

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

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**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 2-2.5x ICS 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).

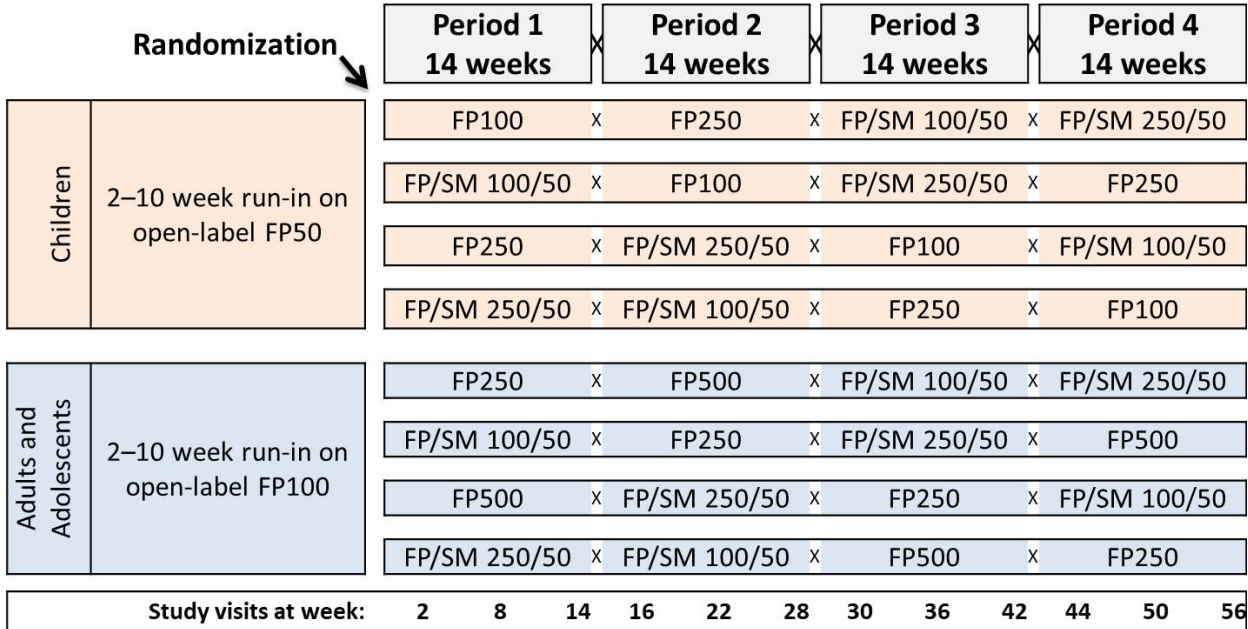


Figure 1: Study Schema. Following a 2–10 week run-in to establish adherence, safety, and eligibility, subjects were randomized to one of four different treatment sequences. These sequences constituted a Latin Square balanced for first order carry-over effects. Twice daily treatments are as follows: FP50=fluticasone 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.
679

Figure S2. CONSORT Diagrams of the of the BARD Trial Protocols in Children (<12 Years of Age).

