VERSION HISTORY

Bond Avillion 2 Development LP

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A Randomized, Double-blind, Single-Dose, 2-Period, Crossover Study to Assess the Efficacy of PT027 Compared with Placebo on Exercise-Induced Bronchoconstriction in Adult and Adolescent Subjects with Asthma (TYREE)

Sponsor: ***Bond Avillion 2 Development LP, Nerine House, St George's Place, St Peter Port, Guernsey, GY1 3ZG***

Version 1.0, 25 Oct 2019
Initial creation

This Clinical Study Protocol has been subject to a peer review according to Bond Avillion 2 Development LP Standard procedures. The Clinical Study Protocol is publicly registered and the results are disclosed and/or published according to the Bond Avillion 2 Development LP Global Policy on Bioethics and in compliance with prevailing laws and regulations.

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CLINICAL STUDY PROTOCOL SYNOPSIS

A Randomized, Double-blind, Single-Dose, 2-Period, Crossover Study to Assess the Efficacy of PT027 Compared with Placebo on Exercise-Induced Bronchoconstriction in Adult and Adolescent Subjects with Asthma (TYREE)

Coordinating Investigator

Craig LaForce, MD

[redacted]

Study site(s) and number of subjects planned

Approximately 6 study sites in the United States are anticipated to be included. A total of 60 adult and adolescent subjects (12 to 70 years of age) will be randomized. Due to an anticipated screen failure rate of 50%, approximately 120 subjects will be screened.

Phase of development

Phase III

Study design

This will be a multicenter, randomized, double-blind, single-dose, placebo-controlled, 2-period, crossover study to evaluate the efficacy and safety of budesonide/albuterol metered-dose inhaler (PT027; hereafter referred to as BDA MDI), as compared with placebo MDI on exercise-induced bronchoconstriction (EIB) in adult and adolescent subjects (12 to 70 years of age) with asthma.

Approximately 60 subjects will be randomized 1:1 to 1 of 2 treatment sequences (ie, A/B or B/A) as specified in Table 1:

Table 1 Treatment sequences

Treatment sequence	***Visit 3/Period 1***	***Visit 4/Period 2***
A/B	*BDA MDI 160/180 µg (given as 2 actuations of BDA MDI 80/90 µg)*	*Placebo MDI (given as 2 actuations)*
B/A	*Placebo MDI (given as 2 actuations)*	*BDA MDI 160/180 µg (given as 2 actuations of BDA MDI 80/90 µg)*

Abbreviations: BDA=budesonide/albuterol; MDI metered-dose inhaler.

Objectives

Primary Objective:	**Outcome Measure:**
To assess the efficacy of a single dose of BDA MDI (160/180 µg) compared with placebo MDI on EIB in adult and adolescent subjects with asthma	*The maximum percentage fall from post-dose, pre-exercise baseline in forced expiratory volume in 1 second (FEV_1) observed up to 60 minutes post-exercise challenge*

Secondary Objective:	**Outcome Measure:**
To further assess the efficacy of a single dose of BDA MDI compared with placebo MDI on EIB in adult and adolescent subