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Efficacy and safety of as-needed albuterol–budesonide versus albuterol in patients with asthma aged 12 to <18 years: design of the randomised, double-blind, parallel-group phase IIIb ACADIA trial

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ABSTRACT

Introduction Asthma among adolescents (aged 12–<18 years) is a common condition with high disease burden. Many are undertreated, at risk of adverse outcomes and exhibit poor adherence to maintenance medication. As-needed albuterol–budesonide 180/160 µg reduced the risk of severe exacerbations by 27% compared with as-needed albuterol 180 µg in patients aged ≥12 years, with moderate-to-severe asthma receiving inhaled corticosteroid (ICS) maintenance therapy in the MANDALA trial. A small number of adolescents were included in MANDALA, but data were inconclusive. The randomised, double-blind, multicentre, phase IIIb ACADIA trial is evaluating as-needed albuterol–budesonide versus as-needed albuterol in adolescents with asthma.

Methods and analysis A planned 440 adolescents (aged 12–<18 years) with asthma using as-needed albuterol with low- to high-dose ICS-containing maintenance medications (with or without other controllers) and who had ≥1 severe exacerbation in the previous 12 months are randomised to as-needed albuterol–budesonide 180/160 µg or as-needed albuterol 180 µg for 52 weeks while continuing their own maintenance therapy. The primary endpoint is the annualised rate of severe asthma exacerbations. Secondary endpoints are the time to first severe asthma exacerbation and annualised total systemic corticosteroid exposure for asthma per participant. To minimise the number of adolescents exposed to study medications, the treatment effect will be estimated by partially extrapolating results from the patient population in the MANDALA trial using a Bayesian dynamic borrowing approach.

Ethics and dissemination Ethical approval was obtained from the investigators' institutional review boards. Enrolment began in May 2024. Results will be presented at respiratory congresses and published in peer-reviewed journals.

Trial registration number NCT06307665.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ As-needed albuterol–budesonide is approved in the USA for the treatment or prevention of bronchoconstriction and to reduce exacerbation risk in patients aged ≥18 years with asthma.

WHAT THIS STUDY ADDS

⇒ This paper presents the protocol of the ACADIA study, which aims to evaluate the efficacy and safety of as-needed albuterol–budesonide in adolescents (aged 12–<18 years) with asthma.

⇒ Bayesian dynamic borrowing will be used to augment data from this study with data from patients in a similar study.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Results of this study could demonstrate the safety and efficacy of as-needed albuterol–budesonide on the risk of severe asthma exacerbations in patients aged 12–<18 years with asthma.

INTRODUCTION

Asthma is a widespread chronic condition in children and adolescents. In 2022, over 2 million adolescents (aged 12–17 years) in the USA had asthma.[1] Adolescents with asthma experience a high disease burden.[2] Between 2016 and 2018 in the USA, the prevalence of asthma attacks among adolescents was around 45–50%, which is comparable to that among 35–64 year olds.[3] In a retrospective study of claims data of patients with asthma in the USA, although 67.9% of adolescents were treated for mild asthma (not receiving inhaled corticosteroid (ICS)-containing maintenance at baseline), 63.1% experienced an asthma-related outpatient visit over the year-long follow-up period.[4] A global cross-sectional epidemiological study in 25 countries found that 26.7% of adolescents with asthma had

severe asthma and that 60.1% of them did not receive ICS-containing medication.[5] Thus, there is an unmet need for the optimal treatment of asthma in adolescents.

Adolescents exhibit poor adherence to asthma therapy, which contributes to inadequate disease control.[2] The global clinical standard of care for patients with asthma is an as-needed fast-acting reliever medication with ICS-containing maintenance medication.[6] Single maintenance and reliever therapy (MART) is a suggested strategy for improving adherence in adolescents and other higher-risk populations.[7] Although MART therapy is approved in >120 countries, ICS–formoterol is not approved in the USA for as-needed use.[8 9] As-needed therapy with ICS-containing reliever medication may be a strategy to improve disease control and clinical outcomes among adolescents with asthma.