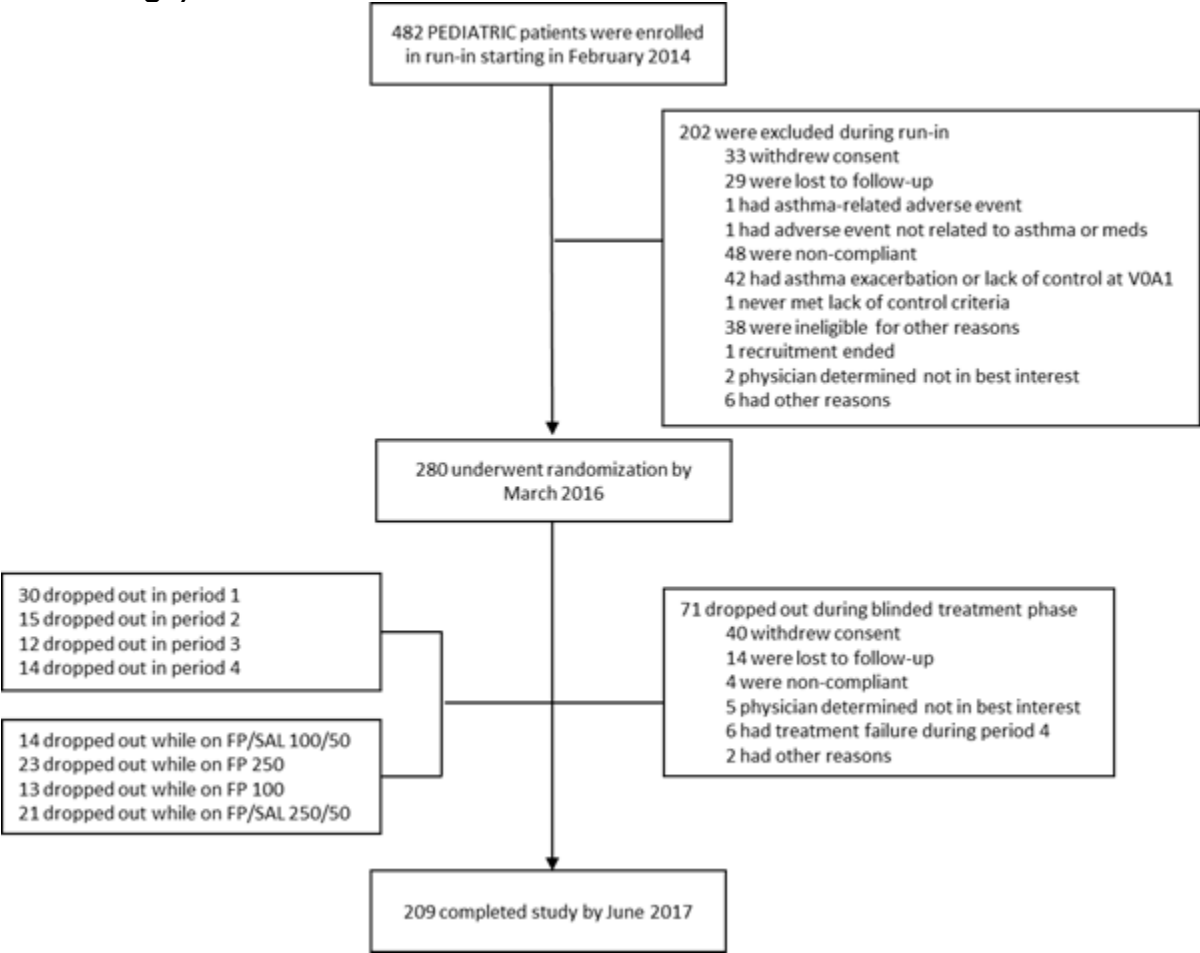


Figure S3 CONSORT Diagram of the BARD Trial Protocols in Adolescents and Adults (12 Years and older).

