

ORIGINAL ARTICLE

Step-Up Therapy in Black Children and Adults with Poorly Controlled Asthma

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ABSTRACT

BACKGROUND

Morbidity from asthma is disproportionately higher among black patients than among white patients, and black patients constitute the minority of participants in trials informing treatment. Data indicate that patients with inadequately controlled asthma benefit more from addition of a long-acting beta-agonist (LABA) than from increased glucocorticoids; however, these data may not be informative for treatment in black patients.

METHODS

We conducted two prospective, randomized, double-blind trials: one involving children and the other involving adolescents and adults. In both trials, the patients had at least one grandparent who identified as black and had asthma that was inadequately controlled with low-dose inhaled glucocorticoids. We compared combinations of therapy, which included the addition of a LABA (salmeterol) to an inhaled glucocorticoid (fluticasone propionate), a step-up to double to quintuple the dose of fluticasone, or both. The treatments were compared with the use of a composite measure that evaluated asthma exacerbations, asthma-control days, and lung function; data were stratified according to genotypic African ancestry.

RESULTS

When quintupling the dose of fluticasone (to 250 μ g twice a day) was compared with adding salmeterol (50 μ g twice a day) and doubling the fluticasone (to 100 μ g twice a day), a superior response occurred in 46% of the children with quintupling the fluticasone and in 46% of the children with doubling the fluticasone and adding salmeterol ($P=0.99$). In contrast, more adolescents and adults had a superior response to the addition of salmeterol than to an increase in the fluticasone (salmeterol–low-dose fluticasone vs. medium-dose fluticasone, 49% vs. 28% [$P=0.003$]; salmeterol–medium-dose fluticasone vs. high-dose fluticasone, 49% vs. 31% [$P=0.02$]). Neither the degree of African ancestry nor baseline biomarkers predicted a superior response to specific treatments. The increased dose of inhaled glucocorticoids was associated with a decrease in the ratio of urinary cortisol to creatinine in children younger than 8 years of age.

CONCLUSIONS

In contrast to black adolescents and adults, almost half the black children with poorly controlled asthma had a superior response to an increase in the dose of an inhaled glucocorticoid and almost half had a superior response to the addition of a LABA. (Funded by the National Heart, Lung, and Blood Institute; BARD ClinicalTrials.gov number, NCT01967173.)

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*A complete list of the investigators in the NHLBI AsthmaNet is provided in the Supplementary Appendix, available at NEJM.org.

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INHALED GLUCOCORTICOIDS ARE EFFECTIVE first-line therapies for asthma control, but when asthma remains poorly controlled, the recommended treatment is the addition of a long-acting β_2 -adrenergic receptor agonist (LABA).¹⁻⁹ However, this recommendation is based on studies that included few patients who identified as black and does not account for differences in genetic ancestry.

Epidemiologic studies involving patients with asthma in the United States show a disproportionately greater burden of asthma (exacerbations, asthma-related urgent-care visits, hospitalizations, and deaths) in persons identified as “black” than in those identified as “white.”¹⁰⁻¹⁷ Although these disparities in asthma morbidity may be due to social, environmental, or cultural factors, such trends persist even after adjustment for contextual factors for which race or ethnic group may serve as surrogates.^{13-15,18} Studies show that black patients often have differential responses to medications for asthma, and they have more glucocorticoid resistance, less cellular sensitivity to glucocorticoids, and more eosinophilic inflammation during inhaled glucocorticoid treatment than do white patients.^{19,20} Furthermore, the response to pharmacotherapy for asthma can be affected by genetic variants that are distributed differentially among persons of diverse self-described races and ancestral backgrounds; these variants may contribute to differences between black patients and white patients with respect to the response to β_2 -agonists and inhaled glucocorticoids.²¹⁻²⁷

Contrary to the findings in white patients,^{4,8} a subanalysis involving black patients in one study indicated that adding a LABA was not superior to increasing the dose of an inhaled glucocorticoid in persons who identify as black.⁸ In addition, a follow-up analysis showed that this finding occurred in black children with eczema.²⁸ Furthermore, a retrospective study involving black adults suggested that the addition of LABAs may not confer the same benefit as an increased dose of inhaled glucocorticoids.²⁹

We conducted two parallel Best African American Response to Asthma Drugs (BARD) trials to determine the preferred “step-up” strategy in children, adolescents, and adults who had at least one grandparent who identified as black. We further examined the extent to which biomarkers, patient characteristics, and ancestral informative genom-

ic variation were predictive of a response to inhaled glucocorticoids or LABAs.

METHODS

OVERVIEW OF THE TRIALS

We conducted two prospective, randomized, double-blind, four-treatment, four-period, 56-week crossover trials. One trial involved children (5 to 11 years of age) with at least one grandparent who identified as black, and the other involved adolescents and adults who were 12 years of age or older and who had family backgrounds that were similar to those of the children. Patients in both trials had inadequately controlled asthma while receiving a low-dose inhaled glucocorticoid (fluticasone propionate at a dose of 50 μ g twice daily in children and 100 μ g twice daily in adolescents and adults) (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).

In the trial involving children, we compared the efficacy of doubling the dose of an inhaled glucocorticoid (fluticasone propionate) to a dose of 100 μ g, administered twice daily (the double-fluticasone group); doubling the dose of fluticasone to 100 μ g and adding a LABA (salmeterol) at a dose of 50 μ g (the salmeterol–double-fluticasone group); quintupling the dose of fluticasone to 250 μ g (the quintuple-fluticasone group); or quintupling the dose of fluticasone to 250 μ g and adding salmeterol at a dose of 50 μ g (the salmeterol–quintuple-fluticasone group). Owing to the lack of a low-dose inhaled glucocorticoid–LABA combination (i.e., salmeterol–fluticasone propionate, both at a dose of 50 μ g), we could not examine the effect of merely adding salmeterol to the baseline dose of inhaled glucocorticoid.

In the trial involving adolescents and adults, we compared the efficacy of adding twice-daily salmeterol at a dose of 50 μ g to baseline twice-daily administration of fluticasone propionate at a dose of 100 μ g (the salmeterol–fluticasone group); increasing the dose of fluticasone by a factor of 2.5 to 250 μ g (the 2.5-fluticasone group); quintupling the dose of fluticasone to 500 μ g (the quintuple-fluticasone group); or increasing the dose of fluticasone by a factor of 2.5 to 250 μ g and adding salmeterol at a dose of 50 μ g (the salmeterol–2.5-fluticasone group).

The trials were identical in design and step-up

dosing strategies. However, the first step-up regimen was different in the two trials because of the above-described differences in available formulations for children.

OVERSIGHT OF THE TRIALS

The trial was funded by the National Heart, Lung, and Blood Institute (NHLBI) and approved by the AsthmaNet steering committee, an NHLBI-appointed protocol review committee, and a data and safety monitoring board. The authors vouch for the accuracy and completeness of the data, for the accuracy of the analyses, and for the fidelity of the trial to the protocol (available at NEJM.org). GlaxoSmithKline donated the medications for the trials but did not have any other role in the design of the trials, in the collection or interpretation of the data, or in the preparation of the manuscript.

PATIENTS

Patients of both sexes who were 5 years of age or older and who reported having or (in the case of children) were reported by a parent or guardian as having at least one black grandparent were recruited from nine AsthmaNet partnership sites. The patients had a baseline forced expiratory volume in 1 second (FEV₁) of at least 40% of the predicted value after bronchodilator use (after four puffs of albuterol [90 µg per puff]) as well as a diagnosis of asthma confirmed by beta-agonist reversibility (an increase in the FEV₁ of at least 12%), a methacholine provocation concentration causing a 20% decrease (PC₂₀) in the FEV₁ of 16 mg per milliliter or less, or an absolute difference in the percentage of the predicted FEV₁ of at least 12 percentage points over two measurements documented within the previous year (Section 1 in the Supplementary Appendix).

RUN-IN PERIOD

Patients who were receiving an inhaled glucocorticoid or an inhaled glucocorticoid–LABA combination were included in the trials, except for those who had inadequately controlled asthma while they were receiving a high-dose inhaled glucocorticoid–LABA. The run-in period consisted of an open-label inhaled glucocorticoid (fluticasone propionate at a dose of 50 µg twice daily in children and fluticasone propionate at a dose of 100 µg twice daily in patients who were at least 12 years of age). Patients could undergo randomization if

they were found to have inadequately controlled asthma within 2 to 10 weeks after they entered the run-in period (Section 2 in the Supplementary Appendix).

TREATMENT PERIODS

Patients who met the randomization criteria (Section 2 in the Supplementary Appendix) were randomly assigned to step-up treatment sequences in a four-way crossover design with add-on LABA, different strengths of increased doses of inhaled glucocorticoid, or an increased dose of inhaled glucocorticoid with LABA in dry-powder Diskus inhalers (Fig. S1 in the Supplementary Appendix). Each treatment period lasted 14 weeks. The initial 2 weeks of each period were considered to be a washout period for the previous treatment and a wash-in period for the new regimen. Data on asthma-control days during those 2 weeks were censored from the analyses.

PRIMARY OUTCOMES

The primary aims of these trials were to evaluate the superiority of different treatments and the effect of the proportion of African ancestry (as informed by ancestry informative markers as detailed below) on the composite clinical outcome. The primary clinical outcome of each trial was a hierarchical composite measure that sequentially evaluated asthma exacerbations (Section 3 in the Supplementary Appendix), asthma-control days, and the percentage of the predicted FEV₁ at the end of the 14-week treatment regimens to determine a differential response.⁸ A treatment was deemed to be superior to another if there was a between-treatment differential response of at least one exacerbation, defined as worsening asthma events leading to treatment with systemic glucocorticoids or unscheduled health care utilization. If no exacerbation difference was identified, a differential of 31 annualized asthma-control days was evaluated, and if no differential in asthma-control days was identified, then an absolute difference of 5 percentage points in the percentage of the predicted FEV₁ was evaluated. (The primary and prespecified comparisons are described in Section 7 in the Supplementary Appendix.)

Whole-blood DNA was genotyped with the use of Illumina Multi-Ethnic Global Array BeadChips and 117,053 informative single-nucleotide polymorphisms (linkage disequilibrium, $r^2 \geq 0.1$) select-

ed for estimation of genetic ancestry. Genotype data were analyzed with 225 HapMap founders representing founders with ancestry from northern and western Europe (described in the Centre d'Etude du Polymorphisme Humain HapMap samples) and central west Africa (Yoruba) (<http://ftp.ncbi.nlm.nih.gov/hapmap/>) and 43 Native Americans to estimate the percentage of African, European, and Native American ancestry in each patient.³⁰⁻³² Ancestry-based genetic analyses evaluated the association of the percentage of African ancestry with the primary composite outcome (Section 7 and Fig. S6 in the Supplementary Appendix).

SECONDARY OUTCOMES

Secondary outcomes included asthma-control days (according to the use of albuterol rescue, use of glucocorticoids, symptoms, unscheduled office visits, and peak flows that were <90% of the reference value determined during the run-in period for each patient) (Section 3 in the Supplementary Appendix); the FEV₁, before or after bronchodilator use; and measures of asthma control. Asthma control was also assessed with the use of the Childhood Asthma Control Test (in which scores range from 0 [uncontrolled] to 27 [well controlled], with a minimally important difference of 2) and the Asthma Control Test (in which scores range from 5 [uncontrolled] to 25 [well controlled], with a minimally important difference of 3); higher values represent better asthma control in both instruments. Quality of life was assessed with the use of the Asthma Quality of Life Questionnaire (AQLQ) (in which scores range from 1 to 7 and higher scores represent less impairment, with a minimally important difference of 0.5).

EXPLORATORY OUTCOMES

The number and type of asthma exacerbations (i.e., visits to the emergency department and hospitalizations) were evaluated. Patient characteristics, including atopy, pulmonary function (e.g., the degree of bronchodilator reversibility and the degree of methacholine responsiveness), and selective biomarkers, (e.g., sputum eosinophils) were examined to evaluate the differential response to trial treatments.

SYSTEMIC EFFECTS

Overnight urine specimens were obtained for measurements of the ratio of cortisol to creatinine at

baseline and after treatment intervals. Recent data from the AsthmaNet Step Up Yellow Zone Inhaled Corticosteroids to Prevent Exacerbations trial³³ showed a reduced linear growth rate associated with the use of high-dose glucocorticoids among children younger than 8 years of age, so we analyzed data stratified according to ages younger than 8 years and 8 years or older.

STATISTICAL ANALYSIS

In the primary analysis, the target sample size of 284 children and 291 adolescents and adults had 90% power with a two-sided alpha of 0.05 to identify an absolute difference of 20 percentage points in the percentage of patients with a superior response to one therapy over another for the composite asthma outcome, assuming a withdrawal rate of 20% among children and 35% among adults before complete trial data acquisition. This analysis modeled the probability of patients having a superior response to one specific treatment over another, defined according to the composite outcome. The composite outcome and its components were fit with the use of nonlinear mixed-effect models for each pair of treatment comparisons (Section 7 in the Supplementary Appendix).^{34,35}

In the trial involving children (5 to 11 years of age), the primary prespecified comparison was between fluticasone propionate at a dose of 250 μ g twice daily (quintuple fluticasone) and twice-daily fluticasone propionate at a dose of 100 μ g plus salmeterol at a dose of 50 μ g (salmeterol–double fluticasone). In the trial involving adolescents and adults, we were able to directly examine step-up regimens with a LABA as compared with increased doses of a glucocorticoid (at two doses), and we prespecified two primary comparisons: fluticasone propionate at a dose of 250 μ g twice daily (2.5-fluticasone) versus twice-daily fluticasone at a dose of 100 μ g plus salmeterol at a dose of 50 μ g (salmeterol–fluticasone), and twice-daily fluticasone at a dose of 500 μ g (quintuple fluticasone) versus twice-daily fluticasone at a dose of 250 μ g plus salmeterol at a dose of 50 μ g (salmeterol–2.5-fluticasone), without adjustment for multiple testing. (Section 7 in the Supplementary Appendix lists prespecified secondary comparisons of the other dose combinations.) The results of the trial involving children and those of the trial involving adults and adolescents were also compared.

RESULTS

BASELINE CHARACTERISTICS OF THE PATIENTS

Between January 2014 and March 2016, a total of 280 children (of 482 enrolled) and 294 adolescents and adults (of 536 enrolled) underwent randomization at nine centers (Figs. S2 and S3 and Table S1 in the Supplementary Appendix). The majority of children were male, and the majority of adolescents and adults were female (Table 1). As compared with the adolescents and adults, more children had a blood eosinophil count of at least 300 cells per cubic millimeter, and children had a higher percentage of the predicted FEV₁, more courses of systemic glucocorticoids, and more unscheduled office visits and hospitalizations because of asthma in the previous year. (Complete baseline characteristics of the patients and of those who completed the trials as compared with those who discontinued the trials are provided in Table S1 in the Supplementary Appendix.)

OUTCOMES IN CHILDREN

The majority of children had a differential outcome between treatments. The maximum percentage of patients who did not have a superior response in any paired intervention comparison was 12% (Fig. 1). There was no significant difference in the probability of a superior response when the dose of inhaled glucocorticoid was increased two steps to a quintupled dose of fluticasone propionate (250 μ g) (46% superior) as compared with a two step-up strategy of adding a LABA (salmeterol) at a dose of 50 μ g and increasing the dose of fluticasone to 100 μ g (46% superior) ($P=0.99$) (Fig. 1B).

In children, 53% of patients (95% confidence interval [CI], 45 to 61) in the salmeterol–double-fluticasone group had a superior response, as compared with 41% (95% CI, 33 to 49) in the double-fluticasone group (Fig. 1A), whereas 43% (95% CI, 35 to 52) in the salmeterol–quintuple-fluticasone group had a superior response, as compared with 47% (95% CI, 39 to 56) in the quintuple-fluticasone group (Fig. 1C). A total of 51% of patients (95% CI, 42 to 59) had a superior response to a higher dose of inhaled glucocorticoid (in the quintuple-fluticasone group) as compared with 37% of patients (95% CI, 29 to 45) who had a superior response to a lower dose of inhaled glucocorticoid (in the double-fluticasone group)

(Fig. 1E). (Differential responses to increasing the dose of inhaled glucocorticoid as compared with adding a LABA in the elements of the composite of FEV₁, asthma-control days, or exacerbations are shown in Figures S4.1 through S4.3 in the Supplementary Appendix.)

OUTCOMES IN ADOLESCENTS AND ADULTS

In all the comparisons in the trial involving adolescents and adults, 20 to 25% of the patients did not have a differential outcome between treatments (Fig. 2). More adolescents and adults had a superior response with the addition of a LABA than with either of the two step-up dose increases in inhaled glucocorticoids (49% in the salmeterol–fluticasone group vs. 28% in the 2.5-fluticasone group) ($P=0.003$) (Fig. 2A), and 49% in the salmeterol–2.5-fluticasone group versus 31% in the quintuple-fluticasone group ($P=0.02$) (Fig. 2C). Differences in superior response rates were driven by differences in asthma-control days and FEV₁ (Figs. S5.2A and S5.2B and S5.3A and S5.3B in the Supplementary Appendix). Exacerbations were infrequent and contributed only minimally to the composite outcome (Fig. S5.1.A and S5.1.B in the Supplementary Appendix). Increasing the dose of glucocorticoid by either a factor of 2.5 (fluticasone propionate at a dose of 250 μ g) or a factor of 5 (fluticasone propionate at a dose of 500 μ g) (Fig. 2D) or from 100 μ g of fluticasone propionate to 250 μ g of fluticasone propionate (accompanied by a LABA) (Fig. 2E) did not result in a significantly higher percentage of patients with a superior response.

COMPARISON OF THE TWO TRIALS

In adolescents and adults, the addition of a LABA was more likely to produce superior responses than increasing the dose of an inhaled glucocorticoid. In contrast, children had a response to stepped increases in the dose of inhaled glucocorticoid (Fig. 3A, and Figs. S4 and S5 in the Supplementary Appendix).