In MANDALA (NCT03769090), as-needed albuterol–budesonide versus as-needed albuterol reduced severe exacerbation risk by 27% in patients aged ≥12 years with moderate-to-severe asthma on ICS-containing maintenance therapy.[10] Although adolescent patients (aged ≥12 to <18 years) were included in MANDALA, enrolment of adolescents was low (n=100; 3.2% of all patients).[10] This resulted in a small number of adolescents experiencing severe exacerbations (20/100 patients). Similarly, the DENALI study (NCT03847896) included only 25 adolescents (2.5% of the efficacy population),[11] and the BATURA study (NCT05505734) included only 68 adolescents (2.8% of patients).[12] Due to the inconclusive findings in the adolescent subgroup of MANDALA and small numbers of adolescent patients in other trials, additional data are needed in this population.

To address this data gap, the ACADIA trial (NCT06307665) is enrolling patients to evaluate the efficacy and safety of as-needed albuterol–budesonide 180/160 µg versus as-needed albuterol 180 µg in participants aged 12 to <18 years with asthma who are continuing their own maintenance therapy.

MATERIALS AND ANALYSIS

Study design

ACADIA is a randomised, double-blind, multicentre, parallel-group, 52-week, phase IIIb study comparing the efficacy and safety of as-needed albuterol–budesonide versus as-needed albuterol in adolescent participants aged 12 to <18 years with asthma treated with ICS-containing maintenance therapy (figure 1). Participants will be enrolled across 120 centres globally, with a majority of the sites in the USA (85 sites) and China (20 sites), with the remaining sites located in South Africa and Mexico.

Study population

Enrolment began in May 2024 and approximately 440 participants are planned, including about 40 participants from China. Participants are aged 12 to <18 years, have asthma, have had ≥1 severe exacerbation in the prior year and are receiving albuterol as needed with low-dose to high-dose ICS-containing maintenance medications, with or without an additional controller but excluding biologics. Other key inclusion and exclusion criteria are shown in table 1.

Screening

The screening period is 7–28 days before the randomisation visit (figure 1) except when a severe asthma exacerbation event occurs during this period. In that case, the period is extended to a maximum of 9 weeks (to account for a course of systemic corticosteroids (SCS) of up to 1 week in duration followed by a 4-week washout period). Screening includes demographic data collection, physical

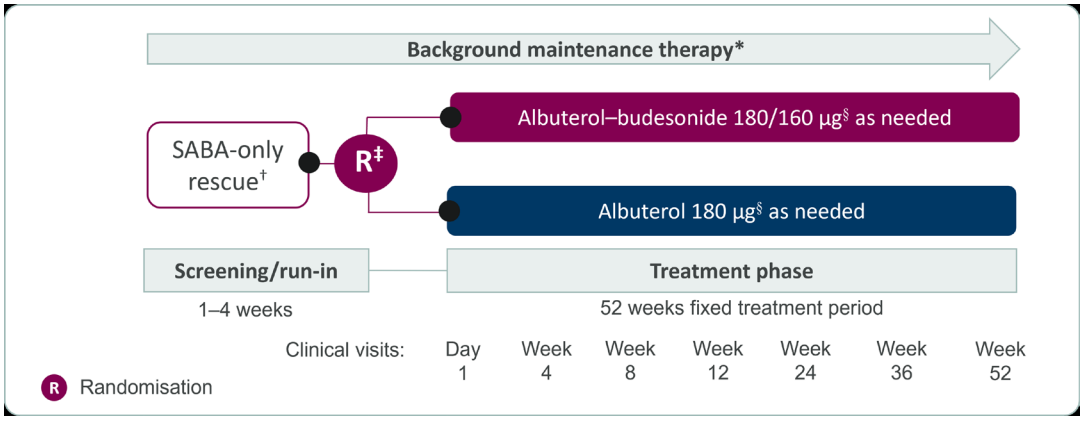

Figure 1 Overview of the ACADIA study design. *Participants continue their own maintenance medications throughout the study. †Sponsor-provided albuterol inhalation aerosol. ‡Participants are stratified by region and number of severe exacerbations (1, >1) in the 12 months prior to the screening visit. §Study medication is administered by participants as they would normally use their rescue medication (ie, in response to symptoms and prior to triggers) via pMDI in two actuations of albuterol–budesonide 90/80 µg or albuterol 90 µg per inhalation up to a maximum of 12 inhalations per day. Participants are advised to contact the investigator if their symptoms necessitate more than eight inhalations per day. pMDI, pressurised metered-dose inhaler; SABA, short-acting β_2-agonist.