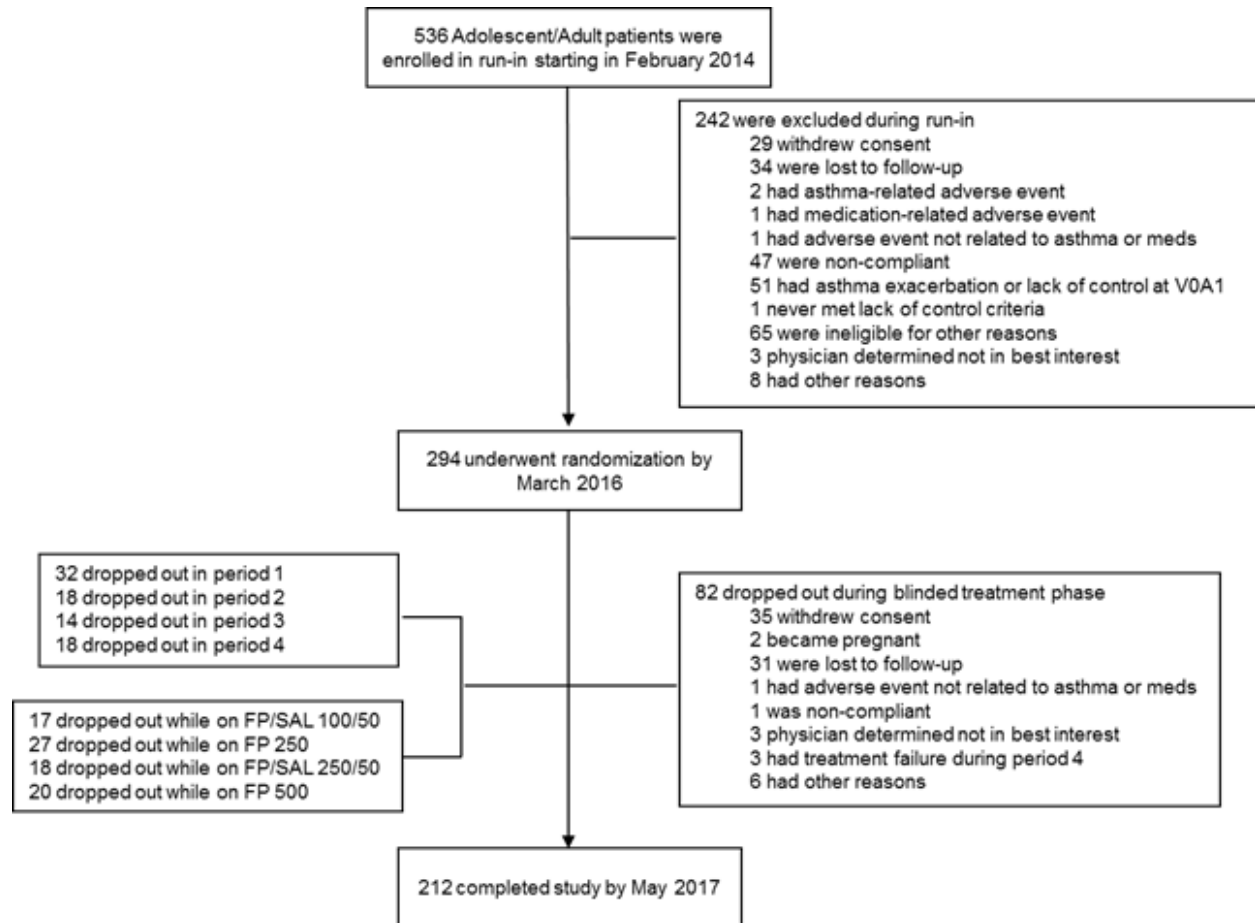
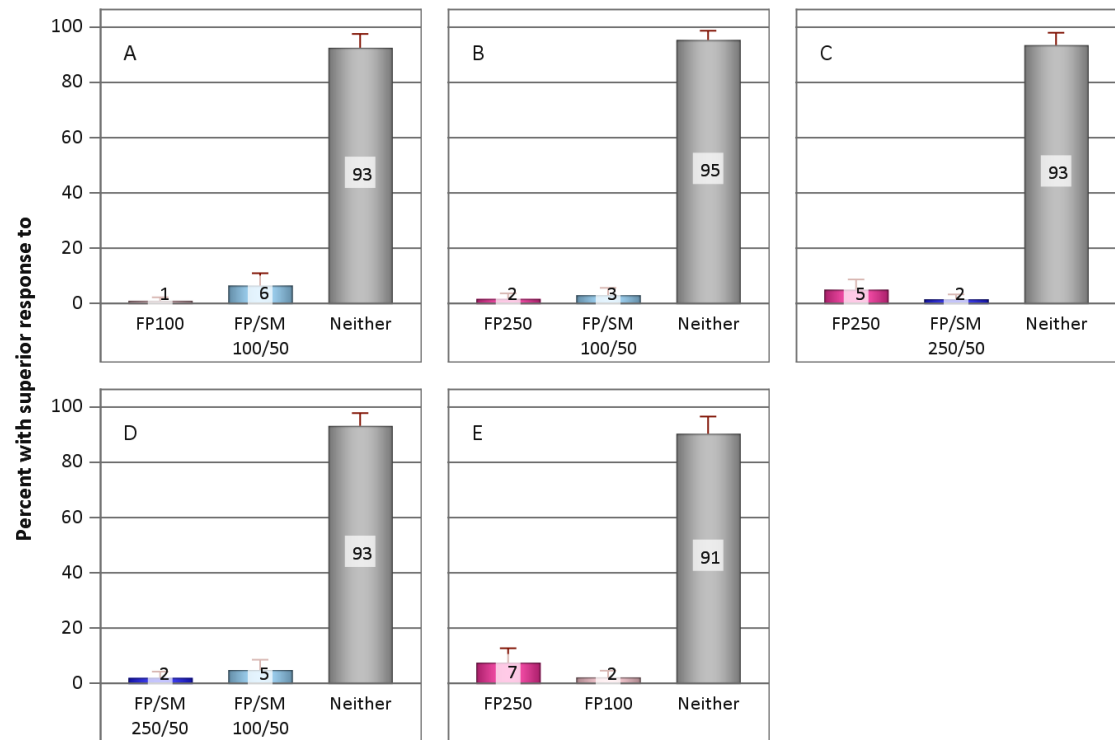
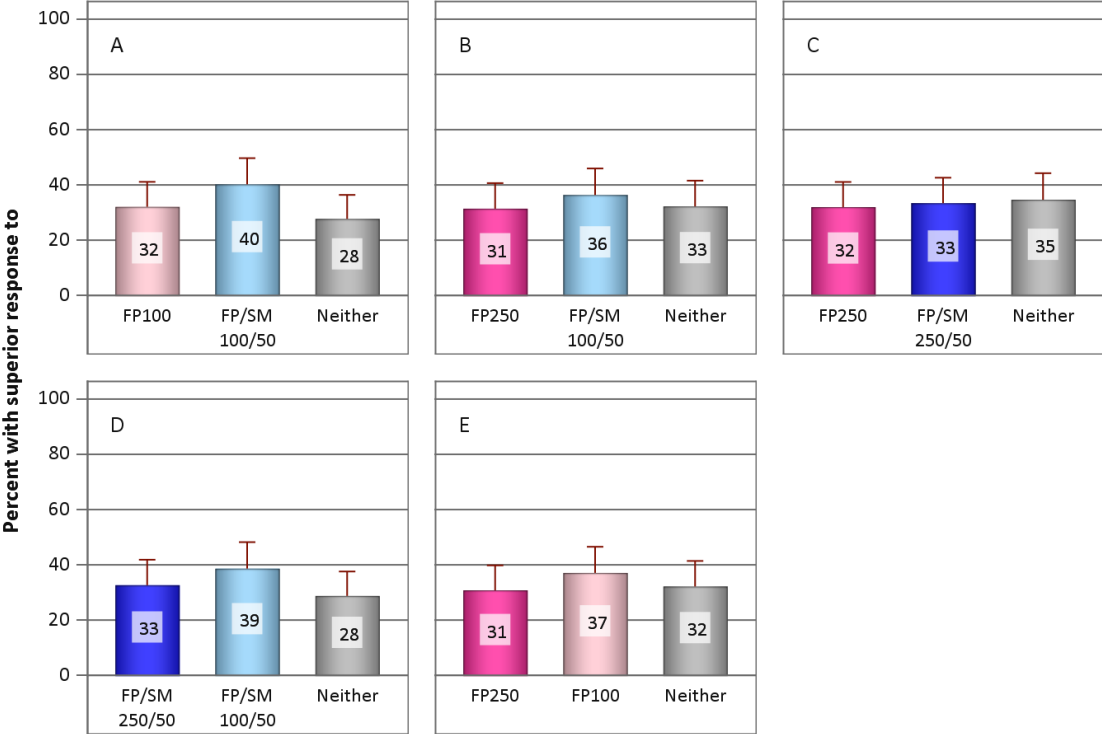


