Visit (V4t) to use in the event of a rare, but severe reaction to one of the investigational agents. Caretakers of participants must sign the epinephrine auto-injector training form and understand its use before the participant can receive the investigational agent.

5.5.5 Management of Acute Exacerbations

Consistent with NAEPP 2007 guidelines, clinicians caring for patients in the PROSE trial will start a course of systemic corticosteroids for severe and/or unresponsive exacerbations of asthma. Clinicians will strongly consider initiation of corticosteroids if:

- Albuterol/levalbuterol is needed by inhaler/spacer or by nebulization for more than six individual treatments in 24 hours or for greater than one day; or
- Moderate-severe wheeze, cough, shortness of breath, and/or chest tightness or pain occurs for at least 5 of the preceding 7 days; or
- Symptoms of wheeze, cough, shortness of breath, and/or chest tightness or pain severe enough to place a patient in his or her "Red Zone" on their Asthma Action Plan (see Section 5.6.6) do not significantly improve after 3 doses of albuterol/levalbuterol. (In such situation, in addition to the initiation of oral corticosteroids, the study physician should consider directing the participant to the nearest emergency department.); or
- There is an unscheduled visit for acute asthma care requiring repeated doses of albuterol/levalbuterol (clinician office, urgent care, emergency department); or
- Hospitalization is needed for asthma.

Because initiation of systemic corticosteroid treatment is a primary outcome, specific measures will be implemented to optimize consistency of its initiation, including (1) re-emphasis of these guidelines to all investigators, (2) inclusion of multiple questions regarding this process in the investigators' certification exam to document their understanding of the process, (3) completion of a reporting form whenever

systemic corticosteroids are started that document the reason(s) for its initiation, and (4) SACCC monitoring for potential disparities of systemic corticosteroid use and deviations from the process.

Permissible drugs for courses of systemic corticosteroid will include prednisone, prednisolone, methylprednisolone, and dexamethasone. The course for prednisone, prednisolone, or methylprednisolone will be 2 mg/kg/day as a single daily dose for 4 days with a minimum dose of 20 mg per day and a maximum dose of 60 mg per day. The course for dexamethasone will be 0.6 mg/kg/day as a single daily dose for 2 days with a minimum dose of 10 mg per day and a maximum dose of 16 mg per day. Failure to respond to initial treatment will result in additional evaluation and possible hospitalization for further management.

5.5.6 Asthma Action Plan

PROSE personnel will provide a written asthma action plan for the participant at each E&M visit (V1, V2, V3, V4, V9, and V10). This plan describes a Green, Yellow, and Red Zone for the participant based on his/her symptoms and not on peak flow maneuvers. In the Green Zone, the participant has no symptoms of an asthma episode and is directed to use his/her usual asthma medications. In the Yellow Zone, the participant is experiencing asthma, allergy, or cold symptoms, and is directed to increase rescue medication use until the symptoms have been resolved. In the Red Zone, the participant is having persistent symptoms that cannot be controlled. The participant is instructed to go to the ED if unable to contact a PROSE clinician.

5.5.7 Basic Asthma Education and Allergen Avoidance

As part of each E&M visit (V1 – V4, V9, V10), participants will be educated on topics related to asthma. These topics include background on asthma as a disease, use of an asthma action plan, proper technique for using medications, adherence to medications, using medications at school, and allergen and irritant avoidance. Allergen and irritant avoidance education will cover strategies to reduce exposure to cockroaches, dust mites, rodents, mold, pets, tobacco smoke and other irritants. Handouts will be provided and the education content will be tailored to each participant. For example, the allergen avoidance education will be based on the participant's aeroallergen skin test results. The participant will receive education about the allergens to which he/she is sensitive. The information contained in the handouts will be based on the EPR 3: Guidelines for the Diagnosis and Management of Asthma (2007) and on experience from the Inner-City Asthma Study. The involvement of the caretaker in these sessions will depend on the age and maturity of the participant.

5.6 Precautionary and Prohibited Medications and Procedures

5.6.1 Prohibited Medications and Procedures

Exclusionary drugs are listed in Sections 4.1.2 and 8.4. Drugs not to be administered prior to specific study procedures are found in the PROSE MOP. Participants are not allowed to begin immunotherapy at any time during the study.

6. STUDY PROCEDURES/EVALUATIONS

6.1 Clinical Evaluations

6.1.1 Vital Signs and Growth Parameters

The following vital signs and growth parameters will be assessed at specified study visits.

- Height (in centimeters, using a calibrated stadiometer)
- Weight in kilograms
- Pulse rate
- Temperature
- Respiratory rate
- Blood pressure

All of these data will be reviewed by the study clinician. Appropriate clinical action will be taken as needed.

6.1.2 Medical History and Physical Examination

The participant's medical history will be obtained at the AoC Visit (V1). A study clinician will perform a complete physical examination at the AoC Visit (V1). Follow-up brief physical examinations will be repeated at all other E&M visits during the run-in (V2–V4) and at V9 and V10.

Significant findings that are present prior to the start of therapy must be included on the appropriate study form. All results of the complete and follow-up physical exams will be recorded on the appropriate study forms.

6.1.3 Aeroallergen Skin Testing

During the screening visit, the participant's atopic status will be assessed with skin prick tests to measure IgE sensitivity to house dust mites, cat, dog, cockroach, mouse, rat, *Alternaria*, and various aeroallergens (see PROSE MOP). The antigens chosen include those that are likely to cause sensitization in people living in the inner-city. If a participant has received allergen skin testing as part of another ICAC study within 12 months of the Screening Visit (V0), the results of these allergen skin tests may be used for the PROSE study.

Skin testing will be done by the prick technique using the Greer[®] Pick[®] system (Greer, Lenoir, NC). Testing will be done according to the instructions in the PROSE MOP. Tests will be read after 15 minutes by measuring the wheal for each antigen and for the controls. For information on treatment of reactions related to skin testing, refer to the PROSE MOP.

6.1.4 Spirometry

Spirometry will be conducted following ATS guidelines (Miller et al, 2005). For children under 8 years of age, ATS preschool criteria will be used for spirometry acceptance evaluation. Details regarding the pulmonary function testing and quality control over-reading procedures are provided in the PROSE MOP.

At V1, the participant's FEV₁ percent predicted will be used in determining his/her control level (Section 5.5.1). At subsequent E&M Visits, the participant's percent personal best FEV₁ will be used in determining his/her control level (Section 5.5.2). After each pre- and post-bronchodilator test session, the technician will judge whether the participant's technique was acceptable. The participant's personal best FEV₁ is defined as the highest acceptable FEV₁ (liters) whether pre- or post- bronchodilator from all prior study visits. The percent of personal best is the FEV₁ (liters) from the current visit divided by the personal best FEV₁ (liters). In the absence of a percent personal best FEV₁, the participant's FEV₁ percent predicted will be used to determine control level.

6.1.5 Dust Sample Collection

At a treatment visit, the caretaker or participant will be given a vacuum and dust collection kit, which includes instructions on how to collect a dust sample. The participant will collect a combined dust sample from his/her bedroom floor and bed. Dust will be collected using a vacuum cleaner with a DUSTREAM™ dust collector (InBio, Charlottesville, VA) attached. The dust collector will be placed into a sealable plastic bag and returned to the study center for temporary storage (frozen).

Crude samples will be batched and shipped to a central laboratory by express mail for sieving, extraction, and analysis. The dust specimens will be assayed to measure the concentration of the following allergens: Der p 1, Der f 1, Bla g 1, Fel d 1, Can f 1, and Mus m 1. Additional allergens of interest and markers of fungal and microbial exposure may be measured if funding permits.

In addition, the caretaker/participant will complete a dust collection questionnaire, which will be returned with the dust collector.

6.1.6 Measurement of Active Smoking and Environmental Tobacco Smoke (ETS) Exposure

ETS exposure and active smoking make asthma harder to control. ETS exposure both in the home and outside the home will be evaluated by questionnaires throughout the study. Urine cotinine (a metabolite of nicotine) will be used to determine active smoking and will be assessed at the Randomization Visit (V4) for all participants.

6.1.7 Measurement of Airborne Nicotine Concentration

Although nicotine is not the only component of ETS that leads to adverse effects on the airways, tobacco smoking is the sole source of nicotine in indoor air, so nicotine provides an excellent metric for estimating relative exposure to ETS among homes. Nicotine in indoor air can be measured using a passive diffusion filter approach that requires no air pump and provides an integrated measure of nicotine concentration over the period that the diffusion filter is exposed.

We will obtain an integrated 2-week measure of indoor air nicotine concentration in the home once during the treatment period using the same method used in the Inner City Asthma Study (Wallace et al., 2003). The monitor is a passive, diffusive sampler. The monitor will be placed in a secure location approximately 3 feet off the floor. After 2 weeks of sampling in the home, the nicotine filter will be sealed, returned to the research center, and shipped in batches to a central laboratory where nicotine concentration will be determined. In addition, the caretaker/participant will complete and return a questionnaire with the sampler.

6.1.8 Measurement of NO₂

An integrated 2-week measurement of NO₂ in the home will also be obtained once during the treatment period. The measurement of NO₂ concentration will be made using a modified diffusion filter sampler (see PROSE MOP) that will be located in a secure location approximately 3 feet off the floor. After 2 weeks of sampling in the home, the samplers will be sealed, returned to the research center, and shipped in batches to a central laboratory for extraction and ion chromatography analysis. In addition, the caretaker/participant will complete and return a questionnaire with the sampler.

6.1.9 Measurement Of Outdoor Pollution Exposure

Outdoor pollution exposure data will be obtained from the U.S. Environmental Protection Agency Air Quality System.

6.1.10 Collection of Nasal Mucus Samples for Viral Analysis

Because the role of Xolair[®] (omalizumab) in attenuating participants' responses to viral infections is a key objective, nasal mucus samples will be collected. These samples will be collected three times by clinic staff: the first at V2 or V3, the second at V4, and the third at V6 or V7. Based on results of pilot tests, the V2/V3 sample may not be needed. In this case, the procedure will only be performed twice. Subsequently, nasal mucus samples will be self-collected by participants weekly during the outcome period. In order to ensure that samples are collected during the entire outcome period, sample collection may begin a few weeks before and end a few weeks after the outcome period. These procedures and their timing are described in the PROSE MOP.

6.1.11 Questionnaire Assessments

Questionnaires will be administered that will collect information on eligibility, baseline, covariate, and outcome data, including:

- School absence
- Asthma symptoms
- Concomitant medications
- Demographics
- Environmental assessment
- Exacerbation/medical utilization outcomes
- Smoking
- Potential AEs
- PCP contact information
- Prior medical history
- Respiratory illness assessment

An interviewer will administer all questionnaires to the participant unless noted otherwise in the PROSE MOP. Refer to the PROSE MOP for a list of all forms and completion guidelines and timing.

6.1.12 Dendritic Cell Studies

Participants included in the dendritic cell studies will provide additional blood once before treatment (V2, V3, V4, or V4t), once during the treatment phase (V6, V7, or V8), and once after treatment is

discontinued (V9). Based on results of blood collected at the earlier visits, the V9 sample may not be needed. In this case, the procedure will only be performed twice. Baseline pDC FcεRI expression and pDC frequency will be determined by flow cytometry on an aliquot of PBMCs from each participant. PBMCs will be isolated from the blood samples and exposed *in vitro* to the following stimuli: control media, RV-16 (major group RV), Influenza, and Gardiquimod (TLR7 agonist). The control media and RV-16 conditions will also be evaluated in the presence and absence of a relevant indoor allergen to determine whether anti-IgE therapy improves allergen-mediated interruption of pDC responses to viral stimulation. At a subset of sites, pDCs will be purified from PBMCs and exposed to similar conditions listed above. IFN-α concentrations will be measured in PBMC and pDC supernatants. The expression of genes involved in the regulation of IFN-α secretion, including but not limited to TLR7, IRF-3, IRF-7, ISG15, RIG-I, and MDA5, will be evaluated by PCR in harvested PBMCs and pDCs. Additionally, baseline PBMCs from each patient (before culture) will be stored for the similar analysis.