Table 1 Study inclusion and exclusion criteria for the ACADIA trial

Inclusion criteria	Exclusion criteria
Aged 12 to <18 years at screening	Life-threatening asthma episode within 5 years of screening*
Confirmed clinical diagnosis of asthma ≥1 year before screening as documented by one of the following within the last 3 years before screening: ► Reversibility testing (≥12% improvement following albuterol) ► FEV_1 variability >12% between any two clinic visits ► Positive bronchial challenge test If none of the above are documented, an in-clinic, non-centralised spirometry must be performed to demonstrate ≥12% reversibility to albuterol (4 inhalations of 90 µg {360 µg}).	>3 severe asthma exacerbations within 12 months before screening
≥1 severe asthma exacerbation within 12 months before screening†	Completed treatment for severe asthma exacerbation with systemic corticosteroids within 4 weeks of screening
Use of low-dose to high-dose ICS or ICS/LABA for ≥3 months, with stable dosing for ≥1 month before screening, with or without an additional controller‡	Completed treatment for lower respiratory infection within 4 weeks of screening
Use of inhaled SABA as needed for ≥3 months prior to screening	Upper respiratory infection involving antibiotic treatment not resolved within 7 days before screening
Use of albuterol as needed in response to symptoms during screening on ≥3 of the 7 days prior to randomisation	Significant lung disease other than asthma or any other significant disease
Demonstrate acceptable MDI administration technique and reproducible PEF measurements and be willing to complete all visit assessments	Current smokers or former smokers with >10 pack-years history or who stopped smoking <6 months before screening
Negative pregnancy test and use of effective birth control	Has received any marketed or investigational biologic within 3 months or five half-lives (whichever is longer) before screening
BMI <40 kg/m^2	Oral or systemic corticosteroid use within 4 weeks of screening or chronic use (≥3 weeks use in 3 months prior to screening)
	Use of any oral SABAs within 1 month of screening

*Any asthma episode(s) requiring intubation associated with hypercapnia, respiratory arrest, hypoxic seizures or asthma-related syncopal episodes.
†Considered to be a deterioration of asthma that led to a temporary bolus/burst of systemic corticosteroids for ≥3 consecutive days, a single depo-injectable dose of corticosteroids, or a 1–2 day course of oral dexamethasone; an emergency department or urgent care visit because of asthma that requires systemic corticosteroids; or inpatient hospitalisation because of asthma.
‡Up to 30% of randomised participants will be permitted to use low-dose ICS; up to 20% will be permitted to use an additional maintenance medication (theophylline, LTRA or LAMA).
BMI, body mass index; FEV_1, forced expiratory volume in the first second; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; MDI, metered-dose inhaler; PEF, peak expiratory flow; SABA, short-acting β_2-agonist.

examination, vital signs determination, concomitant medications review, albuterol reversibility test for participants without a documented clinical diagnosis of asthma, serious adverse events (SAEs) assessment and pregnancy test. A standard medical, medication and surgical history is obtained, and previous asthma-related treatments and their durations are recorded. Non-centralised pre-bronchodilator spirometry is performed on the day of randomisation to characterise disease status and provide a baseline for asthma worsening. Medications with a time limit prior to lung function testing are described in online supplemental methods. During the run-in period, all trial participants use as-needed albuterol (90 µg/inhalation, taken as two inhalations) as needed in response to symptoms and prior to triggers along with the participant's own usual maintenance therapy. Participants turn in their own inhaled rescue therapy to the investigational sites for storage until the participant's last study visit.

Study treatment and allocation

Participants who meet the eligibility criteria are randomised via an interactive response technology/randomisation and trial supply management system to either albuterol–budesonide 180/160 µg (90/80 µg per inhalation) or albuterol 180 µg (90 µg per inhalation), both in pressurised metered-dose inhalers, in a 1:1 ratio as rescue therapy, taken as needed in addition to their usual maintenance therapy. Participants will use their study drug as needed as they would normally use their

rescue medication (ie, in response to symptoms and prior to triggers). The maximum daily dosage will not exceed 12 inhalations (six doses) per day.