Figure S4.1-4.3: Percentage of Pediatric (5-11 Years of Age) Black Asthma Participants Showing a Superior Response to Specific Treatments Based on Exacerbations (3.1), Asthma Control Days (3.2), and FEV1 change (3.3).

S4.1: Exacerbations



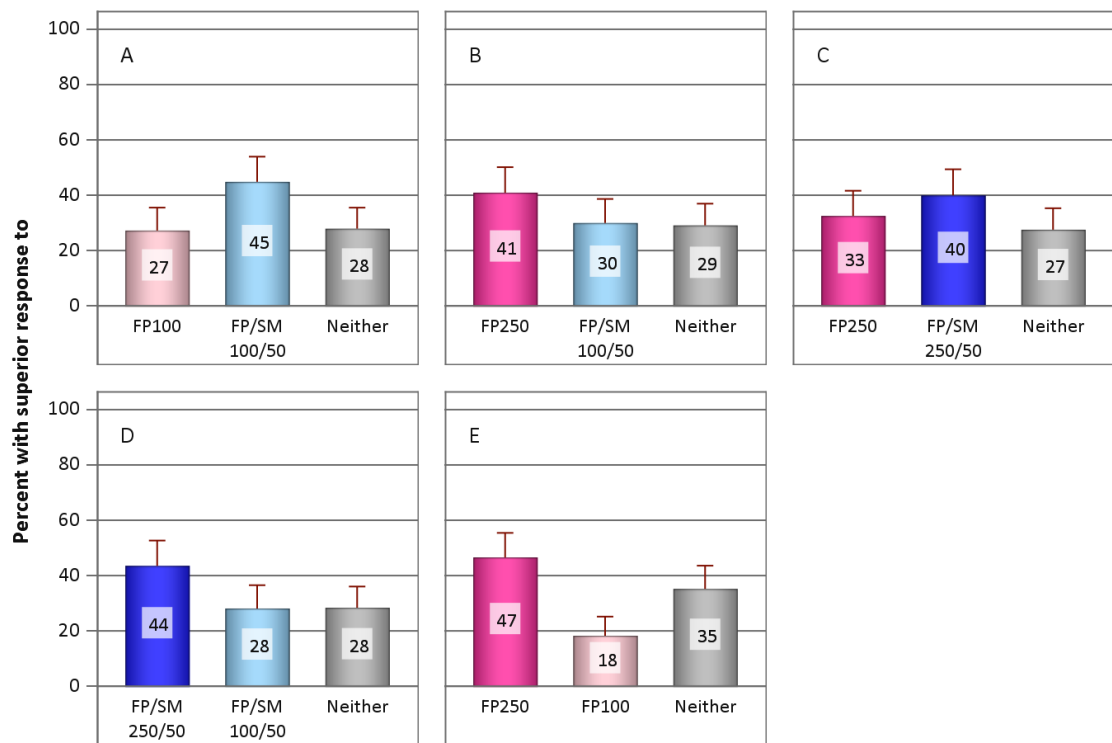
698 **S4.2: Annualized Asthma Control Days**
699