6.1.13 Measurement of Exhaled Nitric Oxide

Measurement of exhaled nitric oxide (eNO) will be obtained at Visit 4t. Exhaled NO will be measured employing a technique following American Thoracic Society guidelines for eNO assessment (Dweik, 2011). This procedure is detailed in the PROSE MOP.

6.2 Laboratory Evaluations

6.2.1 Clinical and Research Laboratory Evaluations and Specimen Collection

6.2.1.1 Urine Pregnancy Testing

All females who have undergone menarche (or who undergo menarche during the study) will be required to have a urine pregnancy test at the Screening Visit and all subsequent study visits. The test will be performed before the injection. If the result is positive, the participant will either not be eligible for assumption of care or will be discontinued from the study. Additional urine pregnancy testing may be performed at clinician discretion. Results of all pregnancy tests will be given to the caretaker (or participant if specified by site IRB guidelines). Pregnancy in girls who have received investigational agent will be reported as an AE and followed to outcome. If the pregnancy results in anything other than a normal birth or elective abortion of a healthy fetus, it will be reported as a SAE. All females ≥ 18 years old who become pregnant during the course of the study will receive information on how to join the Xolair® (omalizumab) Pregnancy Registry. Refer to the PROSE MOP for additional details.

6.2.1.2 Blood Labs

Venous blood samples will be collected at Screening (V0), Visit 2/3, and at the follow-up evaluation (V9). If visits where blood is collected are missed or the sample is not collected or usable, the blood may be collected at a later visit according to the PROSE MOP. A central laboratory will be used for analysis of blood samples. The blood will be handled in accordance with standard, central laboratory protocol. Table 6.2.1.2a shows the planned laboratory evaluations at Visit 0 and Visit 9. See Section 6.2.1.3 for Visit 2/3.

Table 6.2.1.2a Laboratory Evaluations at V0 and V9

Hematology	Blood Chemistry	
Hematocrit (HCT)	Sodium	SGOT
Hemoglobin (HGB)	Potassium	SGPT
Red Blood Cell Count (RBC)	Calcium	Alkaline phosphatase
White Blood Cell Count (WBC) with differential	BUN	Total bilirubin
Platelet Count	Creatinine	Protein Total
	Uric Acid	Albumin
		Glucose

At Visits 0 and 9, a study clinician will review any abnormal lab values to determine the cause and, if necessary, the appropriate management. Participants with clinically significant laboratory abnormalities (not associated with the study indication) at the Screening Visit will be ineligible for participation, based on clinician evaluation.

At Visit 9, in case a platelet count $< 75 \times 10^9/L$ ($75 \times 10^3/\mu L$) or a drop from baseline (Screening) value of $\geq 50\%$ is detected, a second 're-test' blood sample must be taken within 1-2 days. The sample for re-test must be submitted to both the central lab and the local lab for reading of platelet levels. Two tubes of blood (approximately 3 mL/tube) will be collected within 2 days of receipt of the abnormal test results. One tube for re-test will be submitted to the central lab, and one tube will be submitted to the local lab for confirmation.

If the second 're-test' blood sample from the Central Lab confirms a platelet count $< 75 \times 10^9/L$ or a drop from baseline value $\geq 50\%$, the site investigator and NIAID Medical Monitor will be immediately notified of such an event.

- The participant will be evaluated by a hematologist for clinical examination and assessment of drug causality including additional laboratory tests if indicated, and the participant will be followed as clinically appropriate.
- If the decrease in platelet count is found to be transient, clinically not significant and not drug-related, the participant does not need to be followed further.
- If neither of the second samples confirms the low platelet count, the participant does not need to be followed further.

At V0, blood will be collected, DNA extracted and stored for future genetic testing.

In a subset of sites, additional blood will be drawn once before treatment (V2, V3, V4, or V4t), once during the treatment phase (V6, V7, or V8 to accommodate lab processing burden), and once after cessation of treatment (V9) for dendritic cell mechanistic studies. Based on results of blood collected at the earlier visits, the V9 sample may not be needed. In this case, the procedure will only be performed twice. Details of these studies are specified in Section 6.1.12 and in the PROSE MOP.

6.2.1.3 Total and Allergen Specific IgE Assessment

Serum will be collected for analysis of total and allergen specific IgEs. Assays will be performed by blinded staff at a central laboratory. Total IgE will be assessed at Screening (V0) for initial inclusion and will be reassessed at Visit 2 to ensure eligibility and correct dosing level for Xolair® (omalizumab). If Visit 2 is missed or blood is unable to be collected at Visit 2, this will be completed at Visit 3. If the

participant is no longer eligible based on the V2 or V3 total IgE values, the participant will be discontinued. Prior to discontinuation, the total IgE may be repeated per physician discretion. Allergen-specific IgE will be assessed at Screening (V0) only. The allergens to be tested for specific IgE are listed in the PROSE MOP.

6.2.2 Biohazard Containment

As the transmission of HIV and other blood-borne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and shipping and handling of all specimens for this study, as currently recommended by the Centers for Disease Control and Prevention and NIH.

6.2.3 Specimen Preparation, Handling and Shipping

6.2.3.1 Instructions for Specimen Storage

Extra DNA and serum remaining once the specified analyses are conducted will be stored long-term for future research in the field of asthma. Participants will be asked to give permission for long-term storage and future use during the consent process.

6.2.3.2 Specimen Shipment Preparation, Handling and Storage

Instructions for sample preparation, handling, storage, and shipping are included in the MOP. Principal Investigators will be responsible for knowing about and observing all the regulations for classification, packaging and labeling, permits or authorizations, and personnel training for shipment of biological and hazardous materials required for the conduct of this study.

7. STUDY SCHEDULE

A summary table of all activities which are scheduled at each visit is in Appendix 2.

7.1 Recruitment

An estimated 1,000 participants will be consented in order to have an estimated 533 participants (with an attempt to distribute equally across sites) eligible for assumption of care and approximately 453 randomized. Sites may use any IRB-approved means to identify potential participants. Examples include RACR protocol, hospital, clinic, or ED admission records; investigators' specialty clinic records; and advertising (in schools or other public locations and on the radio). Potential participants will be screened and recruited using a standardized questionnaire that collects contact information and inclusion/exclusion criteria information. For inclusion and exclusion criteria, the Recruitment date is the date that the standardized questionnaire is completed. Participants may be recruited by phone or in person. Those who have no obvious characteristics making them ineligible and who are interested will be invited to the clinic for a Screening Visit (V0).

7.2 Screening (V0)

This research study will be explained in lay terms to the parent/legal guardian of each potential research participant. The parent or legal guardian of the potential participant will provide informed consent before the child undergoes any screening study procedures (see Section 12.2). Written informed consent and

Health Insurance Portability and Accountability Act (HIPAA) authorization per site-specific institutional guidelines will be obtained from the caretakers of all participants at the beginning of this visit. Written assent will also be obtained from the children, as applicable, according to each site's institutional guidelines. Study procedures will be stopped and the participant will be deemed ineligible for the study at any point during the Screening Visit (V0) if and when they fail to meet eligibility criteria.

A Screening visit (V0) will occur for all PROSE participants. Dependent on the time frame of PROSE participants' enrollment in other ICAC studies, skin testing and total IgE blood sample measurements may or may not be performed.

After the consent is signed, participants will undergo screening study procedures. Vital signs and growth parameters will be measured, and a urine pregnancy test will be performed on all post-pubertal female participants. Questionnaires will collect baseline and eligibility information. In addition, if required, prick skin testing will be performed to ensure participants are sensitive to at least 1 perennial allergen of interest to be eligible. Positive skin tests to seasonal pollens will not satisfy the eligibility criterion. Participants will be tested with: cockroach, mouse, rat, cat, dog, *Alternaria*, house dust mites, and selected seasonal aeroallergen allergenic extracts (see PROSE MOP) to characterize the study population. The skin test will be scored immediately. PROSE participants who were skin tested as part of another ICAC study within the past 12 months will not need to have their skin testing measurements repeated unless the study physician decides that the test should be repeated.

Blood will be collected by venipuncture to measure total and allergen specific IgE levels and to screen for potential anemia, low platelet count, and liver or renal dysfunction (see Section 6.2.1.2). Approximately 1 week after the Screening Visit (V0), the total IgE level will be available. The eligibility for treatment will be determined by a combination of the participants' weight and total IgE level (see Appendix 1) as well as the results of screening labs. Participants who do not qualify for treatment will be contacted by phone or letter to inform them of their status and will not be invited to participate further. Participants who are eligible will be scheduled for the AoC Visit (V1).

A blood sample will be collected, DNA extracted and stored for future genetic testing.

7.3 Assumption of Care (V1)

At the Assumption of Care (AoC) Visit (V1), after final determination of participant eligibility, the study clinician will begin management of the participant's asthma. A medical history will be taken, body temperature and growth parameters will be measured, and a physical examination will be performed to verify the participant's suitability for inclusion in the study. A urine pregnancy test will also be performed on all post-pubertal female participants.

Spirometry will be performed by all participants to verify the participant's suitability for inclusion in the study. At this visit only, this test will include administration of a bronchodilator and a post-bronchodilator test session. The participant must be able to perform spirometry according to the guidelines outlined in the PROSE MOP in order to be eligible to continue.

Questionnaires will be administered to collect baseline and eligibility information. Refer to the PROSE MOP for a complete list of study forms to be administered.

During the AoC Visit (V1), if it is determined that the participant meets the entry criteria for the study, the study clinician will determine the appropriate asthma control regimen that the participant is to receive to initiate the run-in until their next E&M visit (V2). Along with the participant's medical history and

physical examination results, the run-in controller medication regimen is determined by the participant's symptoms, percent-predicted FEV₁, current level of therapy, and exacerbation history (see Section 5.5.1). PROSE personnel will provide a written asthma action plan that will emphasize adherence to medications.

7.4 Run-in Period (V2–V3)

Study visits are divided into treatment visits and evaluation and management visits (E&M Visits). Participants will have 2 additional E&M visits between AoC (V1) and Randomization (V4). The purposes of these visits are to stabilize the appropriate control level and treatment step, to characterize asthma severity, to assess for medication adherence and to determine eligibility for randomization. E&M visits will be approximately evenly spaced during the Run-in (V1–V4).

Participants will be prescribed an asthma medication regimen based on symptoms, albuterol/levalbuterol use, FEV₁, recent exacerbations, and their current level of therapy (see Section 5.5.2).

Body temperature and growth parameters will be obtained (see Section 6.1.1). Participants will be assessed for adherence to the prescribed medication regimen based on self-report. If participants do not meet the 30% adherence requirement based on the average of the adherence as assessed at Randomization (V4) and the visit directly preceding it (either V3 or, if missed, V2), then he/she will be discontinued (see Section 8.4).

Participants' total IgE levels will be measured again at V2 to ensure that they are suitable for Xolair[®] (omalizumab) dosing prior to randomization. Blood will be collected by venipuncture to reassess total IgE levels. If Visit 2 is missed or blood is unable to be collected at Visit 2, this will be collected at Visit 3. See Section 6.2.1.3 for more information about this assessment and Section 8.4 for information about discontinuation due to this assessment.

Other assessments completed at this visit include a follow-up physical exam (see Section 6.1.2), spirometry (see Section 6.1.4), asthma education (see Section 5.5.7), questionnaires (see Section 6.1.11), and nasal mucus sample collection at either V2 or V3 (see Section 6.1.10). Based on results of pilot tests, the nasal mucus sample may not be needed at this time point. In this case, it will not be collected at either of these visits. Participants will be discontinued if they miss both V2 and V3 E&M visits during the run-in period, since adherence and asthma control measurements obtained from these visits will be necessary to determine eligibility for randomization (see Section 8.4).