SECONDARY OUTCOMES

The results of prespecified secondary outcomes and analyses are provided in Figures S4 and S5 and Table S8 in the Supplementary Appendix. Consistent with the trend seen in the evaluation of the composite outcome, more children had reduced asthma exacerbations with a higher dose of

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Children (5–11 Yr) (N = 280)	Adolescents and Adults (≥12 Yr) (N = 294)
Demographic features		
Age — yr	8.5±1.8	37.3±16.1
Male sex — no. (%)	170 (60.7)	95 (32.3)
Median percentage of African ancestry (IQR) [†]	81.0 (73.4–85.6)	82.1 (75.3–87.6)
Hispanic ethnic group — no. (%) [‡]	24 (8.6)	9 (3.1)
Asthma history in previous 12 mo — no. (%)		
One or more asthma episodes resulting in emergency care or unscheduled office visit	208 (74.3)	132 (44.9)
One or more overnight hospitalizations	43 (15.4)	14 (4.8)
One or more courses of systemic glucocorticoids	172 (61.4)	99 (33.7)
Medications used in previous 12 mo		
Leukotriene-receptor antagonist or 5-lipoxygenase inhibitors — no. (%)	107 (38.2)	50 (17.0)
Oral glucocorticoids — no./total no. (%)	170/277 (61.4)	92/293 (31.4)
Inhaled or nebulized glucocorticoid monotherapy — no./total no. (%)	246/279 (88.2)	193/294 (65.6)
Inhaled glucocorticoid–LABA combination therapy — no./total no. (%)	64/279 (22.9)	139/294 (47.3)
Clinical and spirometric features		
Patients with ≥1 of 13 positive tests for allergens by ImmunoCAP assay — no./total no. (%)	224/273 (82.1)	244/287 (85.0)
Sputum eosinophil level ≥2% — no./total no. (%) [§]	NA	24/220 (10.9)
Median blood eosinophil absolute count — cells/mm ³ (IQR) [¶]	340 (200–510)	200 (100–300)
Median serum total IgE — IU/ml (IQR)	286.5 (92.0–693.5)	174.0 (73.0–468.0)
FEV ₁ — % of predicted value ^{**}	95.5±16.7	83.4±17.4
Bronchodilator response (4 puffs) — % relative change ^{††}	13.79±14.48	12.47±12.43
PC ₂₀ for methacholine — mg/ml ^{‡‡}		
Geometric mean	1.32	1.71
Coefficient of variation	1.61	1.60
Median score on Childhood Asthma Control Test or Asthma Control Test (IQR) ^{§§}	22 (19–24)	19 (16–22)
Asthma-control days during 2 wk before randomization (%) ^{¶¶}	31.2±29.9	24.5±28.2

* Plus-minus values are means ±SD. FEV₁ denotes forced expiratory volume in 1 second, LABA long-acting beta-agonist, and NA not applicable.

[†] Data were missing for 15 children and 10 adolescents and adults.

[‡] Race and ethnic group were reported by the patients or their parents or guardians.

[§] Children younger than 12 years of age did not undergo sputum induction.

[¶] Data were missing for 5 children and 5 adolescents and adults.

^{||} Data were missing for 4 children and 4 adolescents and adults.

^{**} Data were missing for 5 children and 3 adolescents and adults.

^{††} Data were missing for 7 children.

^{‡‡} PC₂₀ denotes the provocative concentration of inhaled methacholine that results in a 20% reduction in the FEV₁. Data were missing for 67 children and 44 adolescents and adults.

^{§§} The score on the Childhood Asthma Control Test ranges from 0 to 27, with higher values representing better asthma control. The score on the Asthma Control Test ranges from 5 to 25, with higher values representing better asthma control. Data were missing for 1 patient in each group.

^{¶¶} Patients who provided asthma-control information on fewer than 7 of the 14 days were excluded from this summary, and data were missing for 3 children and 5 adolescents and adults.

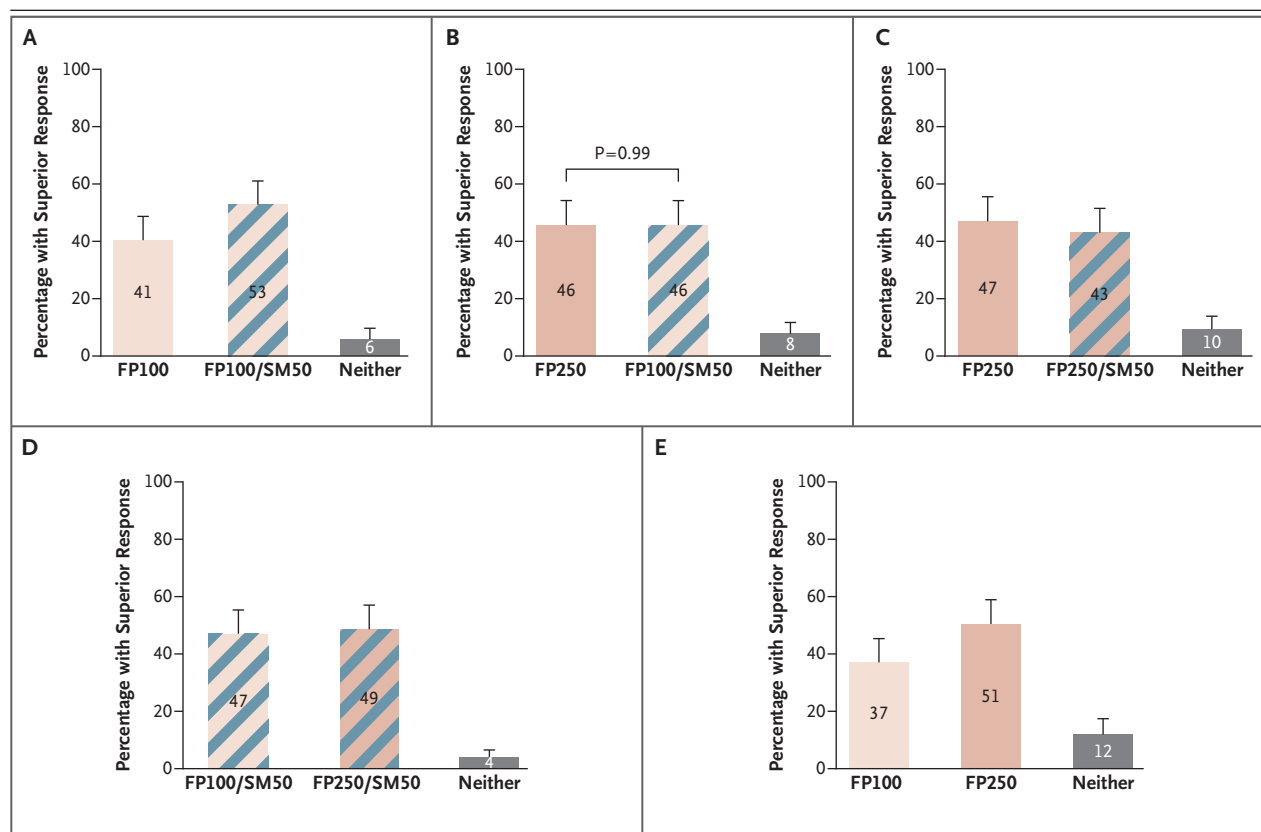


Figure 1. Percentage of Black Children (5 to 11 Years of Age) with Asthma Who Had a Superior Response to Specific Treatments, According to the Composite Outcome, at 14 Weeks.

Shown are the five prespecified comparisons of the percentages of patients with a superior response among those receiving twice-daily treatment with a low-dose inhaled glucocorticoid (fluticasone propionate) at a dose of 50 μ g (FP100, the double-fluticasone group); a dose of fluticasone doubled to 100 μ g with the addition of a LABA (salmeterol) at a dose of 50 μ g (FP100/SM50, the salmeterol–double-fluticasone group); a dose of fluticasone quintupled to 250 μ g (FP250, the quintuple-fluticasone group); or a dose of fluticasone quintupled to 250 μ g with the addition of salmeterol at a dose of 50 μ g (FP250/SM50, the salmeterol–quintuple-fluticasone group) with respect to the hierarchical composite outcome that incorporated asthma exacerbations, asthma-control days, and change in the forced expiratory volume in 1 second (FEV₁). The numbers in each bar represent the percentage of patients who had a superior response to that specific treatment, as compared with the alternative treatment. Gray bars indicate the percentage of patients in whom one treatment was not superior to the other. The P value reflects a test of the coprimary null hypothesis that the probability of a superior response to each treatment would not differ. T bars indicate 95% confidence intervals.

inhaled glucocorticoid (7%; 95% CI, 2 to 13) than with a lower-dose of inhaled glucocorticoid (2%; 95% CI, 0 to 5). Higher-dose inhaled glucocorticoids also produced greater changes in the percentage of the predicted FEV₁ before or after bronchodilator use (2.3%; 95% CI, 0.7 to 4.0) than a lower-dose inhaled glucocorticoid (1.6%; 95% CI, 0.1 to 3.0).

Adolescents and adults had more asthma-control days with the addition of a LABA than with an increase in the dose of inhaled glucocorticoid

(a 14-day-per-year difference [95% CI, 1 to 26] in the salmeterol–fluticasone group vs. the 2.5-fluticasone group and a 14-day-per-year difference [95% CI, 3 to 25] in the salmeterol–2.5-fluticasone group vs. the quintuple-fluticasone group) (Table S8 in the Supplementary Appendix). There was also an absolute difference in the percentage of the predicted FEV₁ before bronchodilator use (the salmeterol–fluticasone group vs. the 2.5-fluticasone group, 1.2 percentage points [95% CI, 0.2 to 2.3]; and the salmeterol–2.5-fluticasone

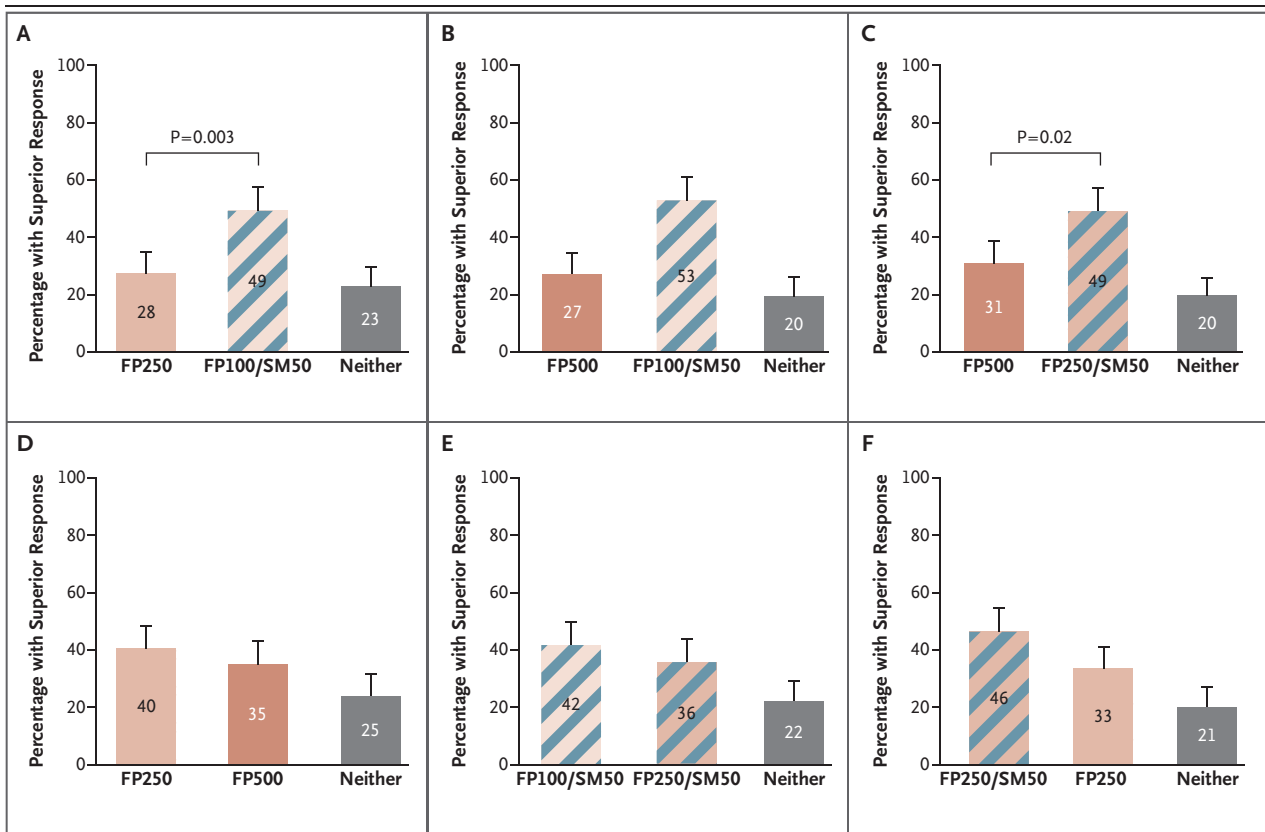


Figure 2. Percentage of Black Adolescents and Adults with Asthma Who Had a Superior Response to Specific Treatments, According to the Composite Outcome, at 14 Weeks.

Shown are all the comparisons of the percentages of patients with a superior response among those receiving twice-daily treatment with fluticasone propionate at a dose of 100 μ g plus salmeterol at a dose of 50 μ g (FP100/SM50, the salmeterol–fluticasone group); a dose of fluticasone increased by a factor of 2.5 to 250 μ g (FP250, the 2.5-fluticasone group); a dose of fluticasone quintupled to 500 μ g (FP500, the quintuple-fluticasone group); or a dose of fluticasone increased by a factor of 2.5 to 250 μ g with the addition of salmeterol at a dose of 50 μ g (FP250/SM50, the salmeterol–2.5-fluticasone group) with respect to the hierarchical composite outcome that incorporated asthma exacerbations, asthma-control days, and the absolute change in the percentage of the predicted FEV₁. The numbers in each bar represent the percentage of patients who had a superior response to that specific treatment, as compared with the alternative treatment. Gray bars indicate the percentage of patients in whom one treatment was not superior to the other. The P values reflect a test of the coprimary null hypotheses that the probability of a superior response to each treatment would not differ. T bars indicate 95% confidence intervals.

group vs. the quintuple-fluticasone group, 0.9 percentage points [95% CI, –0.1 to 1.9]) (Table S8 in the Supplementary Appendix). However, the addition of a LABA did not differentially affect asthma exacerbations, the FEV₁ after bronchodilator use, the results of the Asthma Control Test, or the results of the AQLQ.

GENETIC AFRICAN ANCESTRY AND THERAPEUTIC OUTCOMES

Among patients in both age groups, there was a broad distribution in the percentage of African ancestry, ranging from 2 to 100%, with a mean

of 81.0% in children and 82.1% in adolescents and adults (Table 1, and Fig. S6 in the Supplementary Appendix); this distribution was comparable to that in black populations in previous studies.³⁶ There were no significant interactions between the percentage of African ancestry and the primary composite outcome or any of the individual outcomes (Tables S2 and S3 in the Supplementary Appendix). We were unable to identify a cutoff for the percentage of African ancestry that was predictive of therapeutic response (Tables S4 through S7 in the Supplementary Appendix), and we did not find significant, consistent,

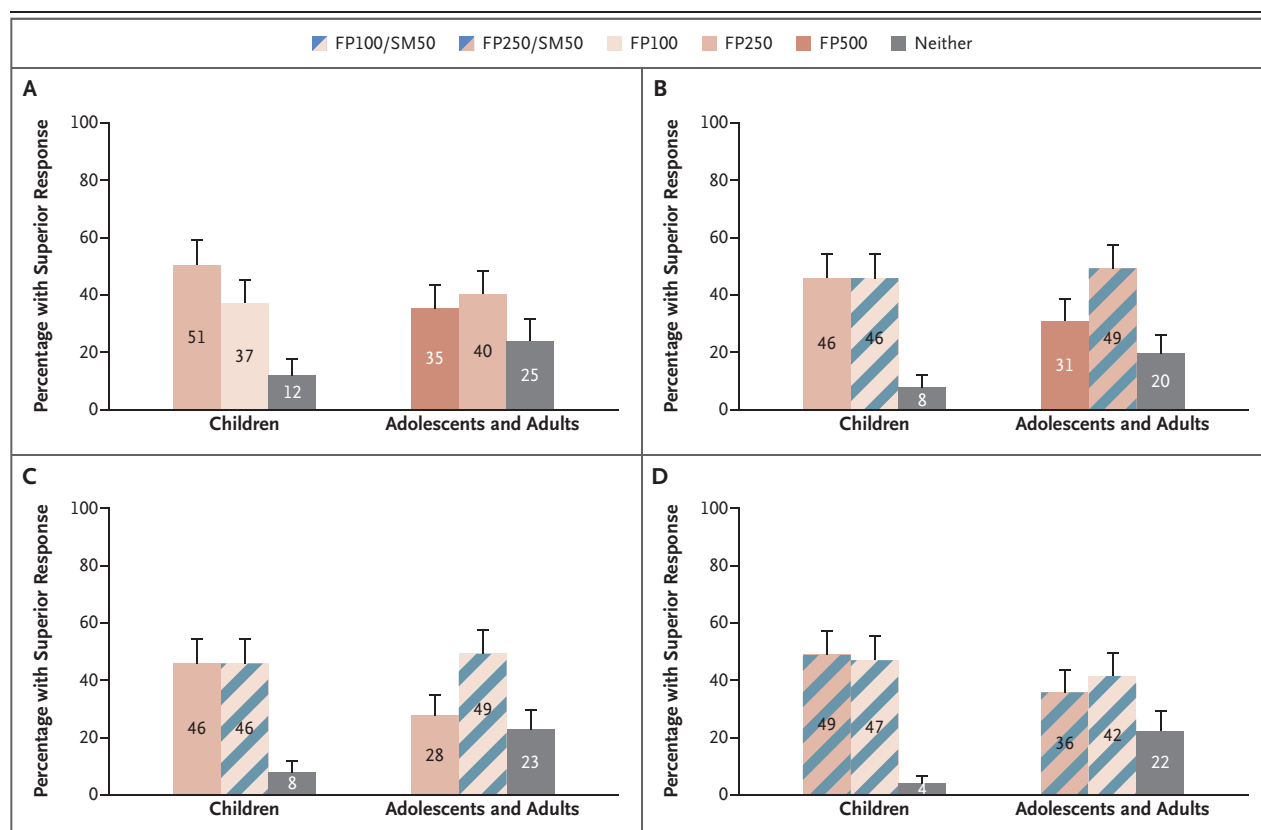


Figure 3. Comparison of the Primary Composite Outcome in the Trial Involving Adolescents and Adults and the Trial Involving Children.

Shown are the prespecified comparisons of the percentages of patients with a superior response. Each panel shows a comparison of a similar step-up in therapy for children and for adolescents and adults. Shown are responses at 14 weeks in adolescents and adults and in children who at baseline had poorly controlled asthma while receiving twice-daily treatment with a low-dose inhaled glucocorticoid (fluticasone propionate) (50 μ g in children and 100 μ g in adolescents and adults). In children, the step-up trial treatments included doubling the dose of fluticasone to 100 μ g (FP100, the double-fluticasone group); doubling the dose of fluticasone to 100 μ g and adding salmeterol at a dose of 50 μ g (FP100/SM50, the salmeterol–double-fluticasone group); quintupling the dose of fluticasone to 250 μ g (FP250, the quintuple-fluticasone group); or quintupling the dose of fluticasone to 250 μ g and adding salmeterol at a dose of 50 μ g (FP250/SM50, the salmeterol–quintuple-fluticasone group). In adolescents and adults, the step-up interventions included adding salmeterol to the baseline dose of fluticasone (FP100/SM50, the fluticasone–salmeterol group), increasing the dose of fluticasone by a factor of 2.5 (FP250, the 2.5-fluticasone group), increasing the dose of fluticasone by a factor of 2.5 and adding salmeterol (FP250/SM50, the salmeterol–2.5-fluticasone group), or quintupling the dose of fluticasone (FP 500). A superior response was determined with respect to the hierarchical composite outcome that incorporated asthma exacerbations, asthma-control days, and the change in the FEV₁. The numbers in each bar represent the percentage of patients who had a superior response to that specific treatment as compared with the alternative treatment. Gray bars indicate the percentage of patients in whom one treatment was not superior to the other. The two groups of patients (patients from the trial involving children and those from the trial involving adolescents and adults) were compared to identify interactions between the two groups and the composite superiority outcome. T bars indicate 95% confidence intervals.

meaningful associations between African ancestry and the treatment response when the extremes of ancestry were compared (Figs. S7.1 and S7.2 in the Supplementary Appendix).