The study is double-blinded, and the randomisation code will not be broken except in medical emergencies in which appropriate patient management requires knowledge of the treatment administered. Randomisation is stratified by region and number of severe asthma exacerbations in the 12 months prior to randomisation (1, >1). The number of participants on maintenance low-dose ICS therapy alone is capped at ≤30% of the total number of patients in this study. The number of participants using additional asthma maintenance medication (theophylline, leukotriene receptor antagonist (LTRA) or long-acting muscarinic antagonist (LAMA)) is capped at ≤20% of the total number of patients in this study, and patients receiving asthma biologic therapy are excluded.

Concomitant medications

ICS with or without long-acting β2-agonist (LABA) and LTRA, theophylline and LAMAs are permitted to be used as maintenance therapy, and participants will maintain stable dosing of their maintenance therapies as used during screening, unless a change is clinically indicated in accordance with Global Initiative for Asthma guidelines. No participant may receive more than three maintenance therapies. Participants receiving maintenance allergy immunotherapy may continue, but initiation of allergy immunotherapy during the study is not permitted. No reliever products other than study medication will be allowed during the treatment period, except as may be required to treat an SAE or severe asthma exacerbation. Other prohibited concomitant medications during the study are listed in online supplemental table 1.

Study withdrawals

Participants are free to discontinue treatment at any time. Other reasons for discontinuation of study medication may include an adverse event (AE), pregnancy, non-compliance with the trial protocol or loss to follow-up. A participant is considered lost to follow-up if they repeatedly fail to return for scheduled visits and are unable to be contacted by the investigational site after three attempts. A participant may be discontinued from the study at any time at the discretion of the investigator for behavioural or compliance reasons.

If a participant experiences ≥2 severe asthma exacerbations or a single severe exacerbation event >20 days in duration, the participant must be fully assessed, including for inhaler technique for maintenance and study medications. A change in maintenance therapy should also be considered, if warranted. The participant should also be evaluated for the benefit and risk of remaining in the study, and the investigator should discuss this with the medical monitor following this assessment and evaluation.

Outcome measures and endpoints

Study endpoints are shown in figure 2. The primary endpoint is the annualised rate of severe asthma exacerbations (defined in online supplemental methods). Throughout the study, participants record the best of three peak expiratory flow measures on arising in the morning and before going to bed in the evening prior to taking any asthma therapy. Participants will use an eDiary for twice-daily symptom reporting. The eDiary alerts the participant and study site when there are signs of change in asthma, which triggers a documented contact between

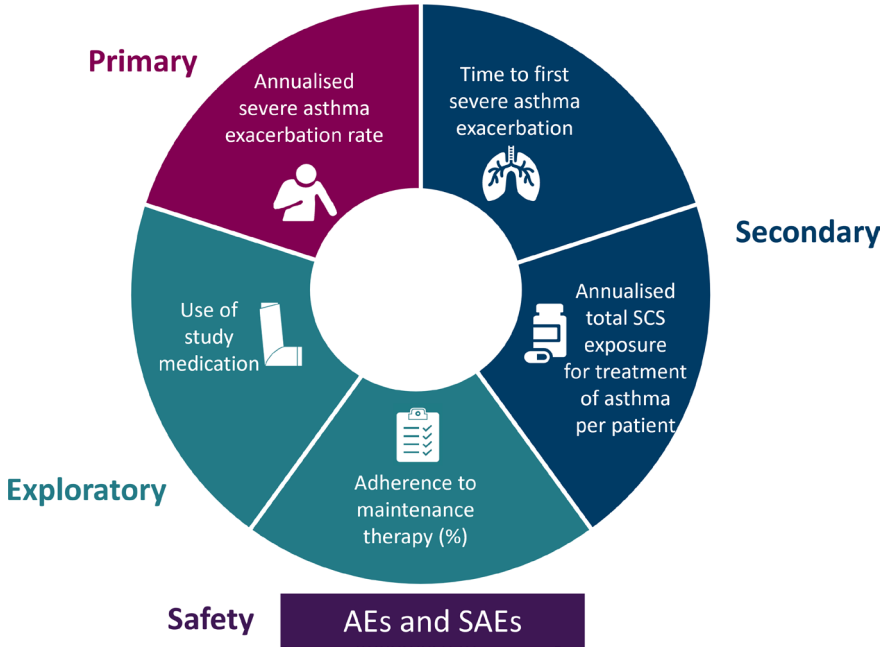

Figure 2 ACADIA study endpoints. AE, adverse event; SAE, serious adverse event; SCS, systemic corticosteroids.

the participant and the site for further evaluation if necessary.