In a subset of sites, blood will be drawn once at V2, V3, V4, or V4t for dendritic cell mechanistic studies. Details of these studies are specified in Section 6.1.12 and in the PROSE MOP.

7.5 Randomization (V4)

The Randomization Visit will be scheduled according to the guidelines in the PROSE MOP. This visit may occur up to 75 days prior to the start of a participant's school year; however, it must occur no later than 4 weeks prior to the start of a participant's school year because the participant must be randomized prior to the first treatment (see Section 7.6).

As at other E&M visits, the study clinician will adjust the participant's asthma medications as necessary according to the treatment algorithm (see Section 5.5.2), write an appropriate prescription, and provide a new asthma action plan (see Section 5.5.6). Participants will receive basic asthma education (see Section 5.5.7).

Other assessments completed at this visit include a follow-up physical exam (see Section 6.1.2), growth parameters and body temperature (see Section 6.1.1), spirometry (see Section 6.1.4), urine cotinine (see Section 6.1.6), urine pregnancy test (see Section 6.2.1.1), nasal mucus sample collection (see Section 6.1.10), and questionnaires (see Section 6.1.11).

In a subset of sites, blood will be drawn at Randomization (Visit 4) for dendritic cell mechanistic studies if it was not collected at V2 or V3. Details of these studies are specified in Section 6.1.12 and in the PROSE MOP.

After they have been found eligible for randomization, participants will be randomized (see Section 10.4.1). Refer to Sections 8.4.1 and 8.4.2 for criteria that would drop a participant prior to randomization.

7.6 Treatment Period (V4t–V8b)

The treatment period will begin with the initial Treatment Visit, Visit 4t. This visit may be combined with Visit 4 into one visit when the visit windows for the two visits overlap. For exact visit windows and details on combining these visits, refer to the PROSE MOP.

Prior to the initial Xolair/placebo injection, written instructions on the proper use, storage, and administration of the epinephrine auto-injectors will be given to caretakers. The parent or guardian must sign the epinephrine auto-injector training form and understand its use before the participant can receive the investigational agent. Participants will receive epinephrine auto-injectors during the first Treatment Visit (V4t), and they will be required to bring the auto-injectors to subsequent injection visits. If they do not bring the auto-injectors to a treatment visit, they will be given additional auto-injectors.

Pregnancy tests will be conducted at each visit during which an injection of study drug is given for female participants who have reached menarche (see Section 6.2.1.1). Home and air sample collection will be completed during the treatment period (see Sections 6.1.5 – 6.1.8). Body temperature will be measured at each visit (see Section 6.1.1). Exhaled nitric oxide (eNO) will be measured at Visit 4t (see Section 6.1.13). Xolair® (omalizumab) or placebo will be administered. Flovent® Diskus® (fluticasone) or placebo DPIs will be provided to the participant. At the initial Treatment Visit, the participant and caretaker will be trained in the use of the Diskus® device. All study drug will be administered by unblinded study staff who will only be permitted to do other study activities that would not compromise the blind. Refer to the PROSE MOP for details regarding activities blinded and unblinded staff members are permitted to perform.

The following assessments will also be completed: safety screening question administration prior to injections, AEs, concomitant and prescribed medications, adherence review, and questionnaires (see Section 6.1.11). Participants who require injections every 2 weeks will complete the outcome assessment forms monthly; they will not complete these forms at the extra injection visits.

During the outcome period, participants will be asked to self-collect weekly nasal mucus samples (see Section 6.1.10 for details on collection and timing). Staff members will oversee this collection at both the 2- and 4-week visits during the treatment period and will call participants weekly to remind them to self-collect these samples at home during the weeks they do not have a study visit. A nasal mucus sample will be collected by clinic staff at V6 or V7.

After V4t, drug administration will be targeted for 14- or 28-day intervals depending on the dosing schedule (see Appendix 1). Participants must be treated until the end of the outcome period. Depending on the date of randomization, the actual number of treatment visits will vary from an estimated 5-6 visits

for participants on the 4-week dosing schedule to an estimated 9-10 visits for participants on the 2-week schedule. Refer to Appendix 2 for a list of all Visits for participants on the 4-week schedule. A similar reference is provided in the PROSE MOP for participants on the 2-week schedule. For all participants, refer to the PROSE MOP for target windows and visit scheduling rules. The treatment period will not be extended for missed visits.

In a subset of sites, blood will be drawn at Visit 4t if it was not drawn at Visit 2, 3, or 4 and once during Visit 6, 7, or 8 (depending on the lab processing burden) for dendritic cell mechanistic studies. Details of these studies are specified in Section 6.1.12 and in the PROSE MOP.

At one of the treatment visits, participants will be instructed on the collection of dust, NO₂, and nicotine samples from their home. Details of these samples are provided in Sections 6.1.5, 6.1.7, and 6.1.8, and in the PROSE MOP.

Participants who miss 1 or more treatment visits will not be dropped from treatment, regardless of the number of visits they miss. They may, however, be excluded from certain analyses. For a description of the analysis populations, refer to Section 10.2.

7.7 Follow-up Visit (V9)

A follow-up clinical evaluation will be targeted for 6 weeks after the final treatment is administered.

The following assessments will be made:

Urine pregnancy test for female participants who have reached menarche (see Section 6.2.1.1), body temperature, plus height (see Section 6.1.1), spirometry (see Section 6.1.4), questionnaires (see Section 6.1.11), blood sample collection (see Section 6.2.1), and follow-up physical examination by study clinician (see Section 6.1.2).

Blood will be collected by venipuncture to reassess for potential anemia, low platelet count, and liver or renal dysfunction (see Section 6.2.1.2). In a subset of sites, additional blood will be drawn at Visit 9 for dendritic cell mechanistic studies. Based on results of blood collected at the earlier visits, the V9 sample may not be needed. Details of these studies are specified in Section 6.1.12 and in the PROSE MOP.

As at other E&M visits, the study clinician will adjust the participant's asthma medications as necessary according to the treatment algorithm (see Section 5.5.2), write an appropriate prescription, and provide a new asthma action plan (see Section 5.5.6). Participants will receive basic asthma education (see Section 5.5.7).

7.8 Final Study Visit (V10)

A final clinical evaluation will be targeted for 12 weeks after the final treatment is administered.

The following assessments will be made:

Urine pregnancy test for female participants who have reached menarche (see Section 6.2.1.1), vital signs, plus height via stadiometry (see Section 6.1.1), spirometry (see Section 6.1.4), questionnaires (see Section 6.1.11), follow-up physical examination by study clinician (see Section 6.1.2), assignment of asthma medication regimen by study clinician (see Section 5.5.3), and asthma education (see Section 5.5.7).

The final treatment regimen prescribed will be up to the discretion of the study clinician (see Section 5.5.3) and a new asthma action plan will be provided (see Section 5.5.6).

The participant will be instructed to return to his/her PCP for all asthma care. Participants who did not have a PCP at the beginning of the study will be referred to one.

7.9 Early Termination Visit

Participants may withdraw or be dropped from the study after assumption of care, during or between study visits, according to the criteria in Section 8.4. For participants who withdraw or are dropped during a study visit, the scheduled study visit will be terminated. Instead, the study clinician and staff will perform a final clinical assessment as described in Section 7.8. In addition, for randomized participants, blood will be collected following the procedures outlined in Section 7.7 for Visit 9. The final treatment regimen prescribed will be up to the discretion of the study clinician (see Section 5.5.3) and asthma education (see Section 5.5.7) and a new asthma action plan will be provided (see Section 5.5.6). The participant will be instructed to return to his/her PCP for all asthma care. Participants who did not have a PCP at the beginning of the study will be referred to one. Activities which are not deemed clinically relevant by the study clinician, depending on the participant's status and reason for discontinuation, may be omitted.

Participants who withdraw or are dropped from the study between visits will be contacted by phone and will be invited to the study center for a final assessment as described above. For participants who refuse to come to the clinic, some components of the final clinical assessment as described above may be conducted over the phone. Besides this visit, no further follow-up will be made, except for participants who are discontinued due to pregnancy or SAEs. These participants will be contacted to determine the outcome of the pregnancy or the SAE. Refer to Section 6.2.1.1, Urine Pregnancy Testing, for more information on pregnancy testing and Section 8.2.7 Reporting Pregnancy, for more information on AE reporting.

7.10 Pregnancy

Females who become pregnant during the study will be discontinued immediately and no further study procedures will be performed. These participants will be followed to determine the outcome of the pregnancy; otherwise no further follow up will be made. See Section 6.2.1.1 for more information on pregnancy.

7.11 Asthma Management during PROSE and Interaction with Primary Care Providers

7.11.1 Overview

It is crucial that each participant receive the same level of asthma care, and treatment should not be altered by non-study clinicians during the course of the study. Thus, study investigators will strive to provide all non-emergent outpatient asthma care during the period that each participant is followed. This will include both scheduled study visits and additional visits prompted by clinical problems, including follow-up visits after ED visits or hospitalizations. Although study investigators will assume total asthma-related outpatient care for the duration of the study, the PROSE study team will inform every participant's PCP and/or non-PROSE asthma specialist of the patient's participation in the PROSE study. In addition, the PROSE study team will encourage follow-up with the PCP for routine health-care maintenance and

problems not related to asthma and will communicate to the PCP that asthma-related care will also be returned to the PCP at the end of the study.

7.11.2 Asthma Management during The Study Period

7.11.2.1 Scheduled Study Visits

Each E&M visit specified in this protocol will include evaluation by a study clinician, selection of an outpatient therapeutic regimen appropriate to the participant's condition, and implementation of the prescribed regimen. Thus, these visits will serve to replace routine clinical visits to non-PROSE asthma PCPs for asthma evaluation and management that would be necessary if the participant were not enrolled in the PROSE study. The regimen will be determined as described in Section 5.5.2. Participants who are at control level 4 at a study visit or who are prescribed systemic corticosteroids for an illness should receive a follow-up phone call within 1–2 weeks of the visit to check the status of their symptoms.

7.11.2.2 Telephone Availability in Case of Illness

Participants will be provided with a phone and/or beeper number to contact a study clinician 24 hours per day, 7 days per week in case of an asthma exacerbation or other asthma-related problems. PROSE study personnel will answer or triage these calls during usual working hours Monday through Friday. During evenings and weekends, a study clinician-investigator or clinician designated by the PROSE study site Principal Investigator will provide beeper coverage to evaluate and advise participants over the phone, to refer for emergency care if warranted, and to facilitate unscheduled visits to the study staff if needed. For details on the management plan, please refer to Sections 5.5.4 and 5.5.5 and the PROSE MOP. Participants who experience an exacerbation and call the study center for management should receive a follow-up phone call within 1–2 weeks to check the status of their symptoms.

7.11.2.3 Unscheduled Visits to the Study Clinic

Participants who experience asthma-related problems (not requiring ED care) or concerns in between scheduled study visits will be seen by a study clinician as warranted by the situation. If the study staff are notified by the participant, his/her family, an ED, a hospital, or clinic that the participant was seen for an unscheduled visit elsewhere, then the study staff will contact the participant within 2 weeks for a follow-up assessment. All therapeutic interventions will be documented on study forms. For details on the management plan, please refer to Sections 5.5.4 and 5.5.5 and the PROSE MOP.