For the primary composite outcome in both trials, none of the prespecified biomarkers or patient characteristics identified a group of patients who were more likely to have a response to the addition of one therapy than to another.

SAFETY

In the trial involving children, the highest dose of inhaled glucocorticoid (250 μ g twice daily) was associated with a decrease in the ratio of urinary cortisol to creatinine in those who were younger than 8 years of age (Table S9 in the Supplementary Appendix), whereas no such effects were seen in adolescents and adults. There were no other significant differences among the treatment groups

in either trial with respect to respiratory tract infections or pneumonia.

DISCUSSION

Studies involving children and adults with asthma have been conducted primarily in white populations; these studies have shown that when escalating asthma therapy, the addition of a LABA is more likely to produce a superior response than an increase in the dose of an inhaled glucocorticoid.⁵⁻⁸ These data have influenced guidelines regarding escalation of therapy when patients present with asthma that is not well controlled; however, black patients with asthma have not been included in the clinical trials on which the guidelines were based.^{10,11,13-16}

In the current trials, almost half the children who had at least one grandparent who identified as black and who had poorly controlled asthma (46%) had improved asthma outcomes when the dose of inhaled glucocorticoid was increased rather than with the addition of a LABA. Furthermore, we discovered that in contrast to both black adults and white adults and white children, black children had a response to stepped increases in the dose of inhaled glucocorticoid. Our results are all the more striking in that in our parallel trial we confirmed that adolescents and adults who had at least one grandparent who identified as black had responses similar to those reported in white adults — that is, the addition of a LABA in adults was more likely to lead to superior responses in a larger group of patients than an increase in the dose of an inhaled glucocorticoid. These findings suggest that data cannot be extrapolated from clinical trials involving mixed populations to specific subgroups, including those of different ages and races.

We found that larger percentages of children than had been previously reported in mixed populations had a response to increasing doses of glucocorticoids than to the addition of a LABA.⁸ Although a recent trial involving predominantly white children with mild-to-moderate persistent asthma showed that quintupling the dose of inhaled glucocorticoids for 7 days at the early signs of loss of asthma control was not better in preventing exacerbations than maintaining the use of low-dose inhaled glucocorticoids,³³ that trial involved short-term administration of higher-dose inhaled glucocorticoids in patients with acute de-

terioration of asthma and thus is not comparable to our trials examining the effects of long-term treatment.

We found evidence of adrenal axis suppression in young children (<8 years of age) (Table S9 in the Supplementary Appendix) at the highest dose of inhaled glucocorticoid we tested (fluticasone propionate at a dose of 250 μ g). Our trial was not long enough to assess effects on growth. However, the findings with regard to the adrenal axis at high doses of inhaled glucocorticoids are of potential concern, although it is not clear how our findings would extrapolate to other formulations of inhaled glucocorticoids.

African ancestry, as determined by patterns of genetic markers, has been associated with asthma-related phenotypes including low lung function and exacerbations.³⁶⁻³⁸ However, we did not find that African ancestry was associated with differential responses in adolescents and adults or with differential responses in children (Figs. S7.1 and S7.2 in the Supplementary Appendix). Nevertheless, the absence of a global ancestral effect does not exclude potential effects of either asthma severity loci or pharmacogenetic loci differentially inherited among persons across varying ancestral backgrounds.²¹⁻²⁷ We were also not able to detect phenotypic or biomarker characteristics that were associated with a differential response to a specific therapy. A larger trial might have the power to determine which phenotypic or specific pharmacogenetic variant panels could have the power to detect such differences.

In conclusion, our prospective, randomized BARD trials comparing several strategies of treatment escalation for asthma in children and in adolescents and adults who had at least one grandparent who identified as black showed that outcomes differed in children and adults, and the results in these children differed from those previously reported in studies involving white children. In contrast to black adults and white persons of all ages, almost half the children who had at least one grandparent who identified as black and who had poorly controlled asthma had a superior response to an increased dose of an inhaled glucocorticoid over the addition of a LABA. A larger, more simplified trial should be undertaken to determine the best treatment approach for black children with poorly controlled asthma despite the use of standard doses of an inhaled glucocorticoid.

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APPENDIX

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Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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Supplementary Appendix

STEP-UP THERAPY IN BLACKS WITH INADEQUATELY CONTROLLED ASTHMA

Michael E. Wechsler, Stanley J. Szeffler, Victor E. Ortega, Jacqueline Pongracic, Vernon Chinchilli, John J. Lima, Jerry A. Krishnan, Susan J. Kunselman, David Mauger, Eugene R. Bleecker, Leonard B. Bacharier, Avraham Beigelman, Mindy Benson, Kathryn Blake, Michael Cabana, Juan Carlos Cardet, Mario Castro, James F. Chmiel, Ronina Covar, Loren Denlinger, Emily DiMango, Anne M. Fitzpatrick, Deborah Gentile, Nicole Grossman, Fernando Holguin, Daniel Jackson, Monica Kraft, Craig LaForce, Stephen C. Lazarus, Robert F. Lemanske Jr., Dayna Long, Njira Lugogo, Fernando Martinez, Deborah A. Meyers, Wendy C. Moore, James Moy, Edward Naureckas, J. Tod Olin, Stephen P. Peters, Wanda Phipatanakul, Loretta Que, Hengameh Raissy, Rachel Robison, Kristie Ross, William Sheehan, Lewis J. Smith, Julian Solway, Christine A. Sorkness, Lisa Sullivan Vedder, Sally Wenzel, Steve White, and Elliot Israel on behalf of the NHLBI AsthmaNet

**STEP-UP THERAPY IN BLACKS WITH INADEQUATELY CONTROLLED ASTHMA:
THE NHLBI BARD TRIAL**

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1. Selected Methods

SECTION 1: INCLUSION AND EXCLUSION CRITERIA TO ENTER RUN-IN

A. Inclusion criteria at Screen Visit A (to enter run-in)

1. Male and female participants, age 5 years and above at enrollment.
2. Individuals who self-report Black ancestry (with at least 1 Black grandparent). Hispanics with at least 1 Black grandparent may be enrolled. Participants who have 1 Black grandparent but who do not necessarily self-identify as Black may also be enrolled.
3. Able to perform reproducible spirometry according to ATS criteria.
4. Able to perform valid peak flow maneuver using the SpiroTel® device.
5. Clinical history consistent with asthma.
6. Baseline FEV₁ ≥ 40% of predicted and/or post-bronchodilator FEV₁ ≥ 40% of predicted (post 4 puffs of albuterol at Screen Visit A).
7. Asthma was confirmed either by: (1) Beta-agonist reversibility to 4 puffs albuterol ≥ 12% OR (2) PC₂₀FEV₁ ≤ 16 mg/ml (if FEV₁ ≥ 55% predicted and ≥ 1.0 liter at baseline in adults or ≥ 70% in participants younger than 18) OR (3) an absolute relative change in %predicted FEV₁ of ≥ 12% over two measurements documented by repeat spirogram over the previous year and done at an AsthmaNet performance site.
(Participants held albuterol, montelukast, theophylline, ipratropium bromide (or other anticholinergics) and long-acting beta-agonists per instructions in the MOP prior to reversibility testing. Thus, if a participant was receiving these types of medications prior to Screen Visit A, he or she was brought back to the performance site after following appropriate medication withholding to attempt qualification by reversibility criteria. If the participant did not meet this requirement, he/she might have qualified if methacholine PC₂₀ is ≤ 16 mg/ml at Screen Visit B. Historical evidence of reversibility or methacholine PC₂₀ was used to meet the inclusion criteria if the source documentation was less than 1 year old and from one of the AsthmaNet performance sites and was performed using AsthmaNet equipment, procedures, and methacholine. All participants performed reversibility testing at Screen Visit A, regardless of source documentation status; all participants who qualified to perform methacholine challenge at Screen Visit B will perform the procedure, regardless of source documentation status.)
8. To enter the run-in, participants were either: A) inadequately controlled on low-, medium- or high-dose ICS monotherapy, or low- or medium-dose ICS/LABA, or B) well-controlled on low-, medium- or high-dose ICS monotherapy, or low-, medium- or high-dose ICS/LABA (see Study Visits, Screen A, at -10 weeks). Participants who required a 2 step step-down were first stepped down to 2-2.5xICS dose for 2 weeks to assess control, as noted below. For purposes of assessing this criterion, inadequate asthma control was defined as an ACT/c-ACT score <20; well-controlled asthma was defined as an ACT/c-ACT score ≥20.
9. Stable asthma controller therapy dose (ICS or ICS/LABA) for the 2 weeks prior to Screen Visit A.

10. Non-smoker (total lifetime smoking history < 5 pack-years if <18, or <10 pack-years if ≥18 years of age; no smoking for at least 1 year).
11. For participants ≥18 years of age: Ability to provide informed consent, as evidenced by signing a copy of the consent form approved by the Institutional Review Board of the participant's respective study institution.
- For participants under 18 years of age: Ability of parent to provide informed consent, as evidenced by signing a copy of the consent form approved by the Institutional Review Board of the participant's respective study institution. Verbal or written assent by the study participant was documented according to local institutional guidelines.

B. Exclusion Criteria at Screen Visit A (to Enter Run-In)

1. Inadequately controlled (per NAEPP guidelines criteria) on high dose ICS/LABA (e.g. Advair 500/50 BID). For purposes of assessing this criterion, inadequate asthma control was defined as an ACT/c-ACT score <20; well-controlled asthma was defined as an ACT/c-ACT score ≥20.
2. Medical contraindication to LABA or history of adverse reactions to ICS or LABA preparations or any of their ingredients.
3. Unwilling to provide a blood sample for DNA extraction and genetic analysis (part of co-primary aims of the study).
4. Major medical problems prohibiting study participation, i.e. presence of chronic or active lung disease other than asthma or history of unstable significant medical illness other than asthma, including thyroid disease, diabetes mellitus, Cushing's disease, Addison's disease, hepatic disease, or concurrent medical problems that could require oral glucocorticoids during the study or that would place the participant at increased risk.
5. Systemic corticosteroid treatment for any condition within 4 weeks of enrollment at Screen Visit A.
6. Current or prior use of medications known to significantly interact with corticosteroid disposition within the two-week period preceding Screen Visit A, including but not limited to: carbamazepine, erythromycin or other macrolide antibiotics (chronic use of macrolides excluded; intermittent use allowed with 2-week washout prior to Screen Visit A), phenobarbital, phenytoin, rifampin, and ketoconazole.
7. History of significant asthma exacerbation requiring systemic glucocorticoids within 4 weeks of Screen Visit A or more than five courses of systemic glucocorticoids in the past year.
8. History of a life-threatening asthma exacerbation requiring intubation, mechanical ventilation, or resulting in a hypoxic seizure within the last 2 years.
9. History of a respiratory tract infection within 2 weeks of Screen Visit A.
10. Evidence that the participant (or family, in case of pediatric participants) may be nonadherent, or may move from the performance site area before trial completion.
11. Inability to perform study procedures.
12. If a female of child-bearing potential, failure to practice abstinence or use an acceptable birth control method.
13. Pregnancy or lactation or planning to get pregnant during the course of the trial.

14. Receiving hyposensitization therapy other than an established maintenance regimen defined as a continuous regimen for ≥ 3 months prior to enrollment.
15. Participation in an intervention trial or use of investigative drugs in the past 30 days or plans to enroll in such a trial during the study.
16. Chronic use of any medication other than beta-agonists or inhaled glucocorticoids, except the following:
- a. oral contraceptives and other hormonal forms of contraceptives (i.e., DepoProvera-7, Norplant-7)
 - b. estrogen / progesterone replacement therapy for post-menopausal women
 - c. vitamins and calcium supplements
 - d. any nasal inhaled corticosteroid used at a stable dose throughout the entire study beginning at Screen Visit A
 - e. acetaminophen
 - f. non-steroidal anti-inflammatory medications (e.g., aspirin, naproxen, ibuprofen, Cox-2 inhibitors)
 - g. thyroid replacement medications
 - h. lipid-lowering medication
 - i. stable dose medical therapy for well-controlled hypertension and well-controlled diabetes, except those meds specifically excluded in the protocol (Table 4)
 - j. medium and low potency topical cutaneous steroids
 - k. nasal saline spray
 - l. topical eye preparations for allergic eye symptoms (e.g. antihistamines, NSAIDs, or antiallergic compounds)
 - m. diuretics and specific antihypertensives (e.g. calcium channel blockers, clonidine, etc.)
 - n. acyclovir
 - o. antihistamines (48 hour washout for oral medications and 6 hour washout for nasal and ocular medications)
 - p. pseudoephedrine and oxymetazoline and other decongestants (48 hour washout for oral medications and 6 hour washout for nasal medications)
 - q. antibiotics for acne
 - r. stool softeners and bulk laxatives
 - s. H2 blockers and proton pump inhibitors for GERD
 - t. Imitrex for migraines
 - u. non-macrolide antibiotics
 - v. macrolide antibiotics used intermittently to treat acute adverse events
 - w. Propecia (finasteride)
 - x. SSRI class antidepressants
 - y. non-SSRI antidepressants
 - z. migraine analgesics (e.g., butalbital)
 - aa. antianxiety agents
 - bb. ACE inhibitors
 - cc. Librax
 - dd. CNS stimulants/appetite suppressants

SECTION 2: INCLUSION AND EXCLUSION CRITERIA PRIOR TO RANDOMIZATION

Randomization criteria (after run-in with low-dose ICS (1xICS))

Participants were randomized if they demonstrated compliance with study medications, e-diary completion, and PEF performance and lack of acceptable control of asthma during the run-in period (see below).

A. Inclusion Criterion for Randomization: Lack of Acceptable Asthma Control in Run-In Period

For individuals aged 12 and older at enrollment, the run-in period consisted of open-label treatment with 1 inhalation twice daily of FP 100 ug/inhalation. For children 5-11 at enrollment, the run-in period consisted of treatment with 1 inhalation twice daily of FP 50 ug/inhalation.

Lack of acceptable asthma control during the run-in period was defined as:

1. On more than 2 days per week for any 1 week period during the run-in, one or more of the following (rolling 1 week periods were used to assess this criterion using data stored in the participant's SpiroTel® e-diary):
 - a. Asthma symptoms (shortness of breath, wheezing, chest tightness, phlegm/mucus rated as mild, moderate or severe, or cough rated as moderate or severe)
 - b. Use of inhaled bronchodilator for symptom rescue (≥ 1 puff) (does not include pre-exercise prophylactic treatment)
 - c. Reduced peak expiratory flow (i.e. Peak flows in the red or yellow zone [$< 80\%$ of the current PEF reference])
 1. If, at any time, the PEF reference value was lower than 50% of the predicted PEF calculated using published equations based on age, height, sex and race (as per AsthmaNet Spirometry Manual of Procedures), then the PEF reference value was set to 50% of the predicted PEF.

OR

2. More than 1 night with awakening(s) due to asthma in a 2-week period

To be eligible for randomization, individuals:

1. met the definition of lack of acceptable asthma control above during any 1-week block (symptoms, rescue use, PEF) or 2-week block (nighttime awakenings) on 1xICS study medications

AND

2. demonstrated adherence with taking study medications ($\geq 75\%$ of scheduled doses) and completing e-diaries and PEFs ($\geq 75\%$ of days) during the visit interval during which lack of control criteria were met

B. Exclusion Criteria for Randomization

Participants who had an exacerbation on low dose ICS (1xICS) during the run-in period (i.e. worsening asthma symptoms resulting in treatment with systemic glucocorticoids-see exacerbation definition in **Section III** below) was eligible for randomization after the exacerbation if appropriately treated with a 5-day course of prednisone. The participant remained on 1xICS during and following treatment of the exacerbation and was eligible to be randomized 14 days (+7 day window) following the final dose of prednisone, unless the exacerbation was severe and required hospitalization. In that case, the participant was terminated from further participation in the trial due to safety concerns.

If a participant experienced a second exacerbation that did not result in hospitalization on low dose ICS during the run-in, the same procedures applied with respect to prednisone treatment and randomization.

If a participant experienced a third exacerbation requiring treatment with prednisone during the run-in, then he or she was terminated from further participation in the trial due to safety concerns.

As noted above, individuals who were in the 2 step step-down group who experienced an exacerbation while on 2-2.5xICS or have an ACQ score ≥ 1.5 at Screen Visit A1 were ineligible for further study participation.

Thus, exclusion criteria for randomization included any of the following:

1. Inadequate adherence ($< 75\%$ of expected medication doses taken or $< 75\%$ of diary recordings and PEFs completed)*
2. Asthma exacerbation requiring hospitalization during the run-in
3. Three significant asthma exacerbations on 1xICS during the run-in
4. For those requiring 2 step step-down: Asthma exacerbation while on 2-2.5xICS during the run-in or ACQ score ≥ 1.5 at Screen Visit A1

Section 3. Select Definitions

Asthma Control days

Asthma Control Day (ACD) was defined as a day without:

1. Albuterol rescue use (pre-exercise treatment permitted)
2. Use of non-study asthma medications including oral steroids. In addition, the 7 days immediately following the end of a course of oral steroids were considered non-ACDs.
3. Daytime or nighttime asthma symptoms (wheezing, coughing, phlegm/mucus, chest tightness, or shortness of breath)
4. Unscheduled health care provider visits for asthma, emergency room visit or hospital admission for asthma, or missed work or school due to asthma
5. AM or PM peak flow less than 90% of the analysis PEF reference value defined as: Average AM PEF from the run-in week (7 days) most proximal to randomization Visit 1 that met the definition as a 'lack of acceptable asthma control' week on the basis of rescue use, asthma symptoms, or PEF as defined in **Section VII.A**. If the participant qualified for randomization on the basis of nighttime awakenings alone, then the reference was the average AM PEF from the week (7 days) prior to the awakening that occurred most proximal to Visit 1. In the unlikely event that the participant qualified for randomization on the basis of having had an asthma exacerbation during the run-in, and he or she did not experience an uncontrolled week or meet the nighttime awakenings definition of 'lack of control', then the reference PEF was the average AM PEF from the week (7 days) prior to the first dose of prednisone used to treat the exacerbation. If an individual experienced two exacerbations prior to randomization, then the reference was the average AM PEF from the week (7 days) prior to the first dose of prednisone used to treat the first exacerbation.