Secondary endpoints are the time to first severe asthma exacerbation and annualised total SCS exposure for asthma treatment per participant. Exploratory endpoints are the use of study medication and adherence to maintenance therapy. In the mornings and evenings, participants enter into their eDiary the number of inhalations of rescue medication used since the previous measure.

Adolescents may have differential exposure to the study medication; as-needed regimens may align treatment with symptom-driven behaviour, potentially improving anti-inflammatory exposure compared with separate maintenance ICS therapy. Therefore, study drug exposure will be estimated using eDiary entries for timing and frequency of as-needed use, together with dispensing records and device-integrated dose counters read at clinic visits without collecting the inhalers. Discrepancies between eDiary and dose counter reading at visits will trigger additional training to improve accurate eDiary capture. Study sites will use visit reminders and brief adherence check-ins between visits per protocol to support consistent reporting. Inhaler technique will be assessed and reinforced at each visit using standardised checklists.

For patients on background maintenance therapy at screening, in addition to pharmacy refill data, self-reported adherence will be monitored through the eDiary. Baseline counselling on correct use will be provided. Inhalers will not be collected for measurement or assessment of adherence.

Safety assessments

Safety endpoints include the type, duration, intensity, investigator-rated causality, action taken and outcome of AEs and SAEs. A complete physical examination will be performed at screening and at the end of treatment or at the premature discontinuation visit; this will include assessments of body mass index, general appearance, respiratory system, cardiovascular system, abdomen, skin, head and neck (including ears, eyes, nose and throat), lymph nodes, thyroid, musculoskeletal system (including spine and extremities) and neurological system. Vital signs (heart rate and blood pressure) will be assessed at screening, and any changes to vital signs will be recorded as an AE. An AE is defined as the development of any untoward medical occurrence in a participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment. Any unfavourable and unintended sign, symptom or disease temporally associated with the use of a medicinal product will be considered an AE. An AE may occur at any time, including run-in or washout periods, even if no study intervention has been administered.

An SAE is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up) that: (1) results in death; (2) is immediately life-threatening; (3) requires inpatient hospitalisation or prolongation of existing hospitalisation; (4) results in persistent or significant disability or incapacity; (5) is a congenital anomaly or birth defect; or (6) is an important medical event that may jeopardise the participant or may require medical treatment to prevent one of the outcomes listed above.

Severe asthma exacerbations will be considered study efficacy endpoints and will not be reported as AEs unless considered an SAE. SAEs will be reported as per standard reporting requirements.

Statistics and data analysis

Efficacy analyses will be conducted using the full analysis set (FAS), which includes all participants who are randomised to treatment and receive ≥1 inhalation of study medication; participants will be analysed according to the treatment assigned at randomisation. The safety population is all randomised participants who receive ≥1 inhalation of study medication post-randomisation; erroneously treated participants are counted in the treatment group of the treatment they received.

A sample size of approximately 440 participants is required for randomisation (1:1) to provide approximately 84% power and control the type I error rate (one-sided) at approximately 30% (see online supplemental methods). The sample size calculations are based on 10 000 simulations and assume a prior weight of 50% on the results borrowed from the ≥12 years old population from the MANDALA trial (rate ratio 0.75; 95% CI 0.61 to 0.91), annualised rate of severe asthma exacerbations in the control arm of 0.6, dispersion parameter of 2.0 and a uniform dropout rate of 10% over the duration of the study. It is expected a priori that the posterior effective sample size will be approximately 1799, such that approximately 76% of the information is contributed by patients in the MANDALA study to support the conclusions in adolescents.

The overall type I error is controlled for the primary and secondary endpoints using a hierarchical fixed-sequence testing strategy (see online supplemental methods). A treatment policy approach will be used for the primary and secondary endpoints, such that the analyses will include all observed data whether or not there was a step-up in maintenance therapy or discontinuation of study drug (table 2). The treatment effect will be estimated using the posterior distribution of the severe asthma exacerbation rate ratio, summarised as the posterior median along with a 95% credible interval.