7.11.2.4 ED and Inpatient Care

Participants requiring emergency care will be instructed to go to the ED. Participants will be given a PROSE study identification card with study contact information at the AoC Visit (V1). They will be educated to identify themselves as PROSE study participants by providing this card when seeking emergency care for asthma and to suggest that the ED or inpatient clinicians contact the PROSE study research team to report the clinical situation and to facilitate PROSE study follow-up within 2 weeks of ED care or hospital discharge. In PROSE study institutions, ED and inpatient staff will be asked to contact the PROSE study team when they care for PROSE study participants. In addition, participants will be educated to contact the PROSE staff following ED and hospital visits to notify staff of the visit and to facilitate follow-up. The PROSE study team will not provide ED or inpatient care as part of the study. They may care for participants if this would occur as part of their regular healthcare delivery responsibilities. For details on the management plan, please refer to Sections 5.5.4 and 5.5.5 and the PROSE MOP.

7.11.3 Communication with Non-PROSE Clinicians

Prior to any contact with the participant's PCP and other non-PROSE asthma specialists, the study staff will ask permission and, if necessary, have the caretaker/participant (age appropriate) sign a release of information document to send information to these clinicians. Information will be sent to the participant's PCP and an asthma specialist, if the caretaker/participant identifies one. If the participant does not have a PCP, a referral will be made at Visit 10.

Following the Assumption of Care Visit (V1), a letter will be sent to the PCP (and non-PROSE asthma specialist, if any) indicating the participant's enrollment in the PROSE study, the participant's current control level, and resulting initial regimen prescribed. After E&M visits, the study team will send a letter reporting the participant's current clinical status and the treatment regimen prescribed. After the final visit (V10), a letter will be sent updating the participant's clinical status and treatment regimen as of discharge from the study. This letter will inform the clinician that PROSE clinicians are no longer providing asthma care for his/her patient.

If a participant withdraws from the study or is discontinued prior to the final visit (V10), a similar letter will be sent to the PCP and/or non-PROSE asthma specialist indicating that the participant is no longer enrolled in the study and has been referred back to them for future asthma care.

8. ASSESSMENT OF SAFETY

This section defines the types of adverse events and outlines the procedures for appropriately collecting, grading, recording, and reporting them. Information in this section complies with ICH Guideline E2A (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting) and ICH E6 (Guideline for Good Clinical Practice), and applies the standards set forth in the National Cancer Institute (NCI), Common Terminology Criteria for Adverse Events (version 4.03, June 14, 2010). This document (referred to herein as the NCI-CTCAE manual) provides a common language to describe levels of severity, to analyze and interpret data, and to articulate the clinical significance of all adverse events. These criteria have been reviewed by the study investigators and the sponsor and have been determined appropriate for this study population. (For additional information and a printable version of the NCI-CTCAE manual, refer to the NCI-CTCAE website: <http://ctep.cancer.gov/reporting/ctc.html>).

8.1 Definitions

8.1.1 Adverse Events

An AE is any untoward medical occurrence in a participant administered a Study Agent(s) and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal Study Agent(s), whether or not related to the medicinal Study Agent(s). Any medical condition that is present at the time that the subject is screened will be considered as baseline and not recorded as an AE. However, if the condition deteriorates or changes in severity at any time during the study it will be recorded and reported as an AE.

8.1.2 Suspected Adverse Reaction and Adverse Reaction

Suspected adverse reaction (SAR) means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event.

An adverse reaction (AR) means any adverse event caused by a drug. Adverse reactions are a subset of all suspected adverse reactions for which there is reason to conclude that the drug caused the event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

8.1.3 Adverse Events Associated with Procedures

AEs that occur due to a study procedure will be collected and recorded. The following clinical situations, when associated with study procedures, are defined as adverse events and will be recorded on the AE CRF. These situations do not limit the principal investigator from reporting to the Study Sponsor any other events, associated or not with these procedures, as AEs.

8.1.3.1 Aeroallergen Skin Testing

- Prolonged (>24 hours) itching at test site
- Swelling (>10 cm) at site of test lasting more than 24 hours
- Worsening of nasal or other respiratory symptoms within 30 minutes of the procedure
- Fainting /Vasovagal event within 30 minutes of the procedure
- Anaphylaxis

8.1.3.2 Venipuncture Procedures

- Fainting /Vasovagal events
- Bruising at puncture site larger than 2 cm diameter
- Bleeding from puncture site lasting more than 5 minutes
- Swelling at puncture site larger than 2 cm

8.1.3.3 Pulmonary Function Testing

- Wheezing or bronchoconstriction requiring treatment with bronchodilators within 30 minutes of the procedure
- Coughing requiring treatment with bronchodilators within 30 minutes of the procedure

8.1.3.4 Nasal Mucus Sample Collection

- Acute sinusitis within 72 hours after the procedure
- Bloody nose

8.1.3.5 Injections

- Bruising
- Redness
- Burning
- Stinging
- Local itching
- Hive formation
- Moderate/severe pain
- Indurations
- Mass
- Inflammation of the skin around the injection site

8.1.4 Serious Adverse Event (SAE)

An AE or SAR is considered “serious” if, in the view of either the investigator or DAIT/NIAID, it results in any of the following outcomes (21 CFR 312.32(a)):

1. *Death.* A death that occurs during the study or that comes to the attention of the investigator during the protocol-defined follow-up.
2. *A life-threatening event.* An adverse event or suspected adverse reaction is considered “life-threatening” if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.
3. An inpatient hospitalization or prolongation of existing hospitalization (with the exception of asthma hospitalizations, see below).
4. Persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions.
5. An important medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based on appropriate medical judgment, it may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.
6. Congenital anomaly or birth defect.

In addition, all events of possible drug-induced liver injury with hyper-bilirubinemia defined as ALT $\geq$ 3xULN and bilirubin $\geq$ 2xULN (>35% direct) (or ALT $\geq$ 3xULN and INR>1.5, if INR measured) termed ‘Hy’s Law’ events are considered “serious” AEs or SARs.

Regardless of the relationship of the adverse event to the study, the event will be reported to the sponsor and FDA if it meets any of the above definitions.

Exacerbations of asthma are ordinary, anticipated complications of asthma observed in patients receiving standard of care. Asthma exacerbations that require hospitalization and are determined to be a SAR will be considered to be an SAE. All other asthma hospitalizations will not be considered SAEs and will be entered only on the appropriate Case Report Forms. The date of onset of the serious adverse event will be

the date of hospital admission and the date of resolution will be the discharge date. The underlying condition will be followed as per protocol.

8.1.5 Unexpected Adverse Event

An AE or SAE (including SAR) is considered “unexpected” if it is not listed in the manufacturer’s investigator brochure or manufacturer’s package insert, or it is not listed at the specificity, frequency, or severity that has been observed, or at an increased rate of occurrence than has been previously observed.

An adverse event related to a study procedure (Section 8.1.3) will be considered “unexpected” when its nature, severity or frequency is not consistent with the information in the protocol.

8.2 Collecting, Recording and Managing Adverse Events

8.2.1 Identifying Adverse Events

Any adverse event that occurs from the moment the subject has signed the consent form until the final clinic visit or the final assessment at the time of dropout or discontinuation from the study will be recorded and is reportable.

Adverse events may be discovered through any of these methods:

- Observing the participant.
- Questioning the participant, with standardized questions/procedures.
- Receiving an unsolicited complaint from the participant.
- An abnormal value or result from a clinical or laboratory evaluation (e.g., a radiograph, an ultrasound, or an electrocardiogram) can also indicate an AE either based on clinical judgment or pre-defined cut-points.

8.2.2 Recording AE/SAEs

Throughout the study all identified adverse events (serious and non-serious) will be recorded on the appropriate source documents and adverse event case report forms regardless of their severity or relation to the study medications. SAEs will be recorded on the serious adverse event case report form and will include a narrative of the event signed and dated by the principal investigator or sub-investigator.

A complete description of all adverse events will include event description, date of onset, investigator assessment of severity, relationship to study medications or procedures, date of resolution/stabilization of the event, and treatment required. A change in the severity of the AE will also be documented. Additional information will be captured regarding SAEs, including event narrative, reason the event was serious, relationship to study medications, and diagnostic test results.

8.2.3 Managing Adverse Events

The site investigator must apply his or her clinical judgment as to whether an AE is of sufficient severity to require that the participant immediately be removed from further treatment under the protocol. The investigator must institute any necessary medical therapy to protect a participant from any immediate dangers.

An adverse event will be followed until any of the following takes place: a) it is resolved, b) participant is stable, or c) a minimum of 30 days after participant is terminated from the study whichever comes first. If an abnormal value or result from a clinical or laboratory evaluation (e.g., a radiograph, an ultrasound, or an electrocardiogram) is determined to be an AE, then the evaluation that produced the value or result can be repeated until the value or result returns to normal, or the result can be explained, or the usual standard of care does not require further follow-up, and the participant's safety is not at risk.

8.2.4 Grading and Attribution

8.2.4.1 Grading Criteria

Assessment should include the intensity (severity) of the event, whether clinical or laboratory, and the relationship to study medications and procedures.

The severity of adverse events experienced by study participants will be graded according to the criteria set forth in the NCI-CTCAE manual, except where otherwise indicated.

All adverse events whether or not listed in the NCI-CTCAE manual will be graded on a scale from 1 to 5 according to the following standards in the NCI-CTCAE manual (a semi-colon indicates 'or' within the description of the grade):

- Grade 1 = Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2 = Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL (preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc).
- Grade 3 = Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL (bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden).
- Grade 4 = Life-threatening consequences; or urgent intervention indicated.
- Grade 5 = Death related to AE.

8.2.4.2 Grading Criteria For Anaphylaxis

This study will grade anaphylaxis as defined by the following table, adapted from the grading scale of Dr. Simon Brown (Brown, 2004).

Table 8.2.4.2a Grading System of Severity of Anaphylaxis

Grade	Defined By
1. Mild (skin & subcutaneous tissues, GI, &/or mild respiratory)	Flushing, urticaria, periorbital or facial angioedema; mild dyspnea, wheeze or upper respiratory symptoms; mild abdominal pain and/or emesis
2. Moderate (mild symptoms + features suggesting moderate respiratory, cardiovascular or GI symptoms)	Marked dysphagia, hoarseness, and/or stridor; shortness of breath, wheezing & retractions; crampy abdominal pain, recurrent vomiting and/or diarrhea; and/or mild dizziness
3. Severe (hypoxia, hypotension, or neurological compromise)	Cyanosis or $SpO_2 \leq 92\%$ at any stage, hypotension, confusion, collapse, loss of consciousness; or incontinence

8.2.4.3 Definition of Attribution

The attribution of a serious adverse event (SAE) to the study will initially be determined by the site investigator. The site investigator will record the determination of attribution on the appropriate serious adverse event form. The attribution of an SAE to the study medications will be determined using the descriptors in the following table.

For the purpose of this study, the Investigator's assessment of attribution is not required for non-serious adverse events with the exception of the following study procedures:

- Blood draws
- Allergen skin testing
- Pulmonary function testing
- Nasal mucus sample collection
- Injections

Table 8.2.4.3a Attribution of adverse events

Code	Descriptor	Definition (guidelines)
UNRELATED CATEGORY		
1	Unrelated	The adverse event is clearly not related to study. The event is completely related to an etiology other than the study product or study intervention (the alternative etiology must be documented in the study subject's medical record)
2	Unlikely	The adverse event is doubtfully related to study and likely to be related to factors other than study product or study intervention.
RELATED CATEGORIES		
3	Possible	The adverse event may be related to study. There is an association between the event and the administration of study product or study intervention and there is a plausible mechanism for the event to be related to the study product; there may also be an alternative etiology, such as characteristics of the subject's clinical status and/or underlying disease.
4	Probable	The adverse event is likely related to study. There is (1) an association between the event and the administration of study product or study intervention, (2) a plausible mechanism for the event to be related to the study product or procedure, and (3) the event could not be reasonably explained by known characteristics of the subject's clinical status and/or an alternative etiology is not apparent.
5	Definite	The adverse event is clearly related to study. There is (1) an association between the event and the administration of the study product or study intervention, (2) a plausible mechanism for the event to be related to the study product, and (3) causes other than the study product have been ruled out and/or the event re-appeared on re-exposure to the study product.