Asthma Exacerbation

In this study an asthma exacerbation was defined according to the recommendation of the NIH Outcomes Workshop as a worsening of asthma requiring the use of a systemic corticosteroid to prevent a serious outcome.⁴⁸ In accordance with the Expert Panel recommendations, data was captured on the following exacerbation-related outcomes:

1. All worsening asthma events in which systemic glucocorticoids were initiated to prevent a serious outcome, including use of systemic glucocorticoids in association with any form of healthcare provider encounter
2. All asthma-specific emergency department or urgent care visits that involved treatment with systemic glucocorticoids
3. All asthma-specific hospitalizations that involved treatment with systemic glucocorticoids (also reported as a serious adverse event)

346 4. All asthma-specific intensive care unit admissions or intubations (also reported as
347 a serious adverse event)

348 5. All deaths (all cause and asthma-related; also reported as a serious adverse event)

349 For the purpose of this study, and to standardize our approach among AsthmaNet
350 studies, two courses of systemic glucocorticoids were separated by at least one week to
351 count as two exacerbations and were documented as such.

SECTION 4: MASKING

To minimize the bias due to possible knowledge of the sequence assignment, the study was double-blinded. Thus, the investigators and the participants did not know which treatments are being administered during the treatment periods. Further, key personnel at the DCC remained blinded through study implementation and analysis phases. This included the data managers, scientific coordinators, and statisticians. Only the project coordinator and a database programmer had access to the unblinding documentation while the trial was being implemented and the data being analyzed for the primary publication.

SECTION 5: PHENOTYPING AND SPECIAL STUDY TECHNIQUES

A. Description of Selected Phenotypes

Participants were extensively phenotyped during screening and during the post-randomization visits to assess predictors of response to each treatment. Phenotyping included, but was not limited to, spirometry, airway hyperresponsiveness (if participant met safety requirements for methacholine challenge), bronchodilator response after 4 puffs albuterol, extensive questionnaires to capture full participant history, medication history, family history, smoking history, exposures, atopic status, presence of co-morbid conditions, and number and severity of exacerbations. Urine, sputum supernatant, serum, plasma and DNA was also collected and stored for future predictor analysis.

1. Bronchodilator reversibility – The bronchodilator reversibility procedure is detailed in the AsthmaNet Spirometry Manual of Operations and included 4 puffs of albuterol.
2. Methacholine bronchoprovocation – The methacholine bronchoprovocation procedure is detailed in the AsthmaNet Methacholine Challenge Manual of Operations.
3. ImmunoCAP – ImmunoCAP testing of standard allergens was performed at Visit 1 and included at a minimum: rat, grass mix, tree mix, weed mix, mite mix, cockroach mix, mouse, penicillium/alternaria/aspergillus/cladosporium (mold mix), cat, dog.
4. Genetics analysis – Blood was obtained at the study site from the participant and shipped to the AsthmaNet Genetics Lab in Tucson, AZ for DNA extraction and storage according to AsthmaNet procedures. DNA was prepared and shipped to the laboratory of the Wake Forest site for study analysis. The use of genetic data was limited to analysis related to drug response, drug metabolism, allergy, asthma and inflammation, including genetic ancestry-based analyses of participant responses to medications.
5. Blood, urine, and sputum samples – Blood (including serum), urine, and sputum was collected and stored for future analyses of biomarkers in these specimens considered directly relevant to asthma and allergies. This will also provide a means to assess whether certain asthma and allergy genes have the potential of increasing or decreasing proteins in these compartments to gain new insights into pathophysiologic mechanisms underlying these diseases. For example, sputum eosinophils in those 12 and above will be measured, as these have been shown to predict asthma control in the context of inhaled corticosteroid use.⁴⁹ Cotinine levels were also measured to assess smoking exposure.

B. Sputum Induction

Sputum induction is a relatively simple, repeatable and noninvasive method of collecting airway secretions. Cellular and biochemical analyses of induced sputum samples collected from asthmatic and non-asthmatic subjects have revealed differences in markers of eosinophilic inflammation and bronchovascular permeability in an asthmatic population. Induced sputum was collected at Visit 1 following inhalation of hypertonic saline according to the AsthmaNet Sputum Induction MOP. Sputum total and differential cell counts were counted by a central reader at the San Francisco adult site. Cell free supernatant and cell pellets were frozen and stored for future analysis. Each participant performed one sputum induction at baseline to

408 assess whether sputum indices can predict response in Blacks. Of note, as sputum
409 induction cannot be done reliably in children down to age 5-6, this procedure was
410 performed only in individuals at least 12 years of age.
411

SECTION 6: RANDOMIZATION

The target sample size for the BARD trial was 291 Black adolescents/adults (ages 12 and older) and 284 Black children (ages 5-11). Each participant's age group was defined at his/her enrollment visit, Screen Visit A. Individuals who were ages 5-11 at enrollment were placed in the child track for data purposes and continued to be treated according to the procedures for children for the duration of their trial participation.

This study incorporated a design in which each participant received each of four treatment regimens over four 14-week periods (known as a four-way crossover design). For adolescents/adults, if we denote the four treatment regimens as A, B, C, and D, then each BARD adult/adolescent was randomized to one of the following four treatment sequences:

ABCD, BDAC, CADB, DCBA

For children, if we denote the four treatment regimens as E, F, G, and H, then each BARD child was randomized to one of the following four treatment sequences:

EFGH, FHEG, GEHF, HGFE

Because BARD invoked a four-way crossover design, a stratified randomization based on prognostic factors was not critical. Instead, we only invoked clinical center partnership within age group at enrollment (adolescents/adults, children) as a stratifying variable with permuted blocks of size four (one complete cycle of the four treatment sequences). When a participant at a particular performance site was deemed eligible for the study at Visit 1, the Clinic Coordinator accessed the AsthmaNet server and indicated to the system that a participant required randomization. After entering the pertinent information with respect to clinical center partnership and eligibility criteria, the Clinic Coordinator was asked to verify that all of the entered information was correct. If so, the Clinic Coordinator was given the number of a blinded Diskus to dispense to the participant. At all post-randomization visits the coordinator accessed the randomization module to generate the number of a new Diskus that contained the regimen consistent with the participant's randomized drug sequence. Some visit intervals were long enough in duration to require the dispensation of two Diskuses, each with its own unique number. In order to maintain security of the randomization schedules, DCC data management and coordination staff automatically received a notice from the AsthmaNet server that a participant was randomized and/or had a new Diskus number generated.

SECTION 7: STATISTICAL ANALYSIS

A. Primary Outcome

The primary outcome was a hierarchical asthma measure that used exacerbations, then asthma control days (ACDs), and then %predicted FEV1 at the end of the 14-week treatment regimen to determine if there were differences in response. A difference in response was defined as (1) 1 exacerbation, (2) 31 annualized ACDs, or (3) a 5% or more difference in % predicted FEV1 which sequentially determined the superior therapy as a composite primary outcome. This composite outcome and its three components were fit into nonlinear mixed-effect models for each pair of treatment comparisons. Treatments were first compared to determine if they differed in terms of exacerbations. If one treatment resulted in fewer exacerbations than an alternate treatment, then the former was classified as the superior treatment. If none of the treatments for a specific participant was superior in terms of exacerbations, then his/her responses were compared by ACDs. If the annualized ACDs did not differ within a participant across the different treatments, then we assessed %predicted FEV1 differences across treatments. If no treatment superiority could be assigned based on FEV1, then the participant was classified as having “no preference”. For each BARD participant, we compared the response between pairs of treatment regimens based on the data from the latter 12 weeks of each treatment periods.

B. Comparisons of Primary and Secondary Analyses

In the pediatric (5-11) BARD study, the following therapies are studied:

- 2xICS (FP 100)
- 2xICS +LABA (FP/SAL 100/50)
- 5xICS (FP 250)
- 5xICS + LABA (FP/SAL 250/50)

The primary comparison to compare addition of LABA vs addition of ICS is:

- ICS/LABA 100/50 vs FP 250

and other secondary comparisons to compare different doses of ICS are:

- FP 100 vs FP 250
- ICS/LABA 100/50 vs ICS/LABA 250/50

In the adult/adolescent BARD study, the following therapies are studied:

- 1xICS +LABA (FP/SAL 100/50)

- 2.5xICS (FP 250)
- 2.5xICS + LABA (Advair 250/50)
- 5xICS (FP 500)

The primary comparisons to compare addition of LABA vs addition of ICS are:

- FP/SAL 100/50 vs FP 250
- FP/SAL 250/50 vs FP 500

and other secondary comparisons to compare different doses of ICS are:

- FP/SAL 100/50 vs FP/SAL 250/50
- FP 250 vs FP 500

We also performed the following secondary comparisons that allow us to compare the effect of adding a LABA to an ICS, and quintupling ICS, in Blacks:

In children:

- FP 100 vs FP/SAL 100/50
- FP 250 vs FP/SAL 250/50

In adults/adolescents:

- FP 250 vs FP/SAL 250/50
- FP 500 vs FP/SAL 100/50

C. Statistical Models for Determining Superiority Between Treatment Groups

We displayed descriptive statistics in the form of frequencies and percentages for binary variables, means with standard deviations for continuous variables, and quartiles or geometric means with coefficients of variations. We fit a nonlinear mixed-effects model to analyze the primary composite outcome and its three components. Let $Y_{i,AB}$ denote the outcome for comparing treatment regimen A to treatment regimen B for the i th study participant. $Y_{i,AB}$ equals +1, 0, or -1 according to whether A is deemed to be superior, equivalent, or inferior to B , respectively, for the i^{th} study participant.

The former represents the log odds of A superiority relative to B superiority for the i^{th} study participant, and the latter represents the log odds of a treatment preference for the i^{th} study participant. We then construct regression models for these two log odds ratio functions that include (1) fixed effects for clinical center partnership, season of treatment administration, and percentage of African ancestry, and (2) random effects for the i^{th} study participant. After fitting the models, we then transformed the estimated log odds ratios into estimated probabilities for each study participant for descriptive and graphing purposes.] We performed secondary statistical analyses by investigating additional regressors including gender, baseline PC20, bronchodilator response, blood eosinophils, sputum neutrophils, sputum eosinophils, immunoglobulin E (IgE), history of eczema, use of systemic steroids during the prior 12 months, asthma exacerbation during the prior 12 months, household education, and household income.

D. Statistical Methods for Evaluation of Ancestry

Ancestry-based genetic analyses evaluated the association of percentage African ancestry with the trinomial composite outcome variable via the nonlinear mixed-effects models with trinary logistic regression as (1) a continuous regressor, (2) a three-dimensional receiver operating characteristic curve to determine the two optimal cutpoints, or (3) partitioned into two extreme ancestry groups below the 40th and above the 60th percentiles.^{50,51}

E. Nonlinear Mixed-effects Model

The full description of the nonlinear mixed-effects model with an embedded multinomial logistic regression is as follows:

Let A, B, C , and D denote the four treatment regimens (either for adolescents/adults or for children). For the A vs B treatment regimen comparison within the i^{th} BARD participant, $i = 1, 2, \dots, N$, define the primary outcome as

$$Y_{i,AB} = \begin{cases} +1, & \text{if } A > B \\ 0, & \text{if } A \approx B \\ -1, & \text{if } A < B \\ ., & \text{if missing} \end{cases}$$

where “ $>$ ” indicates superiority, “ $<$ ” indicates “inferiority”, “ $\approx$ ” indicates equivalence, and “.” indicates that the treatment regimen comparison was not possible due to incomplete or missing data. Thus, there are six realizations of the primary outcome for the i^{th} BARD participant, $i = 1, 2, \dots, N$, namely, $Y_{i,AB}, Y_{i,AC}, Y_{i,AD}, Y_{i,BC}, Y_{i,BD}, Y_{i,CD}$.

We construct three logit functions for the A vs B comparison within the i^{th} BARD participant, $i = 1, 2, \dots, N$ as follows:

$$\mu_{i,AB(1)} = \log_e \left\{ \frac{\Pr [Y_{i,AB} = +1]}{\Pr [Y_{i,AB} = -1]} \right\}$$

$$\mu_{i,AB(2)} = \log_e \left\{ \frac{\Pr [Y_{i,AB} = +1 \text{ or } -1]}{\Pr [Y_{i,AB} = 0]} \right\}$$

$$\mu_{i,AB(3)} = \log_e \left\{ \frac{\Pr [Y_{i,AB} = +1, 0, \text{ or } -1]}{\Pr [Y_{i,AB} = .]} \right\}$$

The first logit represents the comparison of A superiority versus B superiority. The second logit represents the comparison of a superiority determination versus no superiority determination. The third logit represents the comparison of a non-missing observation versus a missing observation.

For each of the three logits for the i^{th} BARD participant, $i = 1, 2, \dots, N$, we construct a linear combination of fixed and random effects as

$$\mu_{i,AB(1)} = \alpha_{AB(1)} + \mathbf{X}_{i,AB}^T \boldsymbol{\beta}_{AB(1)} + \mathbf{Z}_{i,AB}^T \boldsymbol{\gamma}_{i,AB(1)}$$

$$\mu_{i,AB(2)} = \alpha_{AB(2)} + \mathbf{X}_{i,AB}^T \boldsymbol{\beta}_{AB(2)} + \mathbf{Z}_{i,AB}^T \boldsymbol{\gamma}_{i,AB(2)}$$

$$\mu_{i,AB(3)} = \alpha_{AB(3)} + \mathbf{X}_{i,AB}^T \boldsymbol{\beta}_{AB(3)} + \mathbf{Z}_{i,AB}^T \boldsymbol{\gamma}_{i,AB(3)}$$

where

- $\alpha_{AB(1)}$, $\alpha_{AB(2)}$, and $\alpha_{AB(3)}$ represent fixed-effect intercept parameters for the A versus B treatment regimen comparison
- $\mathbf{X}_{i,AB}^T$ contains fixed-effect regressors, which for the primary analyses include partnership effects and seasonal effects
- $\boldsymbol{\beta}_{AB(1)}$, $\boldsymbol{\beta}_{AB(2)}$, and $\boldsymbol{\beta}_{AB(3)}$ represent fixed-effect parameters
- $\mathbf{Z}_{i,AB}^T$ contains random-effect regressors
- $\boldsymbol{\gamma}_{AB(1)}$, $\boldsymbol{\gamma}_{AB(2)}$, and $\boldsymbol{\gamma}_{AB(3)}$ represent random-effect parameters with multivariate normal distributions, which for the primary analyses consist of three independent random effects corresponding to the three logits, and common random effects across the six pairwise treatment regimen comparisons:
 - $Y_{AB(1)} = Y_{AC(1)} = Y_{AD(1)} = Y_{BC(1)} = Y_{BD(1)} = Y_{CD(1)}$
 - $Y_{AB(2)} = Y_{AC(2)} = Y_{AD(2)} = Y_{BC(2)} = Y_{BD(2)} = Y_{CD(2)}$
 - $Y_{AB(3)} = Y_{AC(3)} = Y_{AD(3)} = Y_{BC(3)} = Y_{BD(3)} = Y_{CD(3)}$

This nonlinear mixed-effects model with an embedded multinomial regression is based on an MAR mechanism because the third logit is a function of the observed data. The likelihood contribution of the i^{th} BARD participant, $i = 1, 2, \dots, N$, for the A versus B treatment regimen comparison is

$$\begin{aligned} I(Y_{i,AB} = +1) & \left\{ \frac{1}{1 + \exp(-\mu_{i,AB(1)})} \right\} \left\{ \frac{1}{1 + \exp(-\mu_{i,AB(2)})} \right\} \left\{ \frac{1}{1 + \exp(-\mu_{i,AB(3)})} \right\} + \\ I(Y_{i,AB} = 0) & \left\{ 1 - \frac{1}{1 + \exp(-\mu_{i,AB(2)})} \right\} \left\{ \frac{1}{1 + \exp(-\mu_{i,AB(3)})} \right\} + \\ I(Y_{i,AB} = -1) & \left\{ 1 - \frac{1}{1 + \exp(-\mu_{i,AB(1)})} \right\} \left\{ \frac{1}{1 + \exp(-\mu_{i,AB(2)})} \right\} \left\{ \frac{1}{1 + \exp(-\mu_{i,AB(3)})} \right\} + \end{aligned}$$

$$I(Y_{i,AB} = .) \left\{ 1 - \frac{1}{1 + \exp(-\mu_{i,AB(3)})} \right\}$$

where $I(\cdot)$ denotes the indicator function yielding 1 or 0 depending on whether the event is or is not true. The maximization of the likelihood function leads to marginal fixed effects because the random effects are integrated out.

The maximum likelihood estimates (and their 95% confidence intervals) of the adjusted intercept parameters and the inter-participant variances for the random effects for the first two logits are displayed in the following tables.

Adolescents/Adults – Intercept Parameters for Logit #1

5.0×ICS vs 2.CS/SAL	5.0×ICS vs 2.5×ICS	5.0×ICS vs 1.0×ICS/SAL	2.5×ICS/SAL vs 2.5×ICS	2.5×ICS/SAL vs 1.0×ICS/SAL	2.5×ICS vs 1.0×ICS/SAL
-0.46 (-0.83, -0.09)	-0.13 (-0.51, 0.24)	-0.66 (-1.04, -0.27)	0.33 (-0.05, 0.71)	-0.15 (-0.52, 0.22)	-0.57 (-0.95, -0.20)

Adolescents/Adults – Intercept Parameters for Logit #2

5.0×ICS vs 2.5×ICS/SAL	5.0×ICS vs 2.5×ICS	5.0×ICS vs 1.0×ICS/SAL	2.5×ICS/SAL vs 2.5×ICS	2.5×ICS/SAL vs 1.0×ICS/SAL	2.5×ICS vs 1.0×ICS/SAL
1.42 (1.01, 1.82)	1.14 (0.74, 1.54)	1.40 (0.99, 1.81)	1.37 (0.95, 1.78)	1.24 (0.84, 1.64)	1.22 (0.82, 1.61)

Adolescents/Adults – Variance Parameters

Logit #1	Logit #2
0.69 (0.25, 1.12)	1.74 (1.06, 2.41)

Children – Intercept Parameters for Logit #1

5.0×ICS vs 2.CS/SAL	5.0×ICS vs 2.5×ICS	5.0×ICS vs 1.0×ICS/SAL	2.5×ICS/SAL vs 2.5×ICS	2.5×ICS/SAL vs 1.0×ICS/SAL	2.5×ICS vs 1.0×ICS/SAL
0.09 (-0.27, 0.44)	0.30 (-0.05, 0.66)	0.00 (-0.34, 0.35)	0.33 (-0.03, 0.69)	0.03 (-0.31, 0.37)	-0.26 (-0.61, 0.08)

Children – Intercept Parameters for Logit #2

5.0×ICS vs 2.5×ICS/SAL	5.0×ICS vs 2.5×ICS	5.0×ICS vs 1.0×ICS/SAL	2.5×ICS/SAL vs 2.5×ICS	2.5×ICS/SAL vs 1.0×ICS/SAL	2.5×ICS vs 1.0×ICS/SAL
2.26 (1.72, 2.79)	1.99 (1.47, 2.51)	2.47 (1.90, 3.03)	2.42 (1.85, 2.99)	3.17 (2.52, 3.82)	2.70 (2.10, 3.30)

Children – Variance Parameters

Logit #1	Logit #2
0.61	1.93
(0.26, 0.95)	(0.99, 2.87)

In order to expand this model to account for data that follow a not missing at random (NMAR) mechanism, we adapt an approach from the following article:

Rosenkranz GK. Analysis of cross-over studies with missing data. *Statistical Methods in Medical Research* 2015, 24:420-433.