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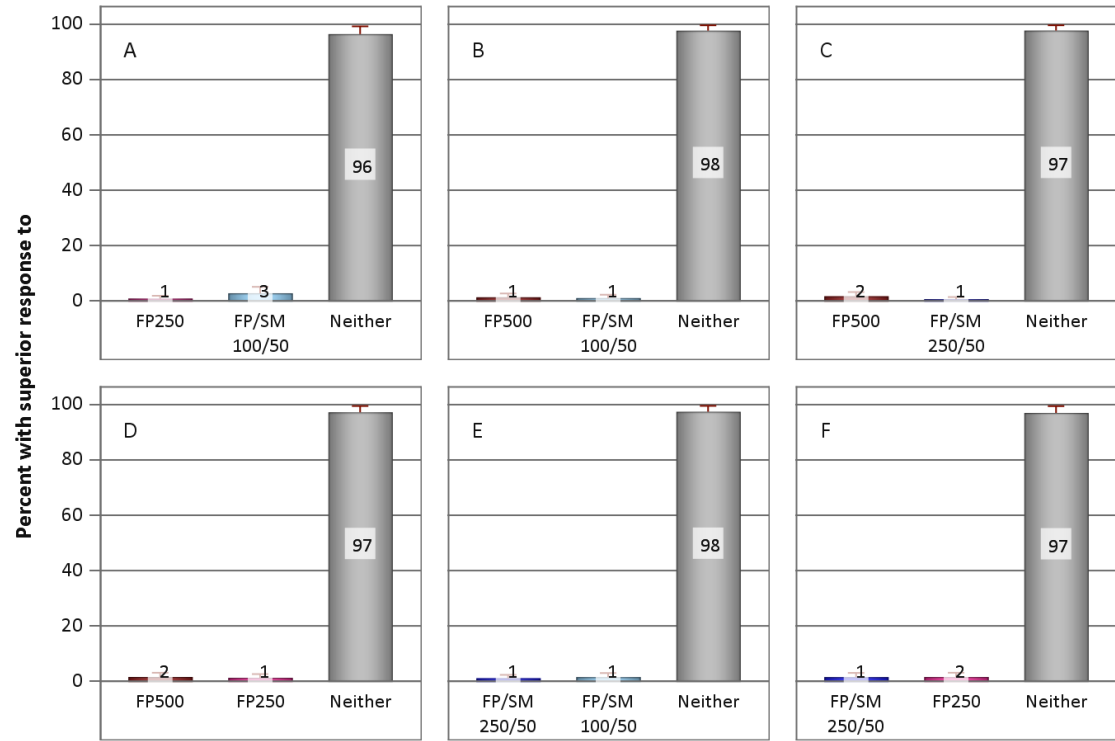
S4.3: FEV1 Change



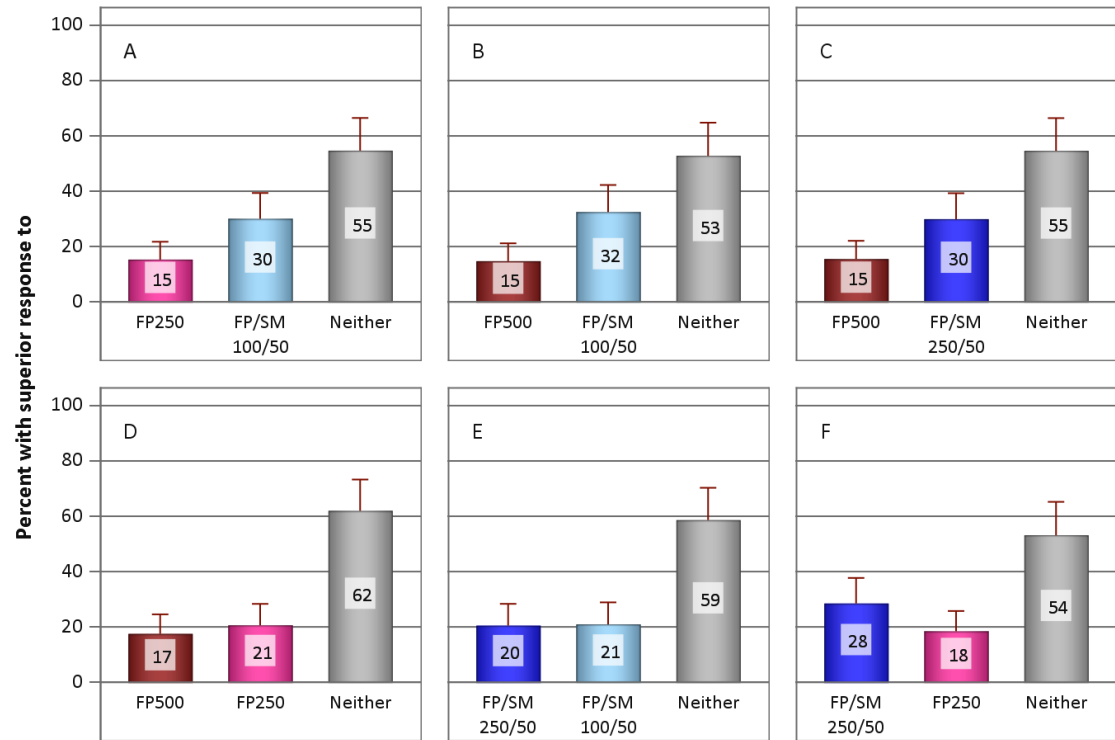
Panels A to E illustrate all comparisons of two treatment arms based on superiority of therapeutic response for exacerbations (4.1), asthma control days (4.2), and FEV1 change (4.3). The number indicated within each column represents the percentage of participants who had a superior response to that 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).