(For additional information and a printable version of the NCI-CTCAE manual, NCI-CTCAE website: <http://ctep.cancer.gov/reporting/ctc.html> will be consulted).

In a clinical trial, the study product/intervention will always be suspect when attributing an SAE and the “unrelated” attribution will be used only when there is an undisputable or likely alternative explanation for the SAE. The investigator's assessment of the attribution of an SAE to study drug/intervention is part of the documentation process, but it is not a factor in determining what is or is not reported to the FDA by the IND sponsor.

8.2.5 Serious Adverse Event (SAE) Reporting

8.2.5.1 SAE Reporting Criteria and Procedures

The following process for reporting a SAE ensures compliance with the ICH guidelines and 21CFR §312.32. When an investigator identifies an SAE, he or she must notify the SACCC Product Safety Department within 1 business day of discovering the event. In addition, the investigator must ensure that

these events are entered on the SAE form. The form will be faxed to the SACCC Product Safety Department within 1 business day. The SACCC will notify the NIAID Medical Monitor within 1 business day of receipt.

8.2.5.2 Unexpected, Non-Serious Adverse Events

An unexpected, non-serious adverse event that is of Grade 2 severity or higher and related to the study treatment(s)/study procedure(s) will be recorded and reported to the NIAID Medical Monitor under the serious adverse event reporting procedure outlined in the SAE Reporting Criteria and Procedures Section (Section 8.2.5.1) of the protocol (i.e. within 1 business day).

8.2.5.3 Notifying the FDA

The following process for reporting a serious adverse event ensures compliance with the ICH guidelines, 21 CFR 46 and 21CFR §312.32.

The IND Sponsor is responsible for FDA safety submissions as follows:

8.2.5.3.1 Expedited Reporting to the FDA (IND Safety Reports)

Expedited Safety Report to the FDA applies if the adverse event is classified as one of the following:

- Serious and unexpected suspected adverse reaction (SUSAR) (Sections 8.1.2, 8.1.4 and 8.1.5)
or
- Aggregate analysis of serious adverse events that suggest a causal relationship to the study medications
or
- Any findings from clinical, epidemiological, pooled analysis of data pooled across multiple studies, published or unpublished scientific papers or any findings from animal or in vitro testing that would result in a safety-related change in the protocol, informed consent, investigator brochure or other aspects of the overall conduct of the trial will be reported.

Safety Reports must be reported by DAIT/NIAID to the appropriate health authorities within 15 calendar days; fatal or immediately life-threatening serious, unexpected, suspected adverse reactions must be reported within 7 calendar days.

SAEs that do not strictly fit the above criteria may be reported to the FDA in an expedited manner if the IND Sponsor deems appropriate.

8.2.5.3.2 Standard Reporting to the FDA

All adverse events, whether serious or non-serious, will be reported in the IND Annual Report.

8.2.5.4 Notifying the Data and Safety Monitoring Board

All SAEs will be sent to the DSMB for planned protocol reviews. An SAE which the medical monitor determines to be an unexpected safety risk will be sent to the DSMB immediately.

8.2.5.5 Notifying the Clinical Sites

The SACCC will ensure the timely dissemination of IND Safety reports (SAE information submitted to the FDA in an expedited fashion) to the site PIs.

8.2.5.6 Notifying the Institutional Review Board

The site investigator will ensure the timely dissemination of IND Safety reports (SAE information submitted to the FDA in an expedited fashion) to the IRB in accordance with IRB regulations and guidelines.

8.2.6 Non-Serious Adverse Event (AE) Reporting

8.2.6.1 Notifying Medical Monitor

The Medical Officer will review reports prepared by the SACCC of all AEs every 3 months at a minimum.

8.2.6.2 Notifying the Data and Safety Monitoring Board

The NIAID Medical Officer will send non-serious adverse event listings to the DSMB on a regular basis. Individual or clusters of AEs may be reported expeditiously to the DSMB either when specified by the DSMB, or upon determination of the NIAID Medical Officer.

8.2.6.3 Notifying the Institutional Review Board

The site Principal Investigator will ensure the timely dissemination of site-specific AE information to the IRB in accordance with applicable regulations and guidelines.

8.2.6.4 Notifying the FDA

All adverse events, whether serious or non-serious, will be reported in the IND Annual Report.

8.2.6.5 Updating Documentation

Since the IND sponsor is not the study drug manufacturer, the IND sponsor will use documents compiled by the study drug manufacturers which describe the safety profile of the study drug, such as the manufacturer's Investigator's Brochure or Package Insert.

8.2.7 Reporting Pregnancy

A pregnancy will be tracked as an adverse event for follow-up purposes. All pregnancies that are identified during the study after the Screening Visit (V0) will be followed to conclusion and the outcome of each will be reported to the IND Sponsor. If the pregnancy results in anything other than a normal birth or elective abortion of a healthy fetus, it will be reported as a serious adverse event to the IND Sponsor and the FDA.

8.3 Halting Rules for the Protocol

Study enrollment will be temporarily suspended pending expedited review of all pertinent data after the occurrence of one death related to the investigational agents.

If the study enrollment is stopped due to meeting the above criteria, it may not be resumed until all pertinent information is discussed with DAIT, NIAID, NIAID Asthma and Allergy DSMB, and the site IRBs, and all parties concur with the resumption of the study. The FDA will be notified if stopping rules are met and also on resumption of the study.

The study may be terminated by DAIT/NIAID or the NIAID DSMB upon review of any observations, events, or new information that merit such action.

8.4 Premature Withdrawal of a Participant

Whenever a participant is determined to be a treatment failure or is assigned dropout status, he/she will be discontinued from the study, and the reason(s) will be recorded. It will be documented whether or not each participant completed the clinical study. Participants who withdraw from the study after receiving study drug will be included in the safety population (see Section 10.2.1).

Participants who withdraw or are dropped from the study after the AoC visit (V1) will be transitioned back to their Primary Care Provider (PCP) as described in Section 7.9. If a participant is determined to be a treatment failure (after V4t), his/her treatment assignment may be unblinded to facilitate clinical care.

The following criteria will define treatment failure or dropout status after V1:

8.4.1 Criteria for Assigning Treatment Failure

- Need for > 4 bursts of systemic corticosteroids for asthma exacerbations from V1 to V4t (Screening to initial Treatment Visit) or > 3 bursts during the treatment period. A burst is defined as a minimum dose of 20 mg or more of prednisone, prednisolone, or methylprednisolone, taken per day for 3 of any 5 consecutive days; or dexamethasone as a minimum dose of 10 mg per day for 1 or more days.
- Need for > 14 days of systemic corticosteroids (equivalent to a dose of 5 mg or more of prednisone per day) over a 21 day period.
- A severe (grade 3) anaphylactoid or anaphylactic reaction after Screening (V0) before the initial Treatment Visit (V4t), or anaphylaxis of any grade during the treatment period.
- Hypoxic seizure due to asthma.
- Intubation due to asthma.

8.4.2 Criteria for Assigning Dropout Status

- Whenever the participant decides that it is in his/her best interest.
- Whenever the investigator considers it advisable or in the participant's best interest.
- Intolerable adverse experiences.
- Loss to follow-up.
- Visits 2 and 3 are missed.
- Visit 4 or Visit 4t is missed.

- Who have inadequate adherence (<30%) during the run-in period (V1 to V4) as defined by the average of the assessments at the Randomization visit (V4) and the visit directly preceding it (either V3 or, if not completed, V2).
- Who are assigned a treatment step level < 2 at Randomization (V4).
- Weight and total IgE (as measured at E&M V2 or V3) measurements not suitable for Xolair® (omalizumab) dosing (see Appendix 1).
- Begins immunotherapy during the study period.
- Becomes pregnant during the study period.
- New diagnosis of malignancy during the study period.
- Development of any medical illnesses that in the opinion of the investigators would a.) increase the risk the subject would incur by participating in the study; b.) interfere with the measured outcomes of the study; c.) interfere with the performance of the study procedures. Examples of such diseases are: cystic fibrosis, bronchiectasis, Type I diabetes, hemophilia, Von Willebrand's disease, sickle cell disease, cerebral palsy, rheumatoid arthritis, lupus, psoriasis, hyperimmunoglobulin E syndrome, parasite infections, Wiskott-Aldrich Syndrome or allergic bronchopulmonary aspergillosis.
- Initiation of chronic medications listed in Section 4.1.2. The exception to this is, if the condition being treated does not exclude the participant, and the participant can be switched to an allowable medication, the participant may continue in the study.
- Continues to drink grapefruit juice on a regular basis after receiving one reminder that it is not allowed.
- Drops out of school between V0 and V4.

8.5 Replacement of a Participant Who Discontinues Study Treatment

Additional participants may be recruited during Year Two as necessary to compensate for participants who discontinue study treatment during Year One. Due to the cohort design of the study protocol, participants who discontinue study treatment during Year Two will not be replaced. Participants who are deemed ineligible for randomization at any point up to V4 may be replaced during either year.

9. CLINICAL MONITORING STRUCTURE

9.1 Site Monitoring Plan

Site monitoring is conducted to ensure the human subject protection, study procedures, laboratory, study medication administration, and data collection processes are of high quality and meet sponsor, GCP/ICH, and regulatory guidelines. Details are provided in the study Clinical Monitoring Plan.

Site monitoring for safety will be conducted to ensure human subject protection and to ensure that study procedures and data collection processes are of high quality and meet sponsor, Good Clinical Practice (GCP)/ICH, and regulatory guidelines. Representatives from the SACCC will visit each site at a frequency to be specified in the PROSE site monitoring plan. The SACCC will review all data collection procedures, including completion of study forms, data entry of study forms, flow of forms and edit reports, filing of forms and edit reports, audit trails, and security measures for study data. Representatives from the NIAID may accompany the SACCC on site visits as needed. Key trial personnel must be available to assist the visitors during these visits. Additional details are included in the clinical monitoring plan and in the PROSE MOP.

9.2 Safety Monitoring Plan

NIAID and the SACCC will jointly decide on a safety monitoring plan for this trial. The DSMB will review any event as requested by the Investigators, SACCC, or NIAID Medical Monitor. The NIAID Medical Monitor will inform the DSMB of any expedited SAEs at the same time as the regulatory authorities. The standard frequency of DSMB review of clinical trials sponsored by DAIT/NIAID (at least once per year) will also be followed.

10. STATISTICAL CONSIDERATIONS

10.1 Overview and Study Objectives

A 3-armed prospective randomized double-blind placebo-controlled trial investigating the efficacy of standard care plus (a) Xolair[®] (omalizumab) versus (b) a boost of inhaled corticosteroid therapy or (c) placebo in reducing exacerbations during the fall season.

10.2 Study Population

10.2.1 Safety population

Safety sample will be defined as all randomized participants who received at least one dose of study medication. Participants in the safety sample will be analyzed with the group according to the medication they actually received, regardless of their randomized assignment.

10.2.2 Intent-to-treat population (ITT)

The intent-to-treat sample will be defined as all randomized participants who received at least one dose of study medication and have at least one outcome assessment after the start of the fall outcome period beginning on the start of each participant's school year for their cohort. Participants in the ITT sample will be analyzed with the group to which they were randomized, regardless of the medication actually received.

10.2.3 Per-protocol population (PP)

Per protocol sample will be defined as participants who:

1. Are part of the ITT population.
2. Remain in the study for at least half of the fall outcome period.
3. Complete at least half of their Xolair[®] (omalizumab) or Placebo injections.
4. Have adherence of at least 50% to both study medication (as measured by self-report) and to steroid boost inhaler or its placebo equivalent (as measured by device counter or self report if the device is not returned).
5. Receive the correct treatment according to their randomization assignment and correct dosage.
6. Do not have any significant protocol deviations.