This involves a modification of the regression model for the third logit, which is the log odds of a nonmissing value relative to a missing value, as

$$\mu_{i,AB(3)}^* = \mu_{i,AB(3)} + Y_{i,AB}\omega_{AB}$$

The $Y_{i,AB}\omega_{AB}$ term in this regression model indicates that the logit for a nonmissing value involves a linear function of $Y_{i,AB}$ itself (which may be unobservable for some BARD participants). Thus, a nonnull value of ω_{AB} corresponds to an NMAR model, whereas a null value of ω_{AB} corresponds to an MAR model. If $Y_{i,AB}$ is non-missing, then the likelihood contribution of the i^{th} BARD participant, $i = 1, 2, \dots, N$, for the A versus B treatment regimen comparison is

$$\begin{aligned} I(Y_{i,AB} = +1) & \left\{ \frac{1}{1 + \exp(-\mu_{i,AB(1)})} \right\} \left\{ \frac{1}{1 + \exp(-\mu_{i,AB(2)})} \right\} \left\{ \frac{1}{1 + \exp(-\mu_{i,AB(3)}^*)} \right\} + \\ I(Y_{i,AB} = 0) & \left\{ 1 - \frac{1}{1 + \exp(-\mu_{i,AB(2)})} \right\} \left\{ \frac{1}{1 + \exp(-\mu_{i,AB(3)}^*)} \right\} + \\ I(Y_{i,AB} = -1) & \left\{ 1 - \frac{1}{1 + \exp(-\mu_{i,AB(1)})} \right\} \left\{ \frac{1}{1 + \exp(-\mu_{i,AB(2)})} \right\} \left\{ \frac{1}{1 + \exp(-\mu_{i,AB(3)}^*)} \right\} \end{aligned}$$

If $Y_{i,AB}$ is missing, then the likelihood contribution of the i^{th} BARD participant, $i = 1, 2, \dots, N$, for the A versus B treatment regimen comparison is

$$\begin{aligned} E & \left\{ 1 - \frac{1}{1 + \exp(-\mu_{i,AB(3)}^*)} \right\} = \\ & \left\{ \frac{1}{1 + \exp(-\mu_{i,AB(1)})} \right\} \left\{ \frac{1}{1 + \exp(-\mu_{i,AB(2)})} \right\} \left\{ 1 - \frac{1}{1 + \exp(-\mu_{i,AB(3)} - \omega_{AB})} \right\} + \\ & \left\{ 1 - \frac{1}{1 + \exp(-\mu_{i,AB(2)})} \right\} \left\{ 1 - \frac{1}{1 + \exp(-\mu_{i,AB(3)})} \right\} + \\ & \left\{ 1 - \frac{1}{1 + \exp(-\mu_{i,AB(1)})} \right\} \left\{ \frac{1}{1 + \exp(-\mu_{i,AB(2)})} \right\} \left\{ 1 - \frac{1}{1 + \exp(-\mu_{i,AB(3)} + \omega_{AB})} \right\} \end{aligned}$$

We used SAS PROC NLMIXED, Version 9.4, to construct and maximize the likelihood functions for the MAR and NMAR models. The maximum likelihood (ML) estimators of the six NMAR parameters (ω_{AB} , ω_{AC} , ω_{AD} , ω_{BC} , ω_{BD} , ω_{CD}), along with their 95% confidence intervals, appear in the following table:

Adolescents/Adults					
5.0×ICS vs 2.5×ICS/SAL	5.0×ICS vs 2.5×ICS	5.0×ICS vs 1.0×ICS/SAL	2.5×ICS/SAL vs 2.5×ICS	2.5×ICS/SAL vs 1.0×ICS/SAL	2.5×ICS vs 1.0×ICS/SAL
-0.35 (-1.23, 0.53)	-0.01 (-0.91, 0.89)	-0.54 (-1.41, 0.32)	0.35 (-0.56, 1.26)	-0.32 (-1.22, 0.58)	-0.42 (-1.51, 0.67)
Children					
2.5×ICS vs 2.5×ICS/SAL	2.5×ICS vs 1.0×ICS	2.5×ICS vs 1.0×ICS/SAL	2.5×ICS/SAL vs 1.0×ICS	2.5×ICS/SAL vs 1.0×ICS/SAL	1.0×ICS vs 1.0×ICS/SAL
0.38 (-0.44, 1.20)	0.29 (-0.59, 1.16)	0.06 (-0.76, 0.87)	0.35 (-0.43, 1.13)	0.22 (-0.58, 1.03)	0.06 (-0.71, 0.83)

The results in the table indicate that all six NMAR parameters for the adults/adolescents and all six NMAR parameters for the children, with respect to the primary outcome variable, are not statistically significant. In addition, we contrasted the Akaike Information Criteria (AIC) from the MAR and NMAR models, and present the results in the following table:

	MAR Model	NMAR Model
Adolescents/Adults	4021.3	4029.6
Children	3632.1	3641.8

The AIC is a function of the total likelihood and has a penalty for the number of estimated parameters. A smaller value of the AIC indicates a better statistical model. In both cases for adolescents/adults and children, the AIC values indicate that the MAR model is a better statistical model for the BARD primary outcome data than the NMAR statistical model.

Supplementary Figures and Tables

Figure S1: Schematic Flow Diagram of the BARD Trial Protocols in Adolescents/Adults (>12 Years) and Children (<12 Years of Age).

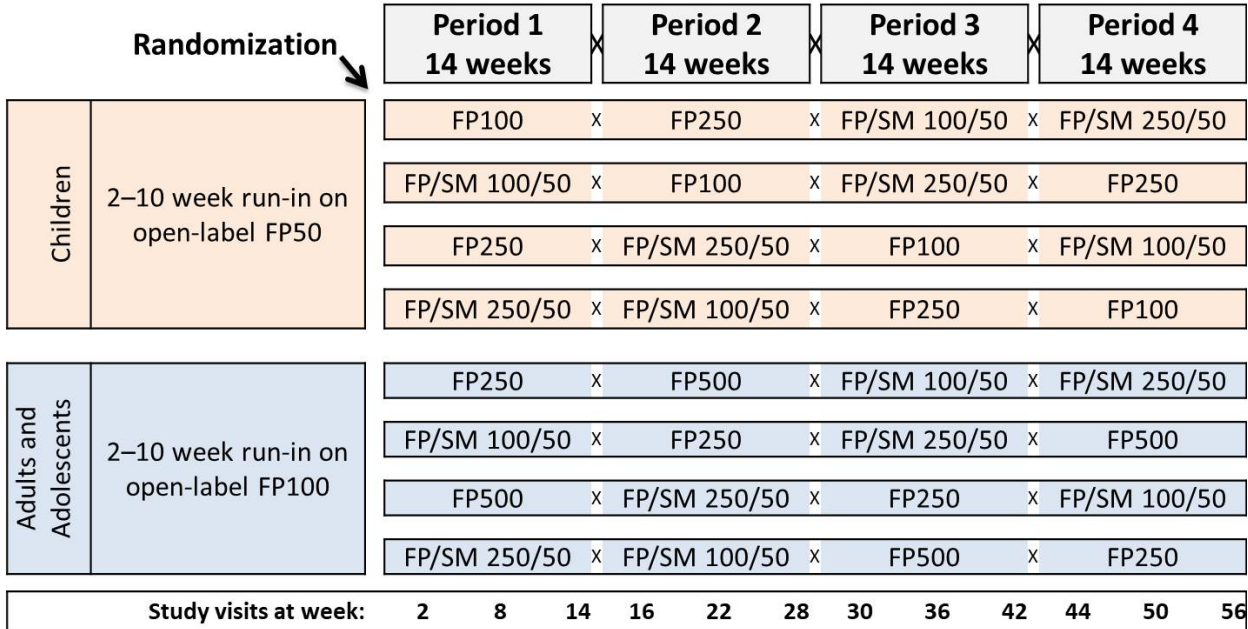


Figure 1: Study Schema. Following a 2–10 week run-in to establish adherence, safety, and eligibility, subjects were randomized to one of four different treatment sequences. These sequences constituted a Latin Square balanced for first order carry-over effects. Twice daily treatments are as follows: FP50=fluticasone 50ug, FP100=fluticasone 100ug, FP250=fluticasone 250ug, FP500=fluticasone 500ug, FP/SM 100/50=fluticasone 100ug/salmeterol 50ug, and FP/SM 250/50=fluticasone 250ug/salmeterol 50ug.

Figure S1: Schematic Flow Diagram of the BARD Trial Protocols in Children (<12 Years of Age) and Adolescents and Adults (12 Years and older). BARD trial design consists of a two to ten-week run-in period until loss of symptom control was achieved on low-dose ICS followed by randomization and cross-over into four 14-week treatments in individuals 12 years of age and older and children (5-11 years of age) inadequately-controlled on low dose ICS. Individuals aged 12 and older were randomized or crossed over into treatments which consisted of adding a LABA, increasing ICS dose 2.5-fold, increasing ICS dose 5-fold, or adding a LABA and increasing ICS dose 2.5-fold. Children aged 5-11 were randomized or crossed over into

674 treatments which consisted of increasing ICS 2-fold, increasing ICS 2-fold and adding a
675 LABA, increasing ICS 5-fold, and increasing ICS 5-fold and adding a LABA.
676 AQ=asthma control questionnaire, AR=adherence review, Blood=biomarkers and
677 genetics, S=spirometry, BDR=bronchodilator reversibility, and McH=methacholine
678 challenge.
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Figure S2. CONSORT Diagrams of the of the BARD Trial Protocols in Children (<12 Years of Age).

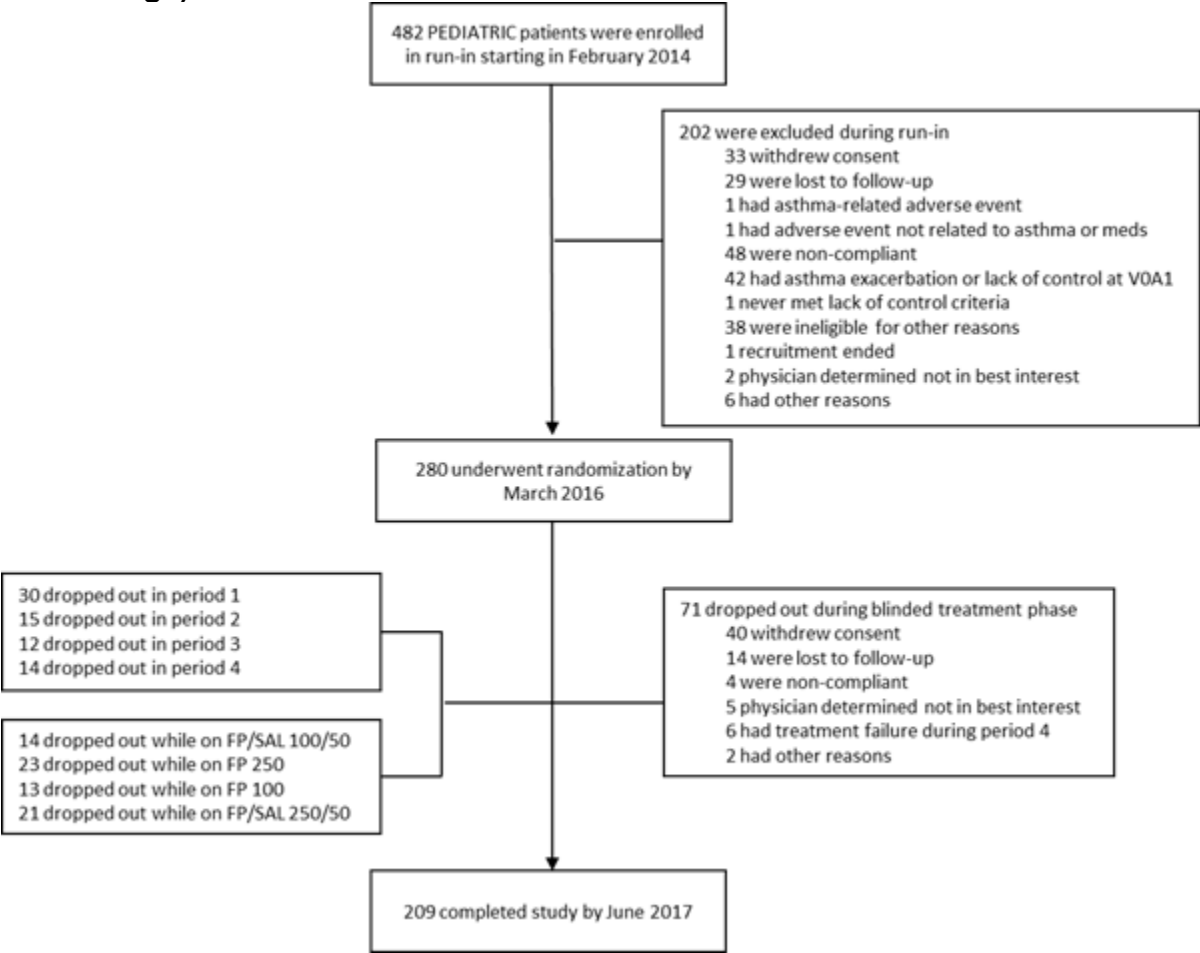


Figure S3 CONSORT Diagram of the BARD Trial Protocols in Adolescents and Adults (12 Years and older).

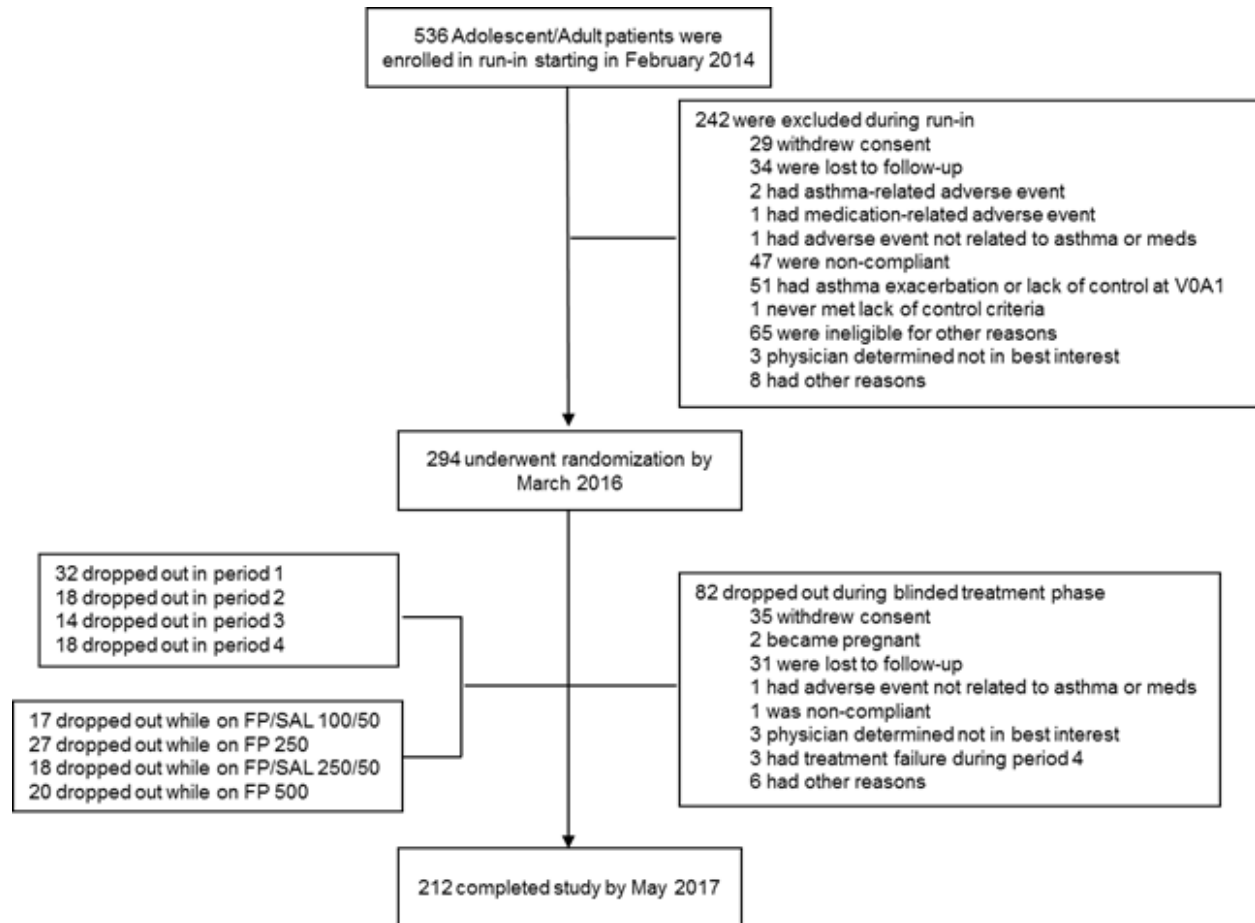
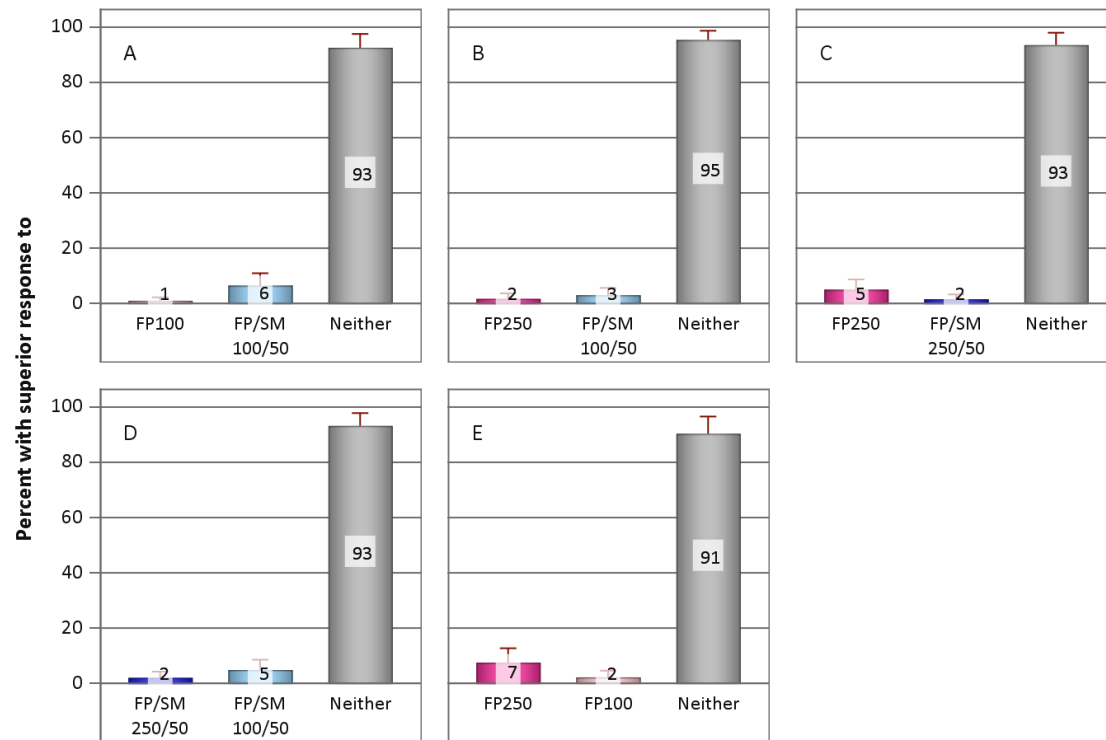
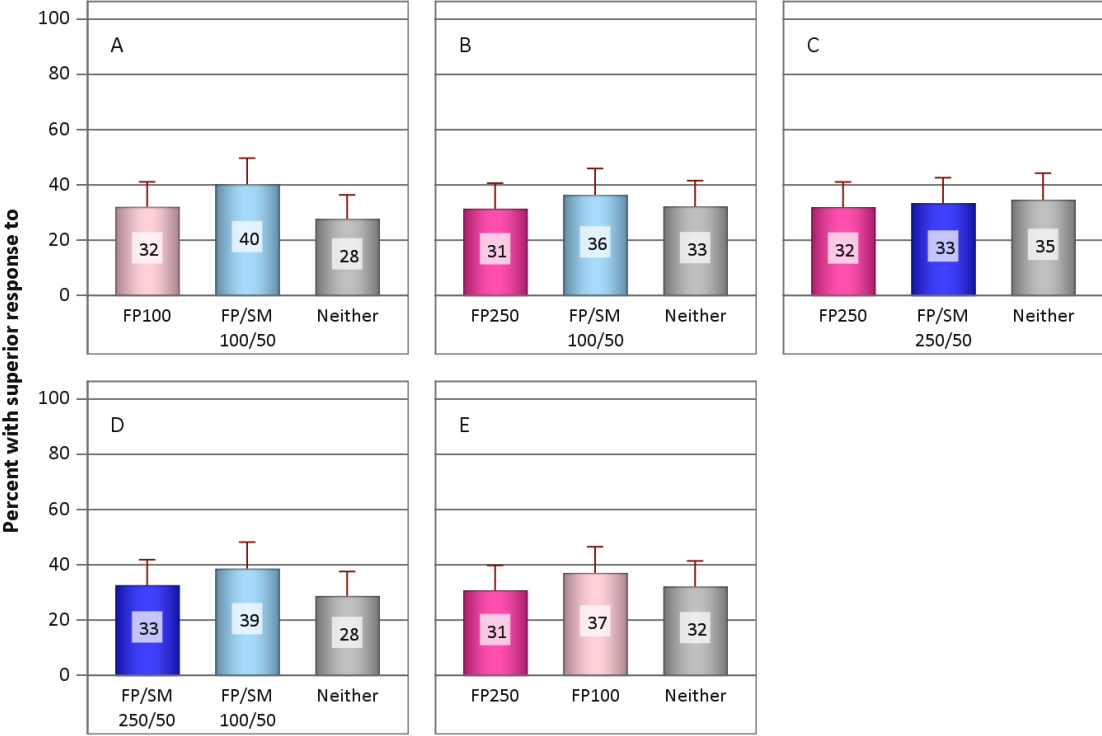