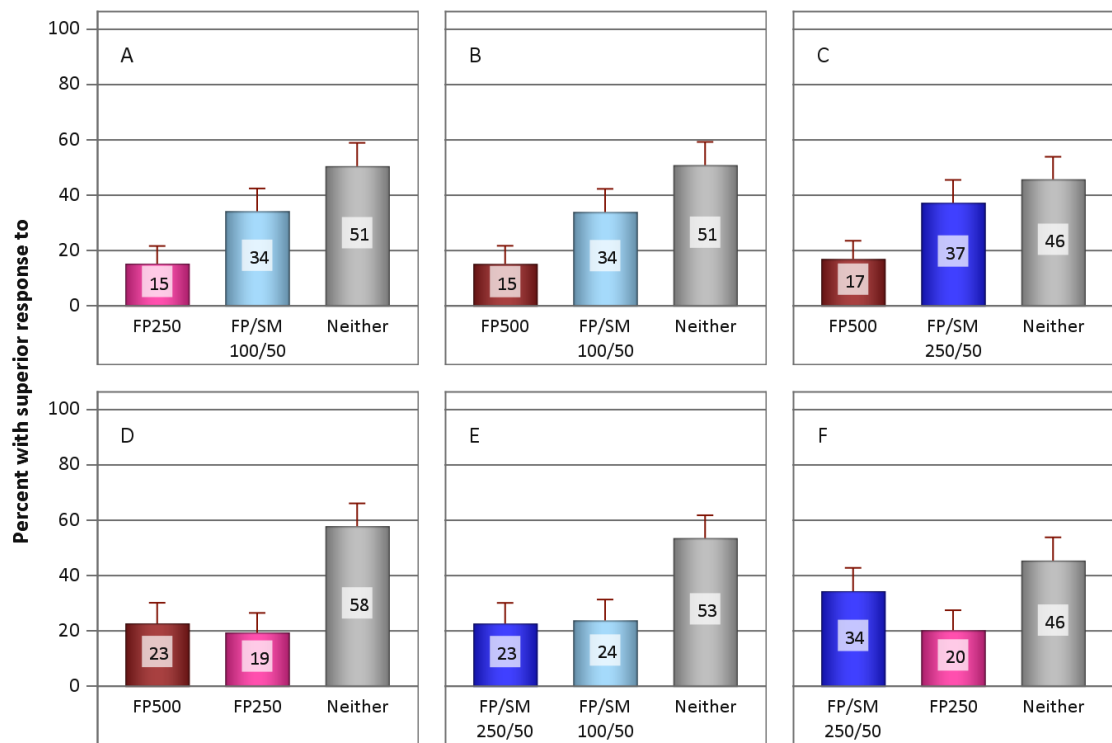
S5.1: Exacerbations



S5.2: Annualized Asthma Control Days.