10.3 Description of the Analyses

The primary hypotheses of this trial are:

- Hypothesis 1: The percentage of participants with fall exacerbations will differ between Xolair[®] (omalizumab) and standard care.
- Hypothesis 2: The percentage of participants with fall exacerbations will differ between Xolair[®] (omalizumab) and corticosteroid therapy boost in participants who are eligible to receive a steroid boost.

The primary outcome is the occurrence of ≥ 1 asthma exacerbation defined as an initiation of systemic steroid therapy or a hospitalization during the fall outcome period (90 day period beginning on the first day of the participant's school year) to prevent a serious asthma outcome. The primary analysis for both hypotheses will be analyzed using logistic regression with adjustment for site and Xolair[®] (omalizumab) dosing schedule.

Additional analysis to address the primary hypotheses will also be conducted. Poisson regression using the number of fall exacerbations as an outcome will be analyzed. Time to onset of the first asthma exacerbation will be summarized using the Kaplan-Meier estimates, and the comparison between Xolair[®] (omalizumab) versus corticosteroid therapy boost, and placebo will be tested using a log-rank test at the 0.05 level of significance. An exploratory analysis of this endpoint will use the Cox proportional hazard model to adjust for possible confounders such as sex, age, etc. Whether the proportional hazard assumptions are met will be evaluated.

Sensitivity analyses comparing participants in the Xolair[®] (omalizumab) and placebo groups who are at step level 5 at randomization will be conducted to see if Xolair[®] (omalizumab) therapy is effective in this high risk sub-population. Comparing the impact of Xolair[®] (omalizumab) vs. placebo therapy on exacerbations that occur in conjunction with nasal respiratory viruses is an important secondary objective. Nasal mucus samples will be collected weekly during the outcome period. Exacerbations will be matched with the closest nasal mucus samples and classified as a "viral exacerbation" or "non-viral exacerbation." The same methods used to analyze overall exacerbation rates (described above) will then be applied to viral exacerbations. Subgroup analysis will be conducted using interaction p-values with a 0.10 cut-off for statistical significance.

All analyses will be performed using the ITT sample and PP samples. In addition, exploratory analysis will use the ITT sample, adjusting for adherence.

10.4 Measures to Minimize Bias

10.4.1 Enrollment / Randomization / Masking Procedures

Randomization will be performed by the statistical and clinical coordinating center (SACCC) using a validated system that automates the random assignment of treatment groups to study ID numbers. To best optimize power and sample size across the primary hypotheses, participants will be randomized using a 3:1 ratio of active (Xolair[®] [omalizumab], steroid boost) and control (placebo) participants. Randomized blocks within site will be used to maintain the appropriate enrollment ratio between the three study arms.

Since participants taking 1000 mcg of Flovent[®] Diskus[®] (fluticasone) are not eligible for randomization to the steroid boost arm, randomization will be stratified by ICS treatment level as follows:

- Participants taking < 1000 mcg of Flovent[®] Diskus[®] (fluticasone) (Steps 2, 3 and 4): Randomize across all groups using a 3:1 ratio between active and placebo arms (3:3:1 ratio for Xolair[®] [omalizumab], steroid boost and control)
- Participants taking 1000 mcg of Flovent[®] Diskus[®] (fluticasone) (Step 5): Randomize to Xolair[®] (omalizumab) and placebo using a 3:1 ratio. Not eligible for randomization to the steroid boost arm.

The randomization scheme will be reviewed by a statistician at the SACCC and locked after approval.

10.5 Appropriate Methods and Timing for Analyzing Outcome Measures

The primary outcome, exacerbations, will be monitored on an ongoing basis during the fall outcome period and the start date of each prednisone burst and each hospitalization will be recorded. Details regarding the various methods of analyzing these data are included in Section 10.3.

10.6 Study Hypotheses

The primary hypothesis of this trial is to compare the efficacy of 4 to 5 months of 3 treatments — Xolair[®] (omalizumab), corticosteroid therapy boost, and placebo — in reducing fall exacerbations in inner-city children and adolescents with allergic persistent asthma when initiated approximately 4 to 6 weeks prior to the first day of each participant's school year.

Specifically, PROSE is powered to make two comparisons between the three groups:

- Hypothesis 1: The percentage of participants with fall exacerbations will differ between Xolair[®] (omalizumab) and standard care.
- Hypothesis 2: The percentage of participants with fall exacerbations will differ between Xolair[®] (omalizumab) and corticosteroid therapy boost in participants who are eligible to receive a steroid boost.

10.7 Sample Size Considerations

10.7.1 Summary

The planned sample size is 453 participants with 223 in the Xolair[®] (omalizumab) arm, 155 in the inhaled corticosteroid arm boost and 75 in the control arm.

Participants receiving less than 1000 mcg of Flovent[®] Diskus[®] (fluticasone) per day at randomization will be randomized at a 3:3:1 ratio between the Xolair[®] (omalizumab), steroid boost and placebo arms. Participants receiving 1000 mcg per day of Flovent[®] Diskus[®] (fluticasone) at randomization will be randomized at a 3:1 ratio between the Xolair[®] (omalizumab) and placebo arms but will not be eligible for the steroid boost group. The distribution of participants by group and treatment is summarized in Table 10.7.1a.

Table 10.7.1a Group Size by Treatment

Group	Treatment at Randomization		All
	Steps 2, 3 and 4 (<1000 mcg/day)	Step 5 (1000 mcg/day)	
Xolair [®] (omalizumab)	155	68	223
Steroid Boost	155	0	155
Placebo	52	23	75
Total	362	91	453

This sample size powers the comparison between Xolair[®] (omalizumab) and placebo (Hypothesis 1) at 99% and the comparison between Xolair[®] (omalizumab) and steroid boost (Hypothesis 2) at 80% and includes a 5% subject dropout rate during the double blind. Participants in each arm will be distributed approximately equally across sites (Table 10.7.1b).

Table 10.7.1b Sample Size Summary

Hypothesis	Effect	Power	Alpha	N Per Group with 5% dropout		
				Placebo	Steroid Boost	Xolair [®] (omalizumab)*
1: Xolair [®] (omalizumab) vs. Placebo	67% decrease (11.8% vs. 35.9%)	>90%	0.05	75	NA	223
2: Xolair [®] (omalizumab) vs. Boost	50% decrease (12.9% vs. 25.8%)	80%	0.05	NA	155	155

*The Xolair[®] (omalizumab) group size for hypothesis 2 (n=155) includes only participants at steps 2–4 at randomization, while the group size for hypothesis 1 (n=223) includes all participants.

10.7.2 Hypothesis 1 – Xolair[®] (Omalizumab) vs. Placebo

We examined the ICAC ICATA (ICAC-08) data with the goal of finding reasonable estimates for percentage of participants with a fall exacerbation for the placebo and Xolair[®] (omalizumab) groups. Using a 3-month September–November definition of the fall, ICATA participants who would have met PROSE eligibility (one or more exacerbations in the previous year and ICS doses of greater than 100 mcg per day) and ITT (at least one fall symptom assessment) requirements had exacerbation rates as shown in Table 10.7.2.

Table 10.7.2 Percentage of ICATA Participants with a Fall Exacerbation by Treatment Level at Randomization

Treatment Step at Randomization*	Treatment Group	
	Placebo	Xolair [®] (omalizumab)
Steps 2, 3 and 4 (<1000 mcg/day)	30.9	12.9
Step 5 (1000 mcg/day)	47.6	9.1
All	33.3	12.1

*PROSE equivalency.

Based on ICATA data, we project that approximately 20% of the total population in PROSE will be on 1000 mcg of Flovent[®] Diskus[®] (fluticasone) at randomization and will thus be ineligible for the steroid boost group. That restriction will inflate the proportion of participants at 1000 mcg to approximately 30% in the placebo and Xolair[®] (omalizumab) groups. Using that projection and the values in Table 10.7.2, we estimate that 35.9% of the placebo participants ($30.9 * 0.7 + 47.6 * 0.3$) and 11.8% of the Xolair[®] (omalizumab) participants ($12.9 * 0.7 + 9.1 * 0.3$) will have a fall exacerbation during PROSE.

Using those rates and a 3:1 randomization ratio between Xolair[®] (omalizumab) and placebo gives the required sample size to achieve 90% power with a 2-sided comparison of proportions at $\alpha=0.05$ as 123 Xolair[®] (omalizumab) and 41 placebo participants. We expect approximately 5% dropout during the double blind since only 1 month of follow-up is necessary for inclusion in the ITT population. Accounting for dropout, the group sizes increase to 130 and 44 for Xolair[®] (omalizumab) and placebo respectively.

However, since the Xolair[®] (omalizumab) and steroid boost comparison (Hypothesis 2) requires more participants in the Xolair[®] (omalizumab) group for 80% power, the final group sizes are actually larger and, as a result, power for Hypothesis 1 is above 90%. Section 10.7.3 shows that 155 participants receiving less than 1000 mcg of Flovent[®] Diskus[®] (fluticasone) are required in the Xolair[®] (omalizumab) group to test Hypothesis 2 with 80% power. Adding in 1000 mcg per day participants gives a total group size of 223 participants. Maintaining the 3:1 randomization ratio gives a placebo group size of 75 participants after rounding.

The final group sizes of 223 participants in the Xolair[®] (omalizumab) group and 75 participants in the placebo group gives 99% power to detect a difference between 11.8% and 35.9% in the Xolair[®] (omalizumab) and treatment groups respectively after 5% dropout. The percentage of participants with an exacerbation in the Xolair[®] (omalizumab) group could be as high as 16.8% to maintain 90% power (or 19.2% for 80% power) for this hypothesis if all other parameters remained the same.

10.7.3 Hypothesis 2 – Xolair[®] (Omalizumab) vs. Steroid Boost

The comparison of the Xolair[®] (omalizumab) and steroid boost groups is designed to detect the percentage of participants with fall exacerbations in the steroid boost group that is twice that of the Xolair[®] (omalizumab) group, a difference that would be of clinical interest. Using the 12.9% Xolair[®] (omalizumab) exacerbation value from ICATA, gives a target of 25.8% in the steroid boost group. Using those values, the required sample size to achieve 80% power using a 2-sided comparison of proportions at $\alpha=0.05$ is 147 participants per group, which increases to 155 per group with 5% dropout.

The predicted 25.8% of participants with a fall exacerbation is higher than the 13.7% observed in ICAC ACE (ICAC-01) intervention participants who received additional steroids based on their eNO levels, but there are many design differences between ACE and PROSE that make projecting ACE data into PROSE conditions difficult. Some of these differences are summarized in Table 10.7.3.

Table 10.7.3 Study design differences in ACE, ICATA and PROSE

	ACE	ICATA	PROSE
Steroids	Provided	Prescribed	Prescribed
Age Range	12–20	6–20	6–17
Steroid Boost	Variable	None	Constant

A major difference between the studies is that the study drugs were provided in ACE but not in ICATA or PROSE. In order to account for this design change, we calculated differences between the rate of fall exacerbations in the ACE and ICATA control groups and assumed that some proportion of that difference is due to the method of study drug distribution. In ACE, 20.5% of the placebo participants had an exacerbation compared to 30.9% of the ICATA placebo participants, a difference of 10.4%. So, although ACE intervention participants had an observed exacerbation incidence (13.7%) that was markedly lower than the projection for PROSE (25.8%), adding in the study difference gives a value ($24.1\% = 13.7\% + 10.4\%$) that is similar to the projection in PROSE.

10.7.4 Secondary Hypothesis – Viral Exacerbations

The ICATA study data indicates that at least 60% of all asthma exacerbations will be associated with a viral infection. As such, we expect to see one or more fall viral exacerbations in approximately 7.1% and 21.5% of the participants in the Xolair[®] (omalizumab) and placebo groups respectively. The stated sample size (223 participants in the Xolair[®] (omalizumab) arm and 75 participants in the placebo arm and 5% dropout) gives 88% power to detect a difference in viral exacerbations.