Figure S4.1-4.3: Percentage of Pediatric (5-11 Years of Age) Black Asthma Participants Showing a Superior Response to Specific Treatments Based on Exacerbations (3.1), Asthma Control Days (3.2), and FEV1 change (3.3).

S4.1: Exacerbations

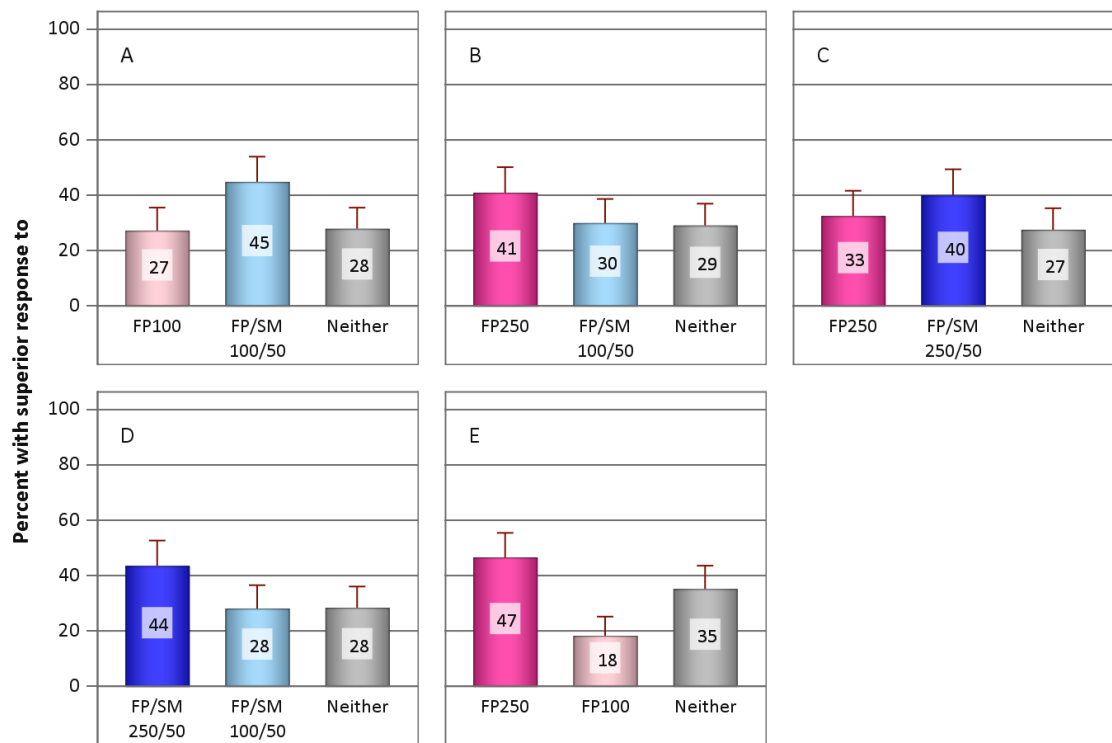


698 **S4.2: Annualized Asthma Control Days**
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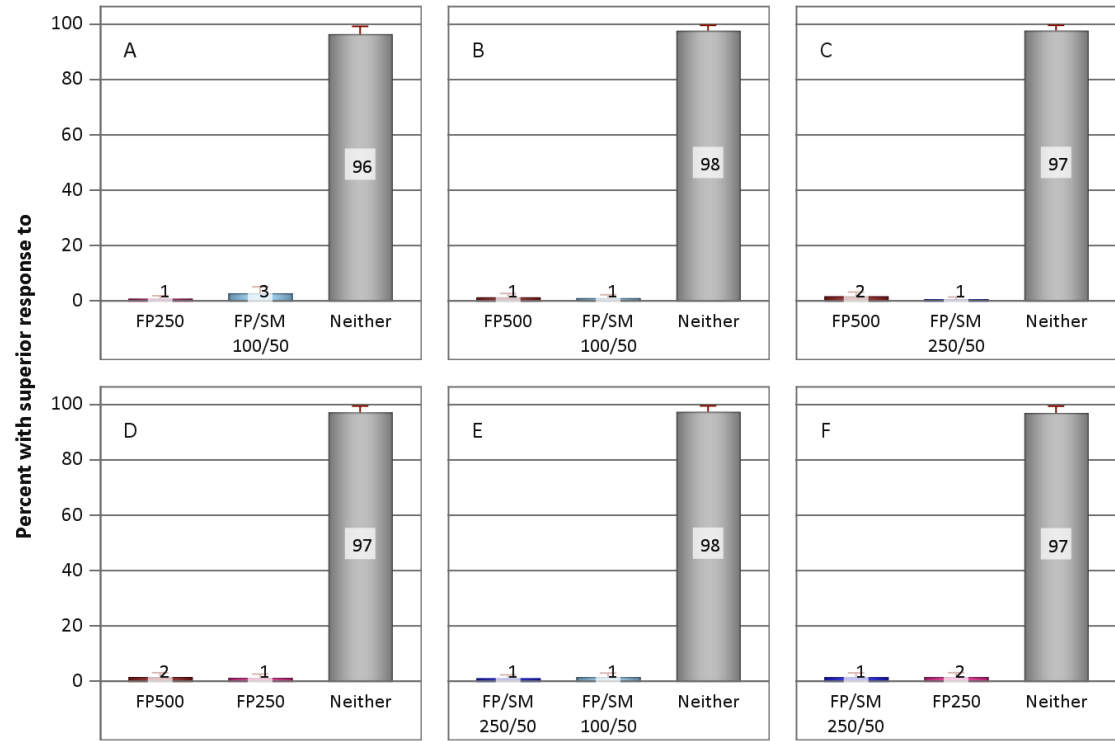
S4.3: FEV1 Change



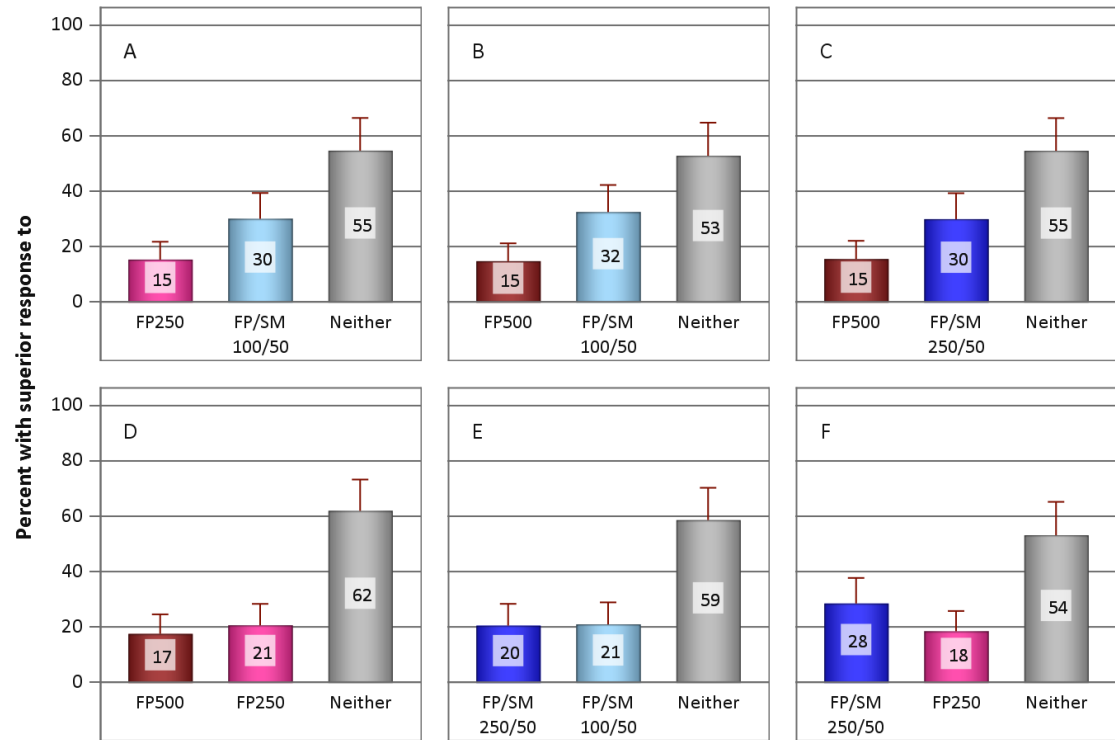
Panels A to E illustrate all comparisons of two treatment arms based on superiority of therapeutic response for exacerbations (4.1), asthma control days (4.2), and FEV1 change (4.3). The number indicated within each column represents the percentage of participants who had a superior response to that specific treatment compared to the alternative treatment based on the hierarchical outcome. The percentage of participants who did not show a superior response for either treatment is shown with grey bars. Bars indicate the 95% confidence interval. 14-week twice daily treatments are as follows: FP/SM100/50=fluticasone 100ug/salmeterol 50ug, FP100=fluticasone 100ug, FP250=fluticasone 250ug, FP/SM 250/50=fluticasone 250ug/salmeterol 50ug.

Figure S5.1-5.3. Percent of Adolescent and Adult Black Asthma Participants Showing a Superior Response to Specific Treatments Based on Exacerbations (4.1), Asthma Control Days (4.2), and FEV1 change (4.3).

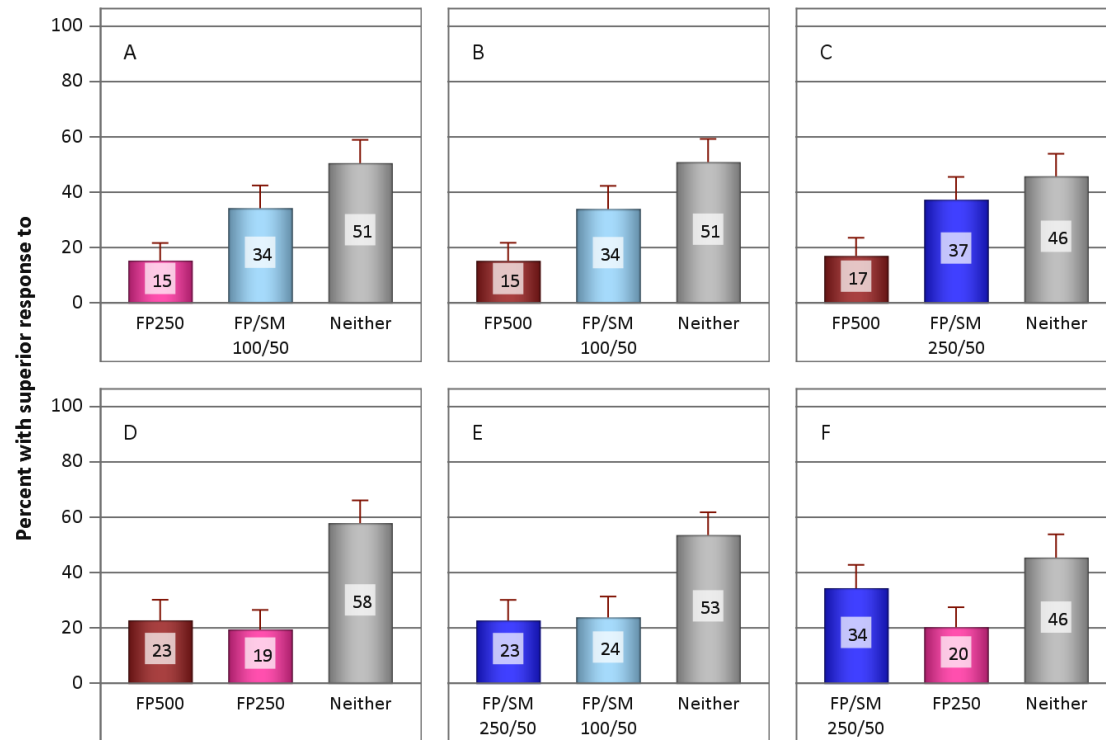
S5.1: Exacerbations



S5.2: Annualized Asthma Control Days.