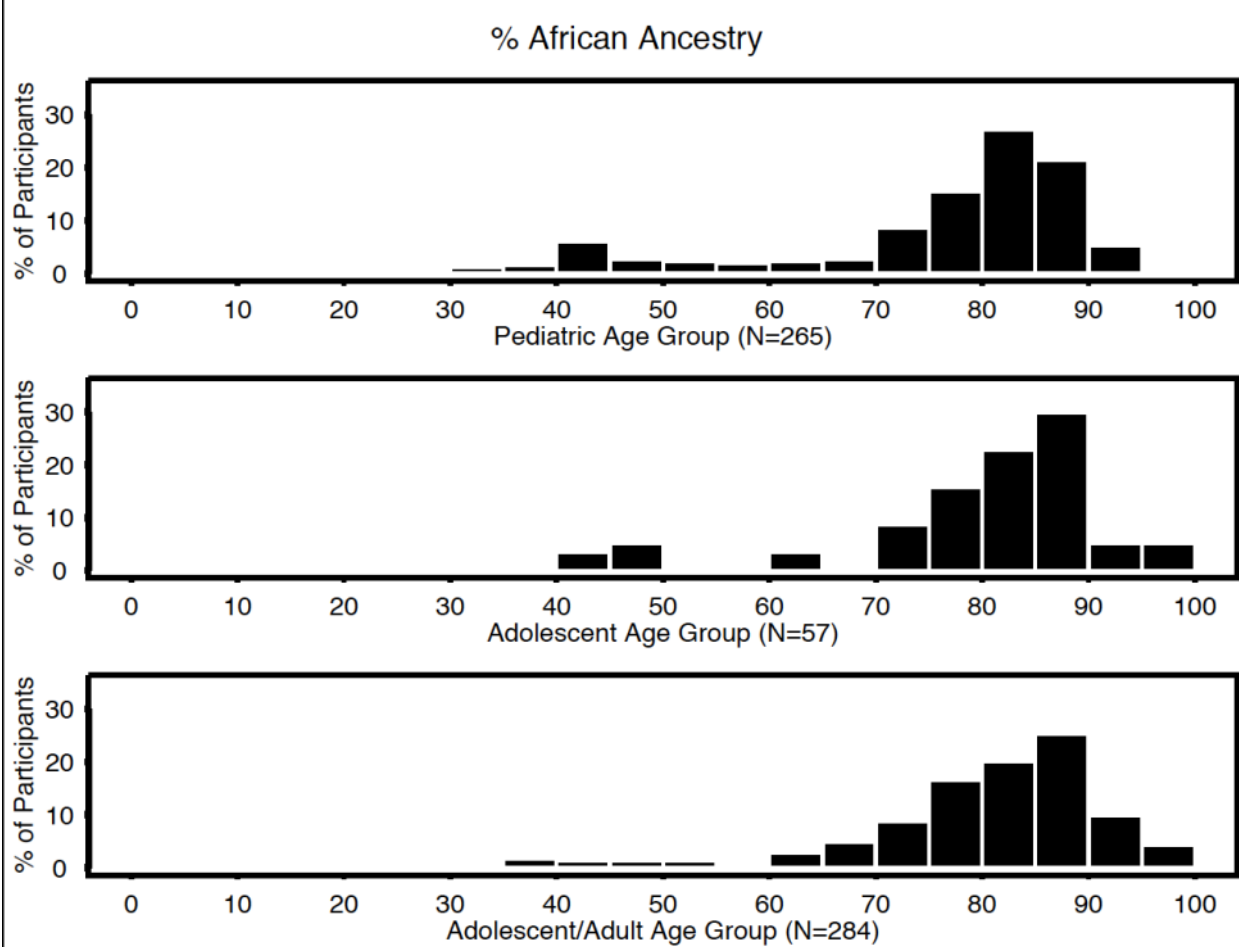


S5.3: FEV1 Change



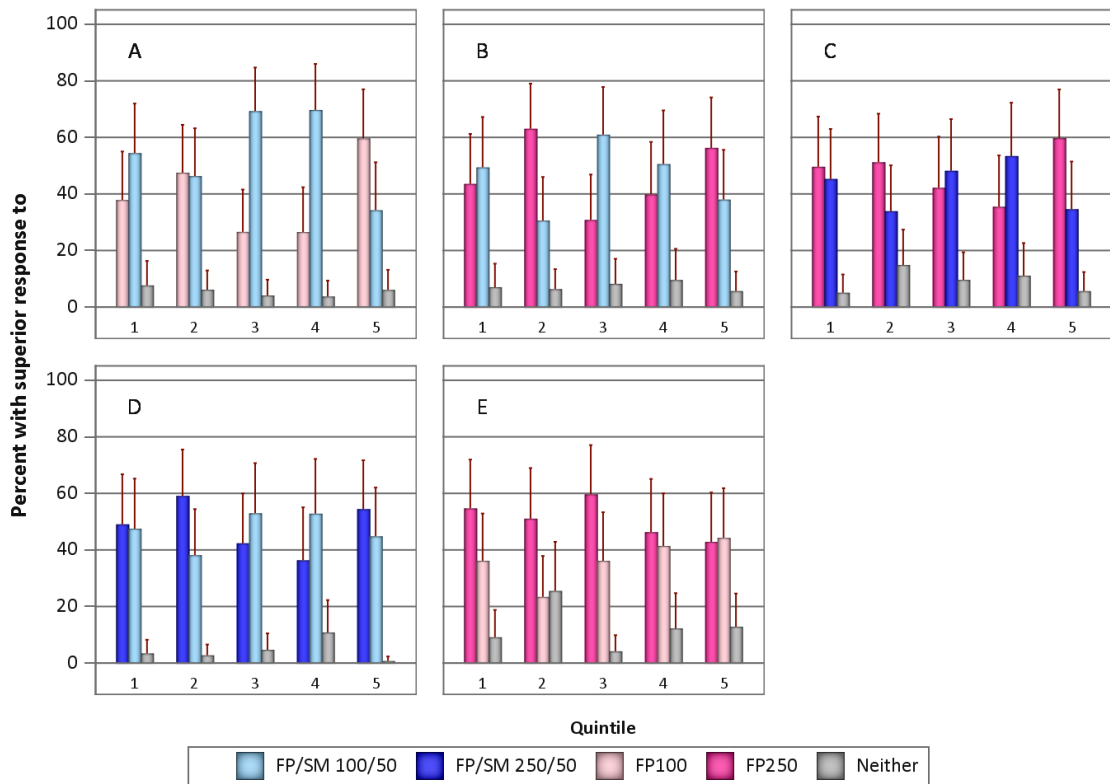
Panels A to F illustrate all comparisons of two treatment arms based on superiority of therapeutic response for exacerbations (4.1), asthma control days (4.2), and FEV1 change (4.3). The number indicated within each column represents the percentage of participants who showed a superior response to that 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.

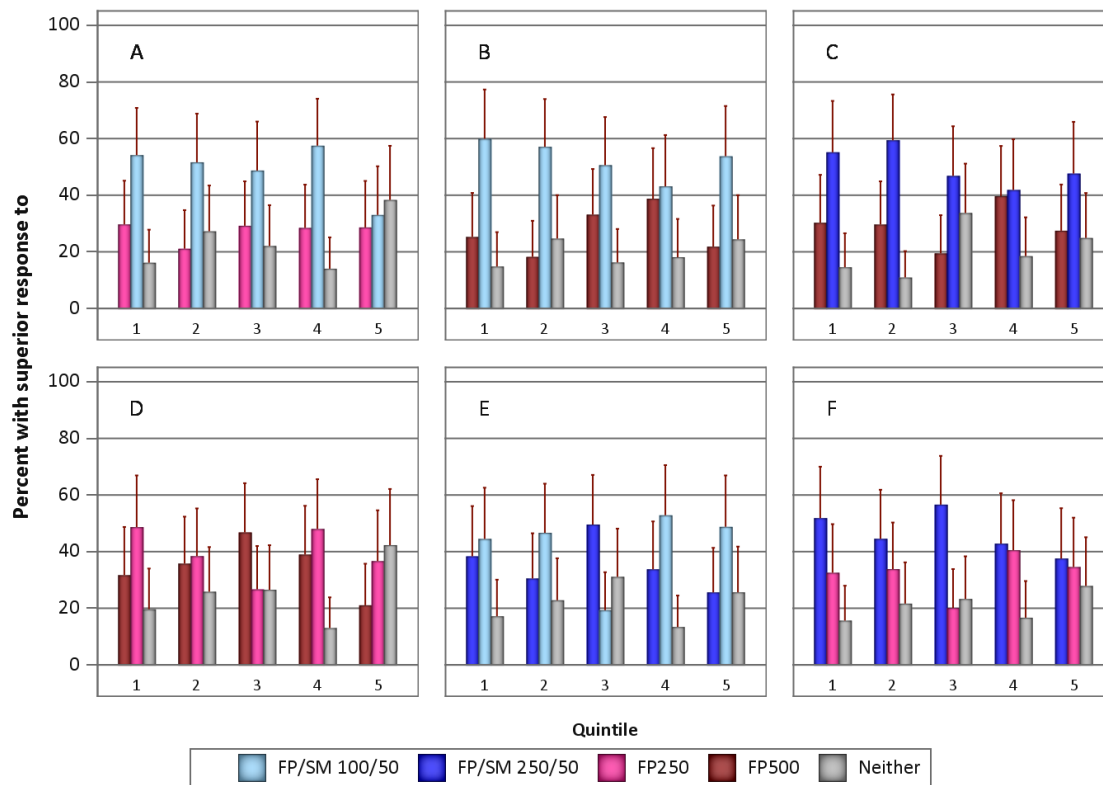
Figure S6: Distribution of Percentage African Genetic Ancestry Estimates Based on Genome-wide Genetic Data in Children, Adolescents, and Adults.



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.*
779

<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

780

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		

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 seven days that were able to be evaluated were excluded.

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

^Geometric means (CV) reported.

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