10.7.5 Secondary Hypothesis – Xolair[®] (Omalizumab) vs. Placebo at 1000 mcg of Flovent[®] Diskus[®] (Fluticasone)

A key secondary hypothesis compares severe participants (those receiving 1000 mcg of Flovent[®] Diskus[®] (fluticasone), step 5, at randomization) in the Xolair[®] (omalizumab) and placebo groups. Using the rates from ICATA (Table 10.7.2) and the projected sample sizes (Table 10.7.1a) at step 5, there is 95% power to detect a difference between the groups. Table 10.7.5 presents two additional power scenarios which demonstrate that power remains adequate even for higher exacerbation rates in the Xolair[®] (omalizumab) group.

Table 10.7.5 Power Scenarios for Xolair[®] (omalizumab) vs. Placebo at 1000 mcg of Flovent[®] Diskus[®] (fluticasone) per day

	Group Size + 5% dropout		Percentage with Exacerbation		Power
	Placebo	Xolair [®] (omalizumab)	Placebo	Xolair [®] (omalizumab)	
ICATA Rates	23	68	47.6%	9.1%	95%
Scenario 2	23	68	47.6%	10.0%	90%
Scenario 3	23	68	47.6%	13.5%	80%

10.7.6 Exploratory Hypothesis – Dendritic Cell Studies

To detect a 0.3 log increase (10% change) in pDC antiviral interferon response between patients in the steroid versus Xolair[®] (omalizumab) group (pooled standard deviation of 0.5), we will need between 45 to 60 participants per group to achieve an 80% to 90% power respectively. Assuming further that interferon response will decrease in the placebo compared to the steroid arm, the sample size required to detect a 0.5 log change (17% change) between placebo and Xolair[®] (omalizumab) will be of 17 to 23 placebo participants to achieve at least 80% to 90% power. All computations assume a two-sided test and 0.05 alpha level.

10.7.7 Adjustment For Multiple Comparisons

We will not adjust for multiple comparisons for the two hypotheses being tested. We recognize that corrections for multiple comparisons are performed in order to avoid making a Type I error — concluding that an association exists when it does not — but, at the same time, such adjustment makes it more likely that a Type II error will be made: concluding that no association exists when an association truly is present. With a three-arm trial, at least seven possible analyses emerge (a vs. b, b vs. c, c vs. a, ab vs. c, ac vs. b, bc vs. a and a vs. b vs. c). In order to limit possible Type I error, we have focused the protocol on just two of these seven hypotheses. Having power above 90% for Hypothesis 1 and basing Hypothesis 2 on a conservative clinical assumption (a doubling of the percentage of participants with a fall exacerbation) further reduces the risk of Type I error. With these steps in place, we do not believe that it is necessary to incorporate a formal statistical adjustment for multiple comparisons.

10.7.8 Dropout before Randomization

Although we will exclude participants taking low levels of Flovent[®] Diskus[®] (fluticasone) (Step 1) at the AoC Visit (V1), we project that approximately 10% of the participants will have their treatment decreased to Step 1 by the time of randomization, and will thus be excluded from the study at that point. Adding in an additional 5% dropout rate during the run-in due to other factors gives a total dropout rate of approximately 15% during the run-in. As such, it is estimated that at least 533 participants would need to complete the AoC Visit (V1) so that 453 participants will be randomized ($533 * 0.85 = 453$). Since the number needed to complete the AoC Visit (V1) is an estimate, in the second cohort, all participants who are eligible for randomization may be randomized, even if the total sample size exceeds 453.

10.8 Maintenance of Trial Treatment Randomization Codes

Randomization data are kept strictly confidential, accessible only to authorized persons, until the time of unblinding. At the conclusion of the trial, the occurrence of any code breaks will be determined. Only when the study has been completed, the data files verified, and the protocol violations determined would the investigational agent codes be broken and made available for data analysis.

If the Data and Safety Monitoring Board (DSMB) requests an unblinded analysis, the minimum number of statisticians necessary at the SACCC will be unblinded to treatment assignment in order to provide the necessary analyses and reports to the DSMB.

10.9 Planned Interim Analyses

If at least 180 participants (approximately 40% of the total sample) are randomized in the first year of PROSE, an interim analysis for futility based on conditional power will be performed after the first cohort completes the fall outcome period. This interim analysis will be for the comparison of Xolair[®] (omalizumab) versus placebo. Conditional power will be calculated using the same test statistics as described for the primary endpoint analysis.

First, conditional power will be calculated using the originally planned sample size, the originally assumed treatment effect, and the currently observed distribution for the primary endpoint. Second, conditional power will be calculated using the originally planned sample size, the currently observed treatment effect, and the currently observed distribution for the primary endpoint. These analyses will permit an assessment of conditional power anticipated at the end of the study based on a range of possible treatment effect sizes that might be anticipated given the data observed at the time of the interim analysis.

Conditional power below 10% for either analysis will be taken as evidence that it is futile to continue the study since it would be extremely unlikely to detect a meaningful treatment effect if it was completed as planned. In that case, the DSMB will consider recommending to stop the trial.

10.10 Safety Review

The assessment of safety will be based mainly on the frequency of AEs. Other safety data will be considered as appropriate.

AEs will be summarized by presenting, for each treatment group, the number and percentage of participants having any AE, having an AE in each body system, and having each individual AE. If an event is experienced by at least 5% of the population, the treatment groups will be compared using a Fisher's Exact test. Analogous analyses will be done for SAEs. Any other information collected (e.g. severity or relatedness to study medication) will be listed as appropriate.

11. QUALITY CONTROL AND QUALITY ASSURANCE

11.1 Training and Certification

Training of study staff will be conducted centrally prior to beginning recruitment. The training will include lecture, demonstration, and practice components to ensure that all staff members are fully trained in all aspects of the study protocol. After the training sessions, staff will complete certification exams

(written and/or practical) to demonstrate acceptable levels of knowledge regarding each study component that they will be involved in performing. Details of the certification exams are provided in the MOP.

11.2 Quality Control Procedures

The site principal investigators and study coordinators will be responsible for ensuring that all procedures are performed according to the protocol. Periodic reviews of procedures will be conducted by the study coordinator or other trained personnel according to an individual schedule for each staff member that is based on the activities he/she is responsible for conducting. Details of the quality control plan are provided in the MOP.

11.3 Operations Manuals

The MOP will describe in detail how to perform each study procedure or activity.

11.4 Quality Assurance

Following written procedures in the Clinical Monitoring Plan, the monitors will verify that the clinical trial is conducted and data are generated, documented, and reported in compliance with the protocol, GCP, and the applicable regulatory requirements. Reports will be submitted to NIAID on monitoring activities.

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

The SACCC will implement quality control procedures beginning with the data entry system and generate data quality control checks that will be run on the database. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

12. ETHICS/PROTECTION OF HUMAN SUBJECTS

12.1 Institutional Review Board/Ethics Committee

This clinical study will be conducted using cGCP as described in the United States Code CFR – 21 (CFR Parts 45, 50, 56, and 312) and the International Conference on Harmonization (ICH) document Guidance for Industry: E6 Good Clinical Practice Consolidated Guidance and according to the criteria specified in this study protocol. Before study initiation, the protocol and the informed consent documents must be reviewed and approved by the IND Sponsor, and an appropriate Ethics Committee or IRB and reviewed by FDA with no outstanding issues. Any amendments to the protocol or to the consent materials must also be approved by the IND Sponsor and local IRBs, and submitted to the FDA before they are implemented.

12.2 Informed Consent Process

The informed consent form is a means of providing information about the trial to a prospective participant and allows for an informed decision about participation in the study. All participants (or their legally acceptable representative) must read, sign, and date a consent form before entering the study, taking the

investigational agent, or undergoing any study specific procedures. Consent materials for participants who do not read English will be read to the participant.

The informed consent form will be revised whenever important new safety information is available, if needed when the protocol is amended, and/or whenever any new information becomes available that may affect participation in the trial.

A copy of the informed consent will be given to prospective participants for review. Study staff, in the presence of a witness, will review the consent and answer questions. Prospective participants will be told that being in the trial is voluntary and that he or she may withdraw from the study at any time, for any reason.

12.2.1 Assent or Informed Consent Process (in Case of a Minor)

Written assent will be obtained from the minor children according to each site's institutional guidelines. A separate IRB-approved assent form or assent statement will be signed by study participants who meet the locally-determined age threshold.

12.3 Participant Confidentiality

Following HIPAA guidelines, a participant's privacy and confidentiality will be respected throughout the study. Each participant will be assigned a sequential identification number and these numbers rather than names will be used to collect, store, and report participant information. Data reported in medical journals or scientific meetings will be presented in aggregate for participants as a whole. No individual participant will be identified in any way.

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participating subjects.

The study protocol, documentation, data and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party, without prior written approval of the sponsor.

The study monitor or other authorized representatives of the sponsor may inspect all documents and records required to be maintained by the Investigator, including but not limited to, medical records (office, clinic or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

12.4 Study Discontinuation

If the study is stopped due to meeting the criteria in Section 8.3, it may not be resumed until all pertinent information is discussed with NIAID, NIAID Asthma and Allergy DSMB and the site IRBs, and all parties concur with the resumption of the study. The FDA will be notified if stopping rules are met and also on resumption of the study.

13. DATA HANDLING AND RECORD KEEPING

This study will use a distributed Data Management System (DMS). Each research site will have a study computer with Internet access to the DMS. The system will be used to maintain databases of recruited, enrolled, and randomized participants. It will not contain any personally identifiable information until a participant has consented. It will facilitate contacting recruited participants, scheduling visits, and entering data.

Study data will be entered via a login-secured web-based DMS. The data will be transferred via https (ssl encryption) to a central database on the SACCC network. The database will reside on a dedicated server in a locked server room that only SACCC IT administrators can access. Remote access to the server will be allowed only via encrypted (ssh) login from within the SACCC internal network, and only by SACCC IT developers. Standardized data backup procedures at the SACCC will be used.

13.1 Data Management Responsibilities

The data management tasks required for this study are a joint responsibility of the SACCC and the research site staff. SACCC data managers are responsible for ensuring the quality of the data at the sites. They monitor the timeliness and accuracy of the data entry process and generate queries regarding the data that have been entered. They are available to the research site staff to assist in resolving queries and answering questions about the data and the data management system. In addition, staff at the SACCC are responsible for medically coding all adverse event data, using MedDRA version 12 or later. SACCC staff create SAS datasets to be used for reports and statistical analyses.

Research site staff are responsible for collecting the data according to the protocol and guidelines in the MOP, reviewing the case report forms and other source documents prior to data entry for accuracy and completeness, entering the data into the web-based data management system in an accurate and timely way, and resolving edits and queries. In addition, they are responsible for maintaining and organizing all original source documents, including the case report forms and any additional sources of data such as spirometry reports and laboratory reports.

The Principal Investigator is responsible for supervising the data collection and data management processes at the site to ensure the overall quality of the data generated by the site staff. The site PI and other study clinicians are involved in data collection. For example, adverse events must be graded, assessed for severity and causality and reviewed by the site Principal Investigator or designee. Certain case report forms, as specified in the MOP, require a study investigator's signature. The Study Completion Status CRF, which is the final form completed for a participant, must be signed by a study clinician indicating that the data have been reviewed and found to be complete and accurate. During the study, the Investigator must maintain complete and accurate documentation for the study.

13.2 Data Capture Methods

Site personnel will record all information required by the protocol onto the designated study forms. The study forms are the source documentation for all data collection. Site coordinators will review the study forms for completeness and accuracy and instruct site personnel to make any required corrections or additions prior to data entry. The original study form will be given to the appropriate personnel at the site for data entry. The SACCC will monitor that the study forms are data-entered in a timely manner. All original study forms will be filed in the designated, secured area at the investigational site.