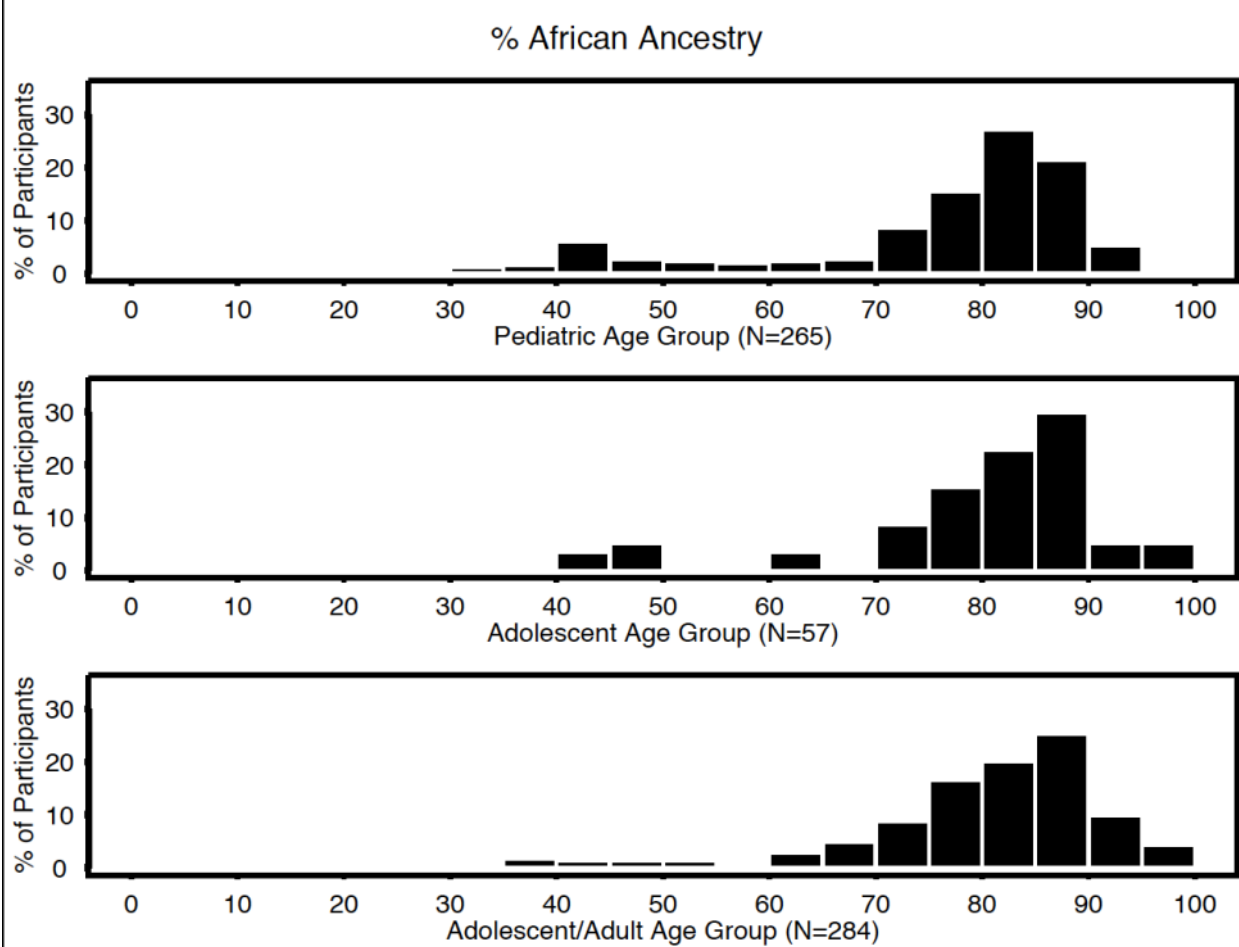


S5.3: FEV1 Change



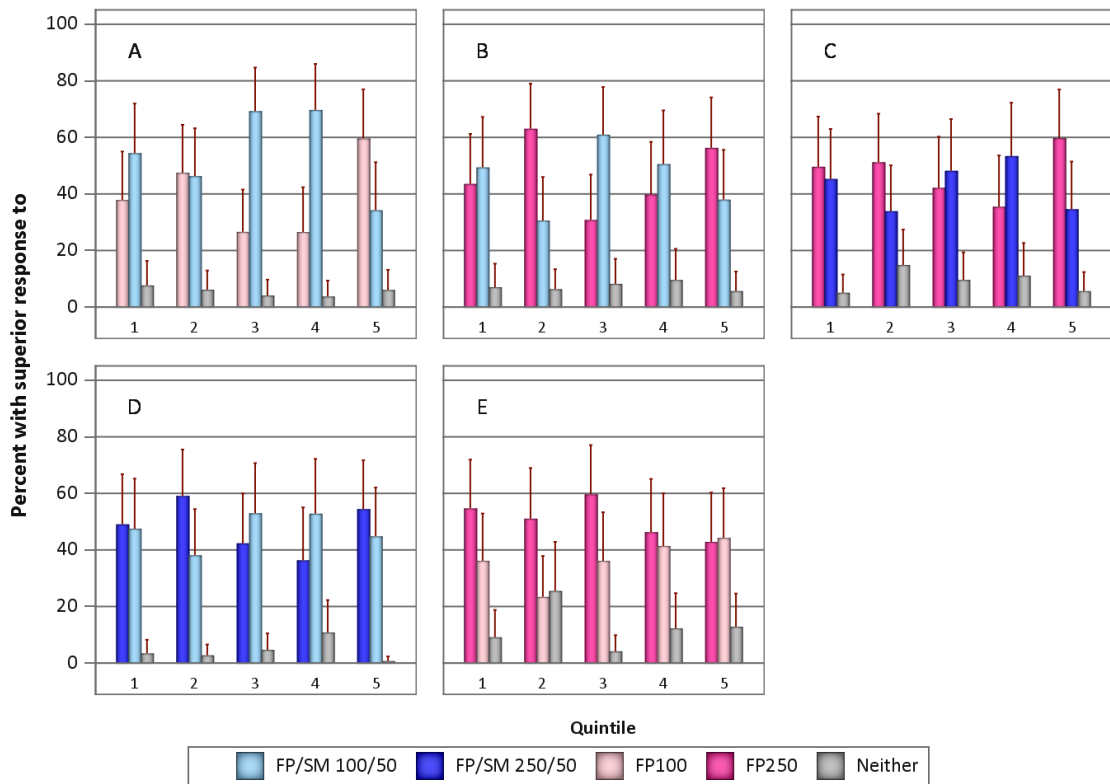
Panels A to F illustrate all comparisons of two treatment arms based on superiority of therapeutic response for exacerbations (4.1), asthma control days (4.2), and FEV1 change (4.3). The number indicated within each column represents the percentage of participants who showed a superior response to that specific treatment compared to the alternative treatment based on the hierarchical outcome. The percentage of participants who did not show a superior response for either treatment is shown with grey bars. Bars indicate the 95% confidence interval. 14-week twice daily treatments are as follows: FP/SM 100/50=fluticasone 100ug/salmeterol 50ug, FP250=fluticasone 250ug, FP500=fluticasone 500ug, FP/SM 250/50=fluticasone 250ug/salmeterol 50ug.

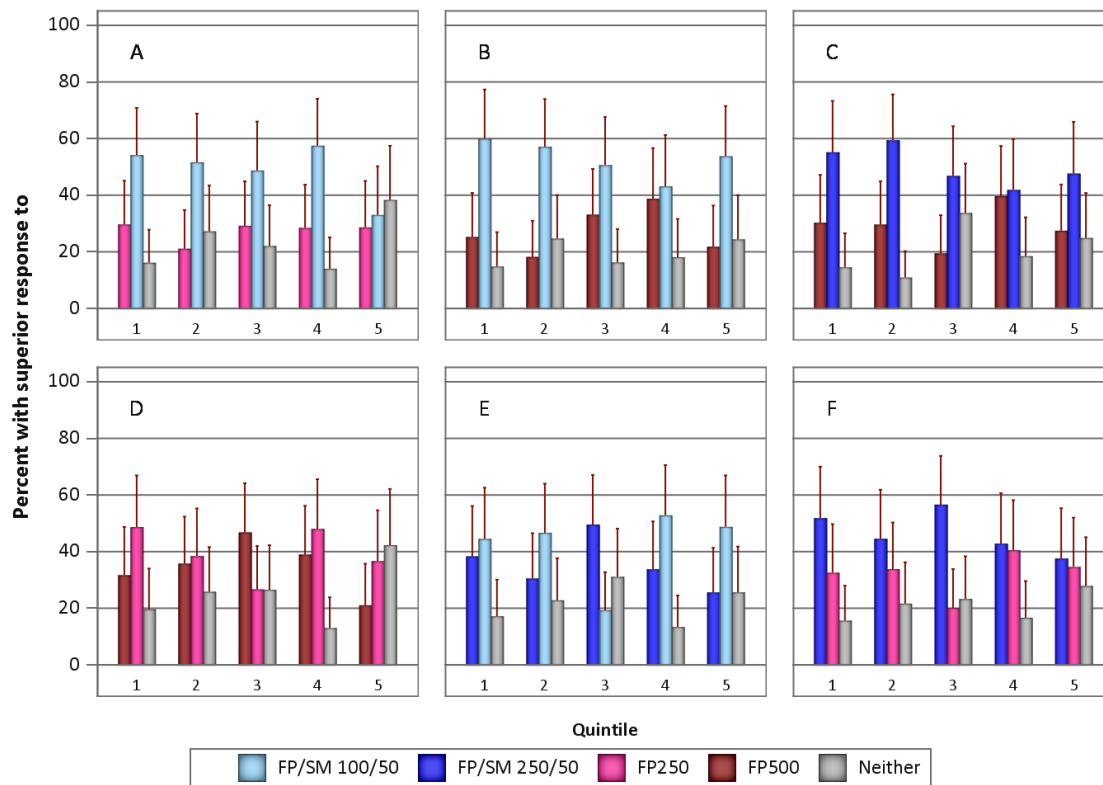
Figure S6: Distribution of Percentage African Genetic Ancestry Estimates Based on Genome-wide Genetic Data in Children, Adolescents, and Adults.



Figures S7.1 and S7.2: Percentage of Children (S7.1) and Adolescents/Adults (S7.2) by Quintile Groups of Increasing Percentage African Ancestry and Showing a Superior Response to Specific Treatments Based on the Composite Outcome.

S7.1: Children





Figures S7.1 and S7.2: Percentages of Children (5.1) and Adolescents/Adults (5.2), by Quintile Groups of Increasing Percentage African Ancestry, Showing Superior Response to Specific Treatments Based on the Composite Outcome. Panels A-F in Figure S7.1 and A-E in Figure 4S7.2 illustrate the comparisons of two treatment arms based on the hierarchical composite outcome in Blacks grouped into quintiles of increasing percentage of African ancestry (quintiles 1-5) in Adolescents/Adults and Children. For each quintile group of Blacks, the height of each column represents the percentage of participants who showed a superior response to that specific treatment compared to the alternative treatment based on the hierarchical outcome. The percentage of participants who did not show a superior response for either treatment is shown with grey bars. The lower first and second quintiles (Q1-2) were compared to the higher fourth and fifth quintiles (Q4-5) to identify interactions between ancestry extremes and the composite superiority outcome with interaction p-values shown ($p_{Q1-2vsQ4-5}$). Bars indicate the 95% confidence interval. In adolescents/adults, 14-week twice daily treatments are as follows: FP/SM 100/50=fluticasone 100ug/salmeterol 50ug, FP250=fluticasone 250ug, FP500=fluticasone 500ug, FP/SM 250/50=fluticasone 250ug/salmeterol 50ug. In children, 14-week twice daily treatments are as follows: 14-week twice daily treatments are as follows: FP/SM 100/50=fluticasone 100ug/salmeterol 50ug, FP100=fluticasone 100ug, FP250=fluticasone 250ug, FP/SM 250/50=fluticasone 250ug/salmeterol 50ug.

777 **Table S1a Number of adults/adolescents and children enrolled per partnership**
778 *Nine AsthmaNet partnerships across 17 different cities participated in the BARD trial.*
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<i>Partnership</i>	<i>Adults/ Adolescents</i>	<i>Children</i>	<i>TOTAL</i>
1	60	20	80
2	53	37	90
3	29	41	70
4	19	27	46
5	24	28	52
6	36	35	71
7	23	26	49
8	18	9	27
9	32	57	89
<i>TOTAL</i>	294	280	574

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Table S1b Full Characteristics of Patients in the BARD Trial Cohort at Baseline.

	Age 5 to 11 years (N=280)	Adolescent and Adult ≥ 12 years (N=294)
	N (%)	N (%)
Male	170 / 280 (60.7%)	95 / 294 (32.3%)
Hispanic Ethnicity	24 / 280 (4.2%)	9 / 294 (3.1%)
At Least One of 13 Positive Allergens by ImmunoCap	224 / 273 (82.1%)	244 / 287 (85.0%)
History of Doctor-Diagnosed Eczema	191 / 280 (68.2%)	119 / 294 (40.5%)
Asthma History in 12 Months Prior to Enrollment: At least one asthma episodes requiring emergency care or unscheduled office visit	208 / 280 (74.3%)	132 / 294 (44.9%)
At least one overnight hospitalizations	43 / 280 (15.4%)	14 / 294 (4.8%)
At least one courses of systemic corticosteroid therapy	172 / 280 (61.4%)	99 / 294 (33.7%)
Asthma Medications Used in 12 Months Prior to Enrollment: LTRA / 5LO Inhibitors	107 / 280 (38.2%)	50 / 294 (17.0%)
Oral Steroids	170 / 277 (61.4%)	92 / 293 (31.4%)
ICS Monotherapy (inhaled or nebulized)	246 / 279 (88.2%)	193 / 294 (65.6%)
ICS/LABA Combination Therapy	64 / 279 (22.9%)	139 / 294 (47.3%)
ICS Dose Level at Enrollment: Low	142 / 280 (50.7%)	150 / 294 (51.0%)
Medium	72 / 280 (25.7%)	139 / 294 (47.3%)
High	66 / 280 (23.6%)	5 / 294 (1.7%)
Sputum Eosinophils $\geq 2\%^{\#}$		24 / 220 (10.9%)
Blood Eosinophils Absolute Count ≥ 300 cells/ul	164 / 275 (59.6%)	84 / 289 (29.1%)
	Mean (SD) +^	Mean (SD)
Percent African Ancestry +	81.0 (73.4,85.6) missing = 15 (5.4%)	82.1 (75.3,87.6) missing = 10 (3.4%)
Age at Enrollment (years)	8.5 (1.8) missing = 0 (0.0%)	37.3 (16.1) missing = 0 (0.0%)
BMI at Enrollment (kg/m ²)	only BMI percentile is relevant	33.4 (8.2) in Adults only (N=236) missing = 0 (0.0%)
BMI Percentile at Enrollment	71.4 (26.3) missing = 0 (0.0%)	82.9 (21.8) Adolescent only (N=58) missing = 0 (0.0%)
Blood Eosinophils Absolute Count (cells/ul) +	340 (200,510) missing = 5 (1.8%)	200 (100,300) missing = 5 (1.7%)

Serum Total IgE (IU/mL) +	286.5 (92.0,693.5) missing = 4 (1.4%)	174.0 (73.0,468.0) missing = 4 (1.4%)
FEV ₁ (% predicted)	95.5 (16.7) missing = 5 (1.8%)	83.4 (17.4) missing = 3 (1.0%)
FEV ₁ /FVC Ratio	0.80 (0.09) missing = 5 (1.8%)	0.74 (0.10) missing = 3 (1.0%)
Bronchodilator Response (4 puffs, % relative change)	13.79 (14.48) missing = 7 (2.5%)	12.47 (12.43) missing = 0 (0.0%)
Methacholine PC ₂₀ (mg/ml) ^	1.32 (1.61) missing = 67 (23.9%)	1.71 (1.60) missing = 44 (15.0%)
ACT ₁ +		19 (16,22) missing = 1 (0.3%)
cACT ₂ +	22 (19,24) missing = 1 (0.4%)	
Asthma Control Days during 2 weeks prior to randomization (%) ³	31.2 (29.9) missing = 3 (1.1%)	24.5 (28.2) missing = 5 (1.7%)
¹ ACT scores range from 5 to 25 with higher values representing better asthma control. ² Childhood ACT scores range from 0 to 27 with higher values representing better asthma control. ³ Participants with fewer than 7 evaluable days were excluded from this summary. + Median (Q1,Q3) reported # children <12 years old did not perform sputum induction ^ Geometric mean (CV) reported		

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785 ¹ ACT scores range from 5 to 25 with higher values representing better asthma control.786 ²Childhood ACT scores range from 0 to 27 with higher values representing better asthma
787 control.788 ³Participants with fewer than seven days that were able to be evaluated were excluded.

789 +Median and Inter-Quartile Ranges (Q1, Q3) reported.

790 ^Geometric means (CV) reported.

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Table S1c. Baseline characteristics of pediatric participants who completed the study vs. those who discontinued

	Completers (N=209)	Drop-outs (N=71)
Male	133 / 209 (63.6%)	37 / 71 (52.1%)
Hispanic Ethnicity	19 / 209 (9.1%)	5 / 71 (7.0%)
At Least One of 13 Positive Allergens by ImmunoCap	169 / 203 (83.3%)	55 / 70 (78.6%)
History of Doctor-Diagnosed Eczema	141 / 209 (67.5%)	50 / 71 (70.4%)
Asthma History in 12 Months Prior to Enrollment: At least one asthma episodes requiring emergency care or unscheduled office visit	154 / 209 (73.7%)	54 / 71 (76.1%)
At least one overnight hospitalizations	35 / 209 (16.7%)	8 / 71 (11.3%)
At least one courses of systemic corticosteroid therapy	132 / 209 (63.2%)	40 / 71 (56.3%)
Asthma Medications Used in 12 Months Prior to Enrollment: LTRA / 5LO Inhibitors	76 / 209 (36.4%)	31 / 71 (43.7%)
Oral Steroids	131 / 207 (63.3%)	39 / 70 (55.7%)
ICS Monotherapy (inhaled or nebulized)	182 / 209 (87.1%)	64 / 70 (91.4%)
ICS/LABA Combination Therapy	45 / 208 (21.6%)	19 / 71 (26.8%)
ICS Dose Level at Enrollment: Low	113 / 209 (54.1%)	29 / 71 (40.8%)
Medium	48 / 209 (23.0%)	24 / 71 (33.8%)
High	48 / 209 (23.0%)	18 / 71 (25.4%)
Blood Eosinophils Absolute Count ≥ 300 cells/ul	127 / 205 (62.0%)	37 / 70 (52.9%)
	Mean (SD) +^	Mean (SD)+^
Percent African Ancestry +	80.7 (72.0,85.6)	82.3 (77.5,85.6)
Age at Enrollment (years)	8.5 (1.8)	8.5 (1.8)
BMI at Enrollment (kg/m ²)	19.1 (4.3)	19.1 (4.4)
BMI Percentile at Enrollment	71.1 (27.5)	72.2 (22.4)
Blood Eosinophils Absolute Count (cells/ul) +	360 (200.0,510.0)	300 (200.0,520.0)
Serum Total IgE (IU/mL) +	285 (90.0,674.0)	375 (94.0,844.0)
FEV ₁ (% predicted)	95.9 (16.2)	94.5 (18.2)
FEV ₁ /FVC Ratio	0.8 (0.09)	0.81 (0.11)
Bronchodilator Response (4 puffs, % relative change)	13.37 (12.73)	15.02 (18.78)
Methacholine PC ₂₀ (mg/ml) ^	1.29 (1.62)	1.39 (1.58)
cACT ² +	22 (20.0,24.0)	21 (18.0,23.0)
Asthma Control Days during 2 weeks prior to randomization (%) ³	33.7 (29.8)	23.9 (29.3)
² Childhood ACT scores range from 0 to 27 with higher values representing better asthma control. ³ Participants with fewer than 7 evaluable days were excluded from this summary. + Median (Q1,Q3) reported ^ Geometric mean (CV) reported		

801 **Table S1d Baseline characteristics of adolescent/adult participants who**
802 **completed the study vs. those who discontinued**

	Completers (N=212)	Drop-outs (N=82)
Male	74 / 212 (34.9%)	21 / 82 (25.6%)
Hispanic Ethnicity	4 / 212 (1.9%)	5 / 82 (6.1%)
At Least One of 13 Positive Allergens by ImmunoCap	169 / 203 (83.3%)	55 / 70 (78.6%)
History of Doctor-Diagnosed Eczema	84 / 212 (39.6%)	35 / 82 (42.7%)
Asthma History in 12 Months Prior to Enrollment: At least one asthma episodes requiring emergency care or unscheduled office visit	91 / 212 (42.9%)	41 / 82 (50.0%)
At least one overnight hospitalizations	11 / 212 (5.2%)	3 / 82 (3.7%)
At least one courses of systemic corticosteroid therapy	69 / 212 (32.5%)	30 / 82 (36.6%)
Asthma Medications Used in 12 Months Prior to Enrollment: LTRA / 5LO Inhibitors	38 / 212 (17.9%)	12 / 82 (14.6%)
Oral Steroids	67 / 211 (31.8%)	25 / 82 (30.5%)
ICS Monotherapy (inhaled or nebulized)	136 / 212 (64.2%)	57 / 82 (69.5%)
ICS/LABA Combination Therapy	104 / 212 (49.1%)	35 / 82 (42.7%)
ICS Dose Level at Enrollment: Low	102 / 212 (48.1%)	48 / 82 (58.5%)
Medium	105 / 212 (49.5%)	34 / 82 (41.5%)
High	5 / 212 (2.4%)	0 / 82 (0.0%)
Sputum Eosinophils $\geq 2\%$	18 / 154 (11.7%)	6 / 66 (9.1%)
Blood Eosinophils Absolute Count ≥ 300 cells/ul	61 / 209 (29.2%)	23 / 80 (28.8%)
	Mean (SD) +^	Mean (SD) +^
Percent African Ancestry +	81.8 (75.4,87.6)	83.4 (74.8,87.6)
Age at Enrollment (years)	37.3 (16.8)	37.2 (14.2)
BMI at Enrollment (kg/m ²)	32.5 (9.3)	32.1 (7.4)
Blood Eosinophils Absolute Count (cells/ul) +	200 (100.0,300.0)	200 (100.0,349.0)
Serum Total IgE (IU/mL) +	179 (79.0,448.0)	165.5 (62.0,515.0)
FEV ₁ (% predicted)	82.4 (17.6)	86 (16.9)
FEV ₁ /FVC Ratio	0.74 (0.11)	0.76 (0.09)
Bronchodilator Response (4 puffs, % relative change)	12.61 (13.03)	12.13 (10.79)
Methacholine PC ₂₀ (mg/ml) ^	1.86 (1.59)	1.42 (1.64)
ACT ¹ +	20 (17.0,22.0)	19 (15.0,21.0)
Asthma Control Days during 2 weeks prior to randomization (%) ³	25.6 (29.2)	21.6 (25.5)
² Childhood ACT scores range from 0 to 27 with higher values representing better asthma control. ³ Participants with fewer than 7 evaluable days were excluded from this summary. + Median (Q1,Q3) reported ^ Geometric mean (CV) reported		