For the primary treatment comparison of albuterol–budesonide 180/160 µg versus albuterol 180 µg, the annualised asthma exacerbations rate ratio will be estimated (table 2). The number of protocol-defined severe asthma exacerbation events over the treatment period will be compared using a Bayesian negative binomial generalised linear model using the Robust Mixture Prior framework,[13 14] borrowing from the MANDALA study in participants aged ≥12 years. Covariates and factors

Table 2 Statistical analyses for the ACADIA trial

Category	Endpoint	Intercurrent event strategy	Population-level summary (analysis)
Primary efficacy	Annualised rate of severe asthma exacerbations	A treatment policy approach that includes all observed data, regardless of the occurrence of an intercurrent event (step-up in maintenance therapy or discontinuation of study drug)	Posterior median rate ratio as obtained from a Bayesian dynamic borrowing model
Secondary efficacy	Time to first severe asthma exacerbation		HR from Cox proportional hazards model
Secondary efficacy	Annualised total SCS exposure for treatment of asthma per participant		Difference in treatment means
Exploratory efficacy	Use of study medication	N/A	Descriptive statistics
Exploratory efficacy	Adherence to maintenance therapy (%)	N/A	Descriptive statistics
Safety	AEs and SAEs	N/A	Descriptive statistics

AE, adverse event; HR, hazard ratio; N/A, not applicable; SAE, serious adverse event; SCS, systemic corticosteroids.

included in the model will comprise treatment group, region and number of prior severe exacerbations (1, >1) in the 12 months prior to randomisation. The Robust Mixture Prior consists of an informative component and a non-informative component prior, which facilitates partial extrapolation. The observed results in MANDALA in the population aged ≥12 years will form the informative part of the mixture prior for the rate ratio (on a log scale) in adolescents, with a prior weight of 50%. The prior weight represents the a priori belief in the consistency of treatment effect in adolescents and adult populations. The prior weight value of 50% was validated using an expert elicitation exercise conducted to gather expert opinions from 12 leading paediatric asthma experts on the extent to which asthma is similar between adults and adolescents. The expert elicitation process gathered estimates for disease similarity, drug pharmacology and response to treatment in adults and adolescents. Experts believed that the extent to which the evidence of efficacy of albuterol–budesonide 180/160 µg generated in the adult population could be applied to the adolescent population was 63%, based on a mean-fitted gamma distribution of Cooke's ranking of experts. Therefore, the prior weight value can be considered appropriate.

To evaluate the sensitivity of the results of the primary endpoint analysis to departure from the underlying assumptions about missing data, multiple imputation analyses will be performed which allow for different underlying assumptions to be used. To assess the sensitivity to the strength of the prior belief in the consistency of the treatment effect in adolescents and adults, a Bayesian tipping point analysis will be performed to identify the prior weight placed on the informative component of the Robust Mixture Prior at which the estimated posterior rate ratio demonstrates efficacy.

The secondary endpoint of time to first severe asthma exacerbation will be analysed via a Cox proportional hazards model (table 2) with factors for treatment group, region and number of prior severe exacerbations (1, >1) in the 12 months prior to randomisation. Participants without an exacerbation will be censored on the date of the last exacerbation assessment. Treatment comparison will be presented as an estimated adjusted HR, and time to first severe exacerbation by treatment will be presented as Kaplan-Meier estimates and descriptive statistics. Supplemental Bayesian borrowing analysis of time to first severe asthma exacerbation will be carried out using a Robust Mixture Prior framework for a Cox model borrowing the observed time to first severe exacerbation results in the MANDALA trial, equivalent to the primary model.

For the secondary endpoint of annualised total SCS exposure for treatment of asthma per participant, each SCS exposure will be normalised to the equipotent dose of prednisone before calculating the annualised total dose. The two groups will be compared using a Wilcoxon rank-sum test. Total SCS exposure will be descriptively summarised as the total number of days with SCS treatment due to asthma for all participants.

For the exploratory endpoint of study medication use, descriptive summaries of the total daily number of inhalations of study medication and rate of use of study medication will be presented for all participants in the FAS by treatment group (table 2). Descriptive summaries of the exploratory endpoint of adherence to maintenance therapy will be presented by treatment for morning, evening and overall (table 2).

For safety data, descriptive statistics will be reported for AEs and SAEs (table 2). Safety data will not be extrapolated from adults in the MANDALA trial; instead, safety will be evaluated based on data from those enrolled in ACADIA for 52 weeks and the 100 adolescents enrolled in MANDALA for at least 24 weeks.