Data items from the study forms will be entered into the study database at each investigational site via the Internet using single data entry with electronic verification. Only designated data entry personnel will have access to the data entry and editing routines in the DMS. The DMS and study database as a whole are password protected.

The data entry screens mirror the original paper copy study forms, facilitating data entry ease and accuracy. Electronic verification of all data fields including range checks and omission of data allows for immediate feedback via error messages to the data entry operator. Errors on the study forms are also captured through this electronic verification process. Printable edit reports with the study form errors are given to the site personnel who completed the study form for resolution. An edit is considered resolved either after the correction has been made to the study form, noted on the edit report, and changed in the data entry system or after the questionable data has been reviewed and verified and thus noted on the edit report and in the DMS. All study form and edit report changes and corrections are initialed and dated by the person making the change. The edit reports are filed with the original study form. Quality control audits are done after the edit checks have been resolved.

In addition to the edits that are run at the time of data entry at each investigational site, the SACCC will perform centralized edit checks on logical consistency, cross-database consistency, and table look-up comparisons. The centralized edit check programs will generate edit reports displaying the questionable data fields and entered values, status flags indicating the type of edit, and explanations of the specific problems. The centralized edit reports will be sent to the sites for resolution. All corrections will be made to the original study form and in the DMS. The resolution is noted on the report and sent back to the SACCC for final review. This process will assist in identifying and rectifying problems with the forms and data collection procedures. Every effort will be made to minimize the latency between the original collection of the data and the feedback to the site about possible errors.

A data entry error rate is determined at each site by re-entering a subset of the data forms as part of the quality control policy. In addition the SACCC will regularly re-enter a subset of the data forms for quality control.

13.3 Types of Data

Clinical, demographic, laboratory, and adverse event data will be collected for this study.

13.4 Source Documents and Access to Source Data/Documents

The investigational sites participating in this study will maintain the highest degree of confidentiality permitted for the clinical and research information obtained from the participants in this clinical trial. Medical and research records will be maintained at each site in the strictest confidence. However, as a part of the quality assurance and legal responsibilities of an investigation, the investigational site must permit authorized representatives of the IND sponsor and Health Authorities to examine (and when required by applicable law, to copy) clinical records for the purpose of quality assurance reviews, audits, and evaluations of the study safety and progress. Unless required by the laws that permit copying of records, only the coded identity associated with documents or with other participant data may be copied (and all personally identifying information must be obscured). Authorized representatives as noted above are bound to maintain the strict confidentiality of medical and research information that is linked to identified individuals. The investigational site will normally be notified before auditing visits occur.

13.5 Timing/Reports

Data are monitored on a daily basis by staff at the SACCC. Status reports on the progress of the study and data collection are generated weekly/bi-weekly and posted on the ICAC website for the site staff and Steering Committee members to review. Weekly or bi-weekly calls are held with the site staff during which relevant data issues are addressed.

Reports are sent to the DSMB approximately twice a year. These reports include data that are relevant to the safety and quality of the data and may include data on enrollment and retention, AEs, protocol deviations, and other protocol issues as determined by the Medical Monitor and SACCC PI.

Reports are sent to the NIAID Project Manager and Medical Officer on a regular basis. These include data on protocol deviations, AEs, and other items specified by the NIAID Project Manager or Medical Officer.

13.6 Study Records Retention

Study documents must be maintained at the research center or a local storage facility for at least 5 years following the completion of the study unless noted otherwise in the PROSE MOP. After this required period, upon authorization from the sponsor the site may continue to maintain or they may destroy the study documents; however, the documents are never to be made public without expressed written permission. Study documents that must be retained during this period include all study forms, laboratory reports, IRB approval documentation and related correspondence, and signed informed consent/assent forms.

13.7 Protocol Deviations

The practices below are consistent with Good Clinical Practice (GCP ICH E6) Sections:

- Compliance with Protocol, Sections 4.5.1, 4.5.2, and 4.5.3
- Quality Assurance and Quality Control, Section 5.1.1
- Noncompliance, Sections 5.20.1 and 5.20.2.

13.7.1 Protocol Deviation Definition

Any change, divergence, or departure from the study design or procedures of a research protocol that affects the subject's rights, safety, or well-being and/or the completeness, accuracy and reliability of the study data constitutes a major protocol deviation. Changes or alterations in the conduct of the trial which do not have a major impact on the subject's rights, safety or well-being, or the completeness, accuracy and reliability of the study data are considered minor protocol deviations. The Principal Investigator is responsible for reporting protocol deviations to the IRB using the standard reporting form. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

13.7.2 Major Protocol Deviation

A major protocol deviation (protocol violation) is a deviation from the IRB approved protocol that may affect the subject's rights, safety, or well-being and/or the completeness, accuracy and reliability of the study data. If the deviation meets any of the following criteria, it is considered a major protocol deviation (protocol violation). Example list is not exhaustive.

1. The deviation has harmed or posed a significant or substantive risk of harm to the research subject. Examples include:
 - A research subject received the wrong treatment or incorrect dose.
 - A research subject met withdrawal criteria during the study but was not withdrawn.
2. The deviation compromises the scientific integrity of the data collected for the study. Examples include:
 - A research subject was enrolled but does not meet the protocol's eligibility criteria.
 - Failure to treat research subjects per protocol in procedures that specifically relate to primary efficacy outcomes. (If it involves research subject safety it meets the first category above.)
 - Changing the protocol without prior IRB approval.
3. The deviation is a willful or knowing breach of human subject protection regulations, policies, or procedures on the part of the investigator(s). Examples include:
 - Failure to obtain informed consent prior to initiation of study-related procedures.
 - Use of outdated or incorrect consent forms.
 - Falsifying research or medical records.
 - Performing tests or procedures beyond the individual's professional scope or privilege status (credentialing).
4. The deviation involves a serious or continuing noncompliance with federal, state, local or institutional human subject protection regulations, policies, or procedures. Examples include:
 - Working under an expired professional license or certification.
 - Failure to follow federal and/or local regulations, and intramural research.
 - Repeated minor deviations.
5. The deviation is inconsistent with the NIH Human Research Protection Program's research, medical, and ethical principles. Examples include:
 - A breach of confidentiality.
 - Inadequate or improper informed consent procedure.

13.7.3 Non-Major Protocol Deviation

A non-major protocol deviation is any change, divergence, or departure from the study design or procedures of a research protocol that has not been approved by the IRB and which DOES NOT have a major impact on the subject's rights, safety or well-being, or the completeness, accuracy and reliability of the study data.

13.7.4 Management of Protocol Deviations

13.7.4.1 Recording and Reporting Protocol Deviations

Upon determination that a protocol deviation (major or non-major) has occurred, the study staff will a) notify the Principal Investigator, b) notify the SACCC, and c) complete the Protocol Deviation form. The Protocol Deviation form will document at a minimum the date the protocol deviation occurred, the date the protocol deviation was identified, a description of event, if the deviation resulted in SAE/AE, the signature of PI or study clinician, report to IRB, and documentation of a corrective action plan. NIAID may request discussion with the Principal Investigator to determine the effect of the protocol deviation on the study participant and his/her further study participation, the effect of the protocol deviation on the

overall study, and corrective actions. The Principal Investigator or study clinician will complete and sign the Protocol Deviation form and submit it to the SACCC and to the site IRB, per IRB regulations.

13.7.4.2 Routine SACCC Review

The SACCC will generate and review reports that compile all newly submitted protocol deviations. Items that are considered questionable, inconsistent, or unexplained will be referred to the site Study Coordinator for confirmation and response.

13.7.4.3 DSMB Review

The DSMB will review any event as requested by the Investigators, SACCC, or the NIAID Medical Monitor.

14. PUBLICATION POLICY

Presentations and publication of the results of this trial will be governed by the ICAC 2 Publication Policy.

15. SCIENTIFIC REFERENCES

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APPENDIX 1: XOLAIR® (OMALIZUMAB) DOSING AND INJECTIONS

Table A1a Xolair® (omalizumab) Dosing Table

		Milligrams of Xolair® (omalizumab) Required per Dose										
		Body Weight (kg)										
Dosing Interval	Baseline IgE (IU/mL)	20-25	>25-30	>30-40	>40-50	>50-60	>60-70	>70-80	>80-90	>90-125	>125-150	
q4wks	≥ 30-100	75	75	75	150	150	150	150	150	300	300	
	>100-200	150	150	150	300	300	300	300	300	225	300	
	>200-300	150	150	225	300	300	225	225	225	300	375	
	>300-400	225	225	300	225	225	225	300	300			
	>400-500	225	300	225	225	300	300	375	375			
	>500-600	300	300	225	300	300	375					
	>600-700	300	225	225	300	375						
q2wks	>700-800	225	225	300	375	Do not dose						
	>800-900	225	225	300	375							
	>900-1000	225	300	375								
	>1000-1100	225	300	375								
	>1100-1200	300	300									
	>1200-1300	300	375									

Table A1b Number of Injections and Total Injection Volumes for Asthma

Dose (mg)	Number of Injections	Total Volume Injected (mL)
75	1	0.5
150	1	1.0
225	2	1.5
300	2	2.0
375	3	2.5

APPENDIX 2: VISIT ACTIVITIES SCHEDULE

Refer to the PROSE MOP for the Visit Activities for participants on the 2 week dosing schedule and for detailed information on the allowable visit windows around the targeted visit dates and rescheduling information for missed visits. In addition, the order in which the activities should be performed will be specified in the MOP.

	Screening	Assumption of Care E&M	E&M	E&M	Randomization / E&M	Treatment Visit	Treatment Visit	Treatment Visit	Treatment Visit	Treatment Visit	Treatment Visit	Follow-up E&M	Final E&M
Visit:	V0	V1	V2	V3	V4	V4t*	V5	V6	V7	V8	V8b**	V9	V10
Target Month(s):	Oct – Mar	Nov – Mar	Jan – May	Mar – Jun	Jun – Aug	Jul – Dec						Dec – Jan	Jan – Mar
ENROLLMENT													
Informed Consent/Assent	X												
STUDY PROCEDURES													
Adverse Event Review	X	X	X	X	X	X	X	X	X	X	X	X	X
Aeroallergen Skin Test	X												
Asthma Medication Assignment													
Initial Regimen Assignment		X											
Adherence Review			X	X	X							X	X
Algorithm Medication Adjustment			X	X	X							X	X
Asthma Education / Action Plan		X	X	X	X	X						X	X
Asthma Symptom and Exacerbation Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood Sample Collection													
Safety Labs	X											X	
Total IgE	X		X	-----									
Allergen Specific IgE	X												
Genetics	X												
Mechanistic			X	-----				X	-----			X	
Concomitant Medications Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X
eNO						X							
Growth Parameters	X	X	X	X	X							X	X
Health Insurance Verification	X												
Home Environmental Sampling					X	-----							
Nasal Mucus Sample Collection													
Staff-collected			X	-----	X			X	-----				
Self-collected							X	X	X	X	X		
Physical Exam													
Full Physical Exam		X											
Brief Follow-up Exam			X	X	X							X	X
Pregnancy Test	X	X	X	X	X	X	X	X	X	X	X	X	X
Spirometry													
Pre-bronchodilator Spirometry		X	X	X	X							X	X
Post-bronchodilator Spirometry		X											
Study Drug Administration / Dispensation						X	X	X	X	X	X		
Adherence Review – ICS Boost							X	X	X	X	X	X	
Urine Cotinine					X								
Vital Signs	X												X
Body Temperature Only		X	X	X	X	X	X	X	X	X	X	X	

* If desired, Visit 4t may be combined with V4 when the visit windows for the two visits overlap. Refer to the PROSE MOP for details.

** If needed to treat participants through the outcome period