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804 **Table S1e: Related BARD subjects and genetic measures of relatedness by**
805 **proportion of identity by descent**

Family Number	Age Groups (Years)	Relationship	PI_HAT*
1	18+	non-identical full sibling	0.4858
1	18+	non-identical full sibling	0.5379
1	18+	non-identical full sibling	0.5379
2	12 to 17	non-identical full sibling	0.496
2	12 to 17	non-identical full sibling	0.496
3	5 to 11	non-identical full sibling	0.4497
3	5 to 11	non-identical full sibling	0.4497
4	12 to 17	non-identical full sibling	0.557
4	12 to 17	non-identical full sibling	0.557
5	12 to 17	biological child	0.2694
5	5 to 11	biological child	0.4999
5	18+	biological mother	0.4999
6	5 to 11	non-identical full sibling	0.553
6	5 to 11	non-identical full sibling	0.553
7	5 to 11	non-identical full sibling	0.4661
7	5 to 11	non-identical full sibling	0.4661
8	5 to 11	half-sibling through mother	0.2744
8	5 to 11	half-sibling through mother	0.2744
9	12 to 17	half-sibling through mother	0.2723
9	5 to 11	half-sibling through mother	0.2723
10	18+	non-identical full sibling	0.2588
10	18+	non-identical full sibling	0.2588
11	5 to 11	biological child	0.498
11	18+	biological mother	0.498
11	18+	biological father	0.5001
12	12 to 17	non-identical full sibling	0.5086
12	18+	non-identical full sibling	0.5086
13	5 to 11	non-identical full sibling	0.5231
13	5 to 11	non-identical full sibling	0.5231
14	5 to 11	non-identical full sibling	0.4758
14	5 to 11	non-identical full sibling	0.4758
15	18+	biological mother	0.4983
15	12 to 17	biological child	0.4983
16	18+	biological mother	0.5003
16	12 to 17	biological child	0.5003
17	18+	biological father	0.5
17	5 to 11	biological child	0.5
18	12 to 17	half-sibling through mother	0.2717

18	18+	half-sibling through mother	0.2717
19	18+	biological mother	0.4993
19	18+	biological child	0.4993
20	5 to 11	biological child	0.4994
20	18+	biological mother	0.4994
21	12 to 17	non-identical full sibling	0.487
21	12 to 17	non-identical full sibling	0.487
22	18+	parent	0.498
22	18+	biological child	0.498
23	12 to 17	half-sibling through mother	0.2352
23	12 to 17	half-sibling through mother	0.2352
24	5 to 11	half-sibling through mother	0.2591
24	5 to 11	half-sibling through mother	0.2591
25	5 to 11	half-sibling through mother	0.2434
25	5 to 11	half-sibling through mother	0.2434
26	5 to 11	half-sibling through mother	0.2743
26	5 to 11	half-sibling through mother	0.2743
27	5 to 11	half-sibling through mother	0.241
27	5 to 11	half-sibling through mother	0.241
28	18+	biological mother	0.5
28	18+	biological child	0.5
29	5 to 11	half-sibling through father	0.2547
29	5 to 11	half-sibling through father	0.2547
30	5 to 11	non-identical full sibling	0.4692
30	12 to 17	non-identical full sibling	0.4692
31	5 to 11	non-identical full sibling	0.5115
31	5 to 11	non-identical full sibling	0.5115
32	5 to 11	Twin	1
32	5 to 11	Twin	1
33	5 to 11	niece or half sib or grandchild	0.2742
33	18+	aunt or half sib or grandparent	0.2742
34	5 to 11	nephew or half sib	0.2419
34	5 to 11	nephew or half sib	0.2061
34	18+	aunt or half sib or grandparent	0.2419
35	12 to 17	non-identical full sibling	0.5397
35	5 to 11	non-identical full sibling	0.5397
36	5 to 11	half-sibling through father	NA
36	5 to 11	half-sibling through father	NA

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807 *PI_HAT refers to the proportion of shared genome identity by descent

Table S2: Linear Effect Model for Percentage African Ancestry and the Superiority Composite Outcome by Treatment Comparisons in Adults and Adolescents

Treatment Comparisons	Estimate	95%CI Lower	95%CI Upper
FP500 vs FP/SM250/50	0.58	-2.46	3.61
FP500 vs FP250	-0.28	-3.09	2.53
FP500 vs FP/SM 100/50	-0.59	-3.44	2.26
FP/SM 250/50 vs FP250	-3.15	-6.54	0.24
FP/SM 250/50 vs FP100/50	-2.73	-5.70	0.24
FP 250 vs FP/SM 100/50	0.11	-2.60	2.82

Trinomial regression models evaluated the association between percentage African ancestry and the primary, composite superiority outcome and are shown by different treatment pair comparisons. The parameter estimates and t-values summarize the trend of the effect of ancestry on the outcomes and the ability of ancestry to predict superior response to the first versus the second treatment listed with the standard error (SE) and degrees of freedom (DF) shown. Significance of these associations is expressed with the p-values and 95% confidence intervals (95%CI) shown.

Table S3: Linear Effect Model for Percentage African Ancestry and the Superiority Composite Outcome by Treatment Comparisons in Children

Treatment Comparisons	Estimate	95%CI Lower	95%CI Upper
FP250 vs FP/SM 250/50	-0.83	-3.01	1.35
FP250 vs FP100	-0.75	-2.98	1.48
FP250 vs FP/SM 100/50	-0.09	-2.36	2.19
FP/SM 250/50 vs FP100	-0.92	-3.12	1.29
FP/SM 250/50 vs FP/SM 100/50	0.01	-2.10	2.11
FP100 vs FP/SM 100/50	0.42	-1.77	2.62

Trinomial regression models evaluated the association between percentage African ancestry and the primary, composite superiority outcome and are shown by different treatment pair comparisons. The parameter estimates and t-values summarize the trend of the effect of ancestry on the outcomes and the ability of ancestry to predict superior response to the first versus the second treatment listed with the standard error (SE) and degrees of freedom (DF) shown. Significance of these associations is expressed with the p-values and 95% confidence intervals (95%CI) shown.

Table S4: Goodness of Fit of the Receiver Operating Characteristic Curve for Percentage African Ancestry and Outcome Superiority for the Composite Outcome in Adolescents and Adults

Treatment Comparisons	c-statistic	SE	95% CI Lower	95% CI Upper
FP500 vs FP/SM 250/50	0.18	0.05	0.08	0.28
FP500 vs FP250	0.17	0.04	0.09	0.26
FP500 vs FP/SM 100/50	0.18	0.05	0.08	0.27
FP/SM 250/50 vs FP250	0.19	0.05	0.10	0.28
FP/SM 250/50 vs FP/SM 100/50	0.21	0.05	0.11	0.30
FP250 vs FP/SM 100/50	0.17	0.05	0.08	0.26

The associations between percentage African ancestry and the primary, composite superiority outcome were evaluated with a three-dimensional receiver operating characteristic curve (ROC) curve to determine two optimal cut points of ancestry with the highest possible agreement between observed and expected values. The goodness-of-fit for each of these models is shown by different treatment pair comparisons and expressed as the c-statistic. This c-statistic is three-dimensional and should be compared to 1/6 (0.167) for the six possible ways to order three ancestry scores that arise from an individual with a response of -1, an individual with a response of 0, and an individual with a response of +1. Significance is expressed as a p-value of <0.05 and 95% confidence interval (95%CI) which does not include values <0.167.

Table S5: Goodness of Fit of the Receiver Operating Characteristic Curve for Percentage African Ancestry and Outcome Superiority for the Composite Outcome in Children

Treatment Comparisons	c-statistic	SE	95% CI Lower	95% CI Upper
FP250 vs FP/SM 250/50	0.18	0.05	0.08	0.29
FP250 vs FP100	0.18	0.05	0.09	0.27
FP250 vs FP/SM 100/50	0.16	0.05	0.06	0.26
FP/SM 250/50 vs FP100	0.16	0.05	0.07	0.26
FP/SM 250/50 vs FP/SM 100/50	0.19	0.06	0.07	0.30
FP100 vs FP/SM 100/50	0.18	0.06	0.07	0.30

The associations between percentage African ancestry and the primary, composite superiority outcome were evaluated with a three-dimensional receiver operating characteristic curve (ROC) curve to determine two optimal cut points of ancestry with the highest possible agreement between observed and expected values. The goodness-of-fit for each of these models is shown by different treatment pair comparisons and expressed as the c-statistic. This c-statistic is three-dimensional and should be compared to 1/6 (0.167) for the six possible ways to order three ancestry scores that arise from an individual with a response of -1, an individual with a response of 0, and an individual with a response of +1. Significance is expressed as a p-value of <0.05 and 95% confidence interval (95%CI) which does not include values <0.167.

Table S6: Optimal Cut-points and Percentiles of African Ancestry Based on the Receiver Operating Characteristic Curve for Percentage African Ancestry and Outcome Superiority for the Composite Outcome in Adolescents and Adults

Treatment Comparisons	Cutpoint 1	Cutpoint 2	Percentile 1	Percentile 2	Wt Kappa	SE	95%CI Lower	95%CI Upper
FP500 vs FP/SM 250/50	0.85	0.91	60.00	88.42	0.14	0.05	0.04	0.24
FP500 vs FP250	0.67	0.75	13.33	23.51	0.26	0.05	0.15	0.36
FP500 vs FP/SM 100/50	0.79	0.84	37.19	56.49	0.20	0.05	0.10	0.31
FP/SM 250/50 vs FP250	0.66	0.78	12.63	32.98	0.20	0.05	0.10	0.31
FP/SM 250/50 vs FP/SM 100/50	0.76	0.92	27.02	93.33	0.26	0.05	0.15	0.37
FP250 vs FP/SM 100/50	0.86	0.88	66.32	78.60	0.12	0.04	0.03	0.20

The associations between percentage African ancestry and the primary, composite superiority outcome were evaluated with a three-dimensional receiver operating characteristic curve (ROC) curve to determine two optimal cut points of ancestry with the highest possible agreement between observed and expected values expressed as the weighted kappa statistic (Wt Kappa). The first and second cutpoints are shown by proportion of African ancestry (cutpoints 1 and 2) and as percentiles (percentiles 1 and 2) and divide the cohort into three groups. There was mild agreement between the observed and expected values for the superiority outcome in these ancestral groups based on weight kappa statistics >0.2 for some treatment comparisons, but no comparison reached a clinically meaningful degree of agreement (kappa statistic >0.5).

Table S7: Optimal Cut-points and Percentiles of African Ancestry Based on the Receiver Operating Characteristic Curve for Percentage African Ancestry and Outcome Superiority for the Composite Outcome in Children

Treatment Comparisons	Cutpoint 1	Cutpoint 2	Percentile1	Percentile 2	Wt Kappa	SE	95%CI Lower	95%CI Upper
FP250 vs FP/SM 250/50	0.75	0.87	28.57	81.95	0.21	0.06	0.10	0.33
FP250 vs FP100	0.84	0.88	70.68	83.83	0.17	0.06	0.06	0.28
FP250 vs FP/SM 100/50	0.44	0.79	8.65	40.98	0.31	0.06	0.19	0.42
FP/SM 250/50 vs FP100	0.81	0.90	53.38	92.11	0.19	0.06	0.08	0.31
FP/SM 250/50 vs FP/SM 100/50	0.79	0.90	39.47	93.98	0.23	0.06	0.11	0.35
FP100 vs FP/SM 100/50	0.78	0.85	38.35	71.80	0.21	0.06	0.09	0.33

The associations between percentage African ancestry and the primary, composite superiority outcome were evaluated with a three-dimensional receiver operating characteristic curve (ROC) curve to determine two optimal cut points of ancestry with the highest possible agreement between observed and expected values expressed as the weighted kappa statistic (Wt Kappa). The first and second cutpoints are shown by proportion of African ancestry (cutpoints 1 and 2) and as percentiles (percentiles 1 and 2) and divide the cohort into three groups. There was mild agreement between the observed and expected values for the superiority outcome in these ancestral groups based on weight kappa statistics >0.2 for some treatment comparisons, but no comparison reached a clinically meaningful degree of agreement (kappa statistic >0.5).

Table S8: Secondary and Exploratory Outcomes

	Exacerbations + risk (95% CI)	AACD mean (95% CI)	Pre-BD FEV1 mean (95% CI)	Post-BD FEV1 mean (95% CI)	ACT mean (95% CI)	AQLQ mean (95% CI)	Exacerbations with ED visits N (%) ++	Exacerbations with Hospitalizations N (%) ++
Adolescents/Adults								
FP 500	0.09 (0.06, 0.15)	123 (106, 139)	85.1 (82.9, 87.3)	91.7 (89.5, 93.8)	20.2 (19.7, 20.7)	5.9 (5.7, 6)	9 (38%)	4 (17%)
FP/SM 250/50	0.08 (0.05, 0.13)	137 (120, 153)	86 (83.8, 88.1)	91 (88.8, 93.1)	20.2 (19.8, 20.7)	5.9 (5.8, 6)	5 (23%)	2 (9%)
FP 250	0.08 (0.05, 0.14)	124 (107, 141)	84.7 (82.5, 87)	91.4 (89.2, 93.6)	20.1 (19.6, 20.6)	5.9 (5.7, 6)	3 (12%)	1 (4%)
FP/SM 100/50	0.09 (0.06, 0.14)	138 (121, 155)	86 (83.8, 88.2)	91.6 (89.5, 93.7)	20.4 (20.0, 20.9)	5.8 (5.7, 6)	8 (32%)	3 (12%)
Treatment Differences								
FP 500 vs. FP/SM 250/50	1.15 (0.63, 2.09)	-14 (-25, -3)	-0.9 (-1.9, 0.1)	0.7 (-0.3, 1.7)	0.0 (-0.4, 0.4)	0.0 (-0.1, 0.1)		
FP 500 vs. FP 250	1.11 (0.60, 2.07)	-2 (-13, 10)	0.3 (-0.7, 1.4)	0.3 (-0.8, 1.3)	0.1 (-0.3, 0.5)	0.0 (-0.1, 0.1)		
FP 500 vs. FP/SM 100/50	1.05 (0.59, 1.87)	-15 (-27, -3)	-0.9 (-1.9, 0.1)	0.1 (-0.8, 1)	-0.2 (-0.6, 0.2)	0.0 (-0.1, 0.1)		
FP/SM 250/50 vs. FP 250	0.97 (0.52, 1.81)	13 (0, 25)	1.2 (0.1, 2.4)	-0.4 (-1.6, 0.7)	0.1 (-0.3, 0.6)	0.0 (-0.1, 0.1)		
FP/SM 250/50 vs. FP/SM 100/50	0.92 (0.51, 1.65)	-1 (-12, 10)	0.0 (-0.9, 0.9)	-0.6 (-1.5, 0.3)	-0.2 (-0.6, 0.2)	0.0 (0.0, 0.1)		
FP 250 vs. FP/SM 100/50	0.94 (0.50, 1.77)	-14 (-26, -1)	-1.2 (-2.3, -0.2)	-0.2 (-1.2, 0.9)	-0.3 (-0.7, 0.1)	0.0 (-0.1, 0.1)		
	Exacerbations + risk (95% CI)	AACD mean (95% CI)	Pre-BD FEV1 mean (95% CI)	Post-BD FEV1 mean (95% CI)	c-ACT mean (95% CI)	PAQLQ mean (95% CI)	Exacerbations with ED visits N (%) ++	Exacerbations with Hospitalizations N (%) ++
Children								
FP 250	0.12 (0.08, 0.18)	134 (117, 151)	96.2 (93.6, 98.9)	104.4 (102.0, 106.9)	23.2 (22.7, 23.6)	6.3 (6.1, 6.4)	15 (32%)	7 (15%)
FP/SM 250/50	0.14 (0.10, 0.21)	135 (117, 152)	97.2 (94.6, 99.8)	103.8 (101.3, 106.3)	23.4 (23.0, 23.9)	6.3 (6.2, 6.4)	7 (15%)	1 (2%)
FP 100	0.2 (0.14, 0.29)	133 (116, 151)	93.9 (91.4, 96.4)	102.8 (100.4, 105.2)	22.9 (22.4, 23.4)	6.2 (6.0, 6.3)	12 (21%)	1 (2%)
FP/SM 100/50	0.09 (0.06, 0.15)	140 (123, 158)	95.9 (93.2, 98.6)	103.7 (101.2, 106.2)	23.1 (22.6, 23.6)	6.2 (6.0, 6.3)	9 (27%)	2 (6%)
Treatment Differences								
FP 250 vs. FP/SM 250/50	0.86 (0.54, 1.38)	-1 (-15, 14)	-1.0 (-2.7, 0.8)	0.6 (-1.0, 2.2)	-0.2 (-0.7, 0.2)	0.0 (-0.2, 0.1)		
FP 250 vs. FP 100	0.62 (0.39, 0.98)	1 (-12, 14)	2.3 (0.7, 4.0)	1.6 (0.1, 3.2)	0.3 (-0.1, 0.7)	0.1 (0.0, 0.2)		
FP 250 vs. FP/SM 100/50	1.3 (0.76, 2.21)	-6 (-22, 10)	0.4 (-1.5, 2.3)	0.8 (-0.9, 2.4)	0.1 (-0.4, 0.5)	0.1 (0.0, 0.2)		
FP/SM 250/50 vs. FP/SM 100/50	1.5 (0.88, 2.57)	-6 (-20, 9)	1.3 (-0.6, 3.2)	0.1 (-1.5, 2.5)	0.3 (-0.1, 0.7)	0.1 (0.0, 0.3)		
FP/SM 100/50 vs. FP 100	0.48 (0.29, 0.79)	7 (-7, 21)	2.0 (0.2, 3.8)	0.9 (-0.9, 2.7)	0.2 (-0.3, 0.7)	0.0 (-0.1, 0.1)		
+ Risk (treatment differences are odds ratios)								
++ percentage denominator is exacerbations, not subjects								

Table S9: Urine Cortisol/Creatinine Ratios at Baseline and at the End of Each Treatment Period in Children and in Adolescents/Adults

Age Groups		FP250		FP/SM 250/50		FP100		FP/SM100/50	
	Baseline	End of Trt	Ratio to Baseline	End of Trt	Ratio to Baseline	End of Trt	Ratio to Baseline	End of Trt	Ratio to Baseline
Children	0.94	0.73	0.77	0.85	0.91	0.92	0.98	0.91	0.97
< 8 years (n=122)	1.15	0.79	0.69	0.86	0.75	1.19	1.03	1.10	0.96
≥ 8 years (n=155)	0.81	0.71	0.87	0.89	1.09	0.76	0.93	0.81	1.00
		FP500		FP/SM 250/50		FP250		FP/SM 100/50	
	Baseline	End of Trt	Ratio to Baseline	End of Trt	Ratio to Baseline	End of Trt	Ratio to Baseline	End of Trt	Ratio to Baseline
Adol/Adult	0.62	0.61	0.97	0.65	1.05	0.69	1.12	0.74	1.19
Adolescent	0.55	0.47	0.86	0.55	1.00	0.73	1.34	0.86	1.28

Trt=Treatment