Patient and public involvement

This study was designed with patient and public involvement. During study design development, the sponsor conducted a 'voice of the patient' research project to better understand paediatric patients with asthma and

the views of their parents/caregivers (n=30) on their experiences of living with asthma and attitudes towards clinical trials. This multi-stage assessment consisted of a digital ethnographic diary that recorded the experience of the patient and their parent/caregiver over 14 days, 60-minute telephone interviews with both the patient and their parent/caregiver, and 30-minute follow-up interviews with the patient and their parent/caregiver. This project revealed that parents/caregivers wished to explore new treatment options, sought a greater sense of normalcy and required trial designs to fit into a busy schedule. Central to the patient's participation in a trial were clear and transparent information, realistic expectations from trials and an understanding of how a trial would differ from currently approved treatments from the perspective of safety, benefit, risk and time.

ACADIA was designed in line with these insights: (1) an asthma diagnosis will most often be documented with historical medical chart information, (2) only one spirometry assessment will be conducted at baseline, (3) health-related outcomes will not be collected at baseline or during the treatment period, (4) clinic visits will be shorter and have few procedures so that patient burden is minimised and (5) age-appropriate consent materials will be shared to ensure clear understanding of the benefit-risk profile for the participants and their parents/caregivers.

Ethics and dissemination

This study involves human participants and ethics approval of the trial protocol was obtained from the investigators' institutional review board (Coordinating Investigator's IRB approval ID: Site 7817, Vanderbilt University Medical Center, Human Research Protections Programme, IRB #241495). Ethics approval was also obtained from all other local ethics committees (see online supplemental methods).

The study is being conducted in accordance with the Declaration of Helsinki and International Council on Harmonisation Good Clinical Practice guidelines, and all participants and caregivers will provide written informed consent.

Participants are assigned a unique identifier, and participant records or datasets transferred to the Sponsor will only contain the identifier and no names or other identifiable information. The trial is registered on ClinicalTrials.gov, ID NCT06307665, and the summary of main results will be posted there once available. Key results will be presented at national and international respiratory congresses and published in peer-reviewed publications. This clinical trial protocol is reported according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) reporting guidelines.[15] Further details on ethics and dissemination are provided in online supplemental methods.

DISCUSSION

Improving outcomes for adolescents with asthma remains an important unmet need due to the high disease burden they experience. MANDALA provided evidence on the efficacy of as-needed albuterol–budesonide versus albuterol in patients with moderate-to-severe asthma, but had sparse data on adolescents, as did other trials testing this medication. The ACADIA trial will fill this gap by evaluating the efficacy and safety of as-needed albuterol–budesonide versus as-needed albuterol in participants aged 12 to <18 years with asthma. In addition, ACADIA allows continued use of the patient's current maintenance therapy.

The ACADIA trial was designed to be patient-friendly, and several aspects are aligned with patient and caregiver insights from a prior 'voice of the patient' project. Fewer procedures are required at clinic visits (the main study requires no serial spirometry or venipuncture), making trial participation more appealing to adolescent participants and shortening the time needed for study visits. The fewer required procedures and no centralised spirometry in the ACADIA trial create less of a time burden for patients and study investigators.

The US Food and Drug Administration (FDA) recommends that, for products being developed for use in both adults and children, effectiveness studies in adults should be conducted and appropriately extrapolated to children to minimise the need to recruit children in clinical trials.[16] The International Council for Harmonisation Guideline E11A on paediatric extrapolation, adopted by the European Medicines Agency and the US FDA, supports Bayesian approaches as a methodology for integrating data.[17 18] Bayesian dynamic borrowing is used in ACADIA to support the estimation of treatment effect with existing data to allow for the partial extrapolation of results from the MANDALA population to adolescents.[13] The dynamic borrowing approach uses the treatment effect estimate from the MANDALA study to support the estimation in adolescents by increasing the effective sample size in adolescents through borrowing. The amount borrowed is reactive to how similar the new data in adolescents are to the existing data from the MANDALA study, borrowing more when the data are similar and less when they are dissimilar.[13]

Bayesian methods facilitate the extrapolation of adult data, enabling the sample size of adolescents to be smaller, thus reducing the number of adolescents exposed to study medications and procedures. The bridging of information from adults to adolescents can also facilitate more timely access to medications or treatments. The Bayesian approach is appropriate for this trial and is aligned with the International Council for Harmonisation guidelines on paediatric extrapolation. Moreover, the similarities in disease characteristics, expected pharmacology and treatment response between adults and adolescents support the extrapolation of adult data to adolescents.[19] More specifically, the pathophysiology and endotypes of asthma exhibit similarities and differences between ages, but during periods of bronchoconstriction and asthma worsening, the disease processes are sufficiently similar. Further, the mechanisms of action of albuterol and

budesonide are the same across ages. Fast-acting bronchodilator–ICS combinations used as rescue treatments uniformly demonstrate efficacy in both adolescents and adults versus increased scheduled doses of ICS without a fast-acting bronchodilator, which uniformly do not demonstrate efficacy in both adolescents and adults. Finally, rescue inhaler use is similar in adolescents and adults.

The MANDALA trial data are suitable for Bayesian borrowing due to similarities between the trials. Inclusion criteria were similar between MANDALA[10] and ACADIA. The dosage level of albuterol–budesonide (180/160 µg) in ACADIA is identical to that in MANDALA[10] and is the approved dose for adults.[20] In addition, the primary endpoint of ACADIA aligns with a key secondary endpoint in MANDALA[10] and with the approved albuterol–budesonide indication of reduction in the risk of exacerbations.[20] Secondary endpoints of ACADIA align with the primary endpoint of time to first severe asthma exacerbation and the key secondary endpoint of total SCS exposure for asthma in the MANDALA study.

A limitation of this study is that adolescents treated with SABA alone are excluded from the trial. However, many adolescents use SABA alone[4 5]; therefore, a trial that enrols adolescents on SABA alone versus albuterol–budesonide alone is still needed.

Bayesian borrowing will have an increase in type I error when compared with traditional designs; as detailed prior, the one-sided type I error rate is expected to be 30%. However, the type I error rate will be controlled across the primary and secondary endpoint analyses using a fixed-sequence hierarchical testing strategy to evaluate in sequence the ordered null hypotheses. It is worth noting that the increased type I error is under the conservative assumption that there is no treatment effect, which is contradicted by the existing data from the MANDALA trial that has established as-needed albuterol–budesonide 180/160 µg as effective in reducing severe exacerbations in patients aged ≥12 years.[10]

Even though the combination of anti-inflammatory therapy with rescue use may mitigate traditional adherence barriers to daily ICS use, differences in study drug exposure may influence the observed efficacy of an as-needed regimen. Patterns of medication use in the adolescent data will be summarised and reported along with the efficacy results. In the MANDALA study, among adolescents, mean daily use of as-needed rescue therapy was 2.9 and 2.6 inhalations per day of albuterol–budesonide 180/160 µg and albuterol 160 µg, respectively. Among adults, mean daily use of as-needed rescue therapy was 2.6 and 2.8 inhalations per day of albuterol–budesonide 180/160 µg and albuterol 160 µg, respectively.[21] Daily as-needed inhalations of rescue therapy in a number of budesonide–formoterol MART studies have shown that use of as-needed budesonide–formoterol was low in both adults and adolescents, but sufficiently similar between the two populations. However, we note that adherence measures based on dose counters and self-report have inherent inaccuracies; technique and device loss may complicate the interpretation of data, and the study is not powered to detect the causal effect of adherence on outcomes.

Bayesian dynamic borrowing has been used in several prior instances, including to extrapolate the treatment effect of mepolizumab in adolescents from a trial in patients with severe asthma in which only about 4% of the patients were aged 12–17 years.[13] This approach has also been used to extrapolate data on exposure to belimumab from adults to children with lupus nephritis[22] and to leverage data from adult trials to support data from a paediatric clinical trial on empagliflozin and linagliptin in type 2 diabetes.[23] In addition, Bayesian dynamic borrowing was used to supplement the sample size for a trial in China to meet the governmental requirement of testing in Chinese patients for approval of a new drug.[24]

In summary, by focusing solely on an adolescent population and employing a Bayesian dynamic borrowing analysis, ACADIA will provide data on the efficacy of as-needed albuterol–budesonide in adolescents with asthma and will minimise exposure of this vulnerable group with asthma to clinical investigation, providing access to this medicine in a timelier manner than a traditional study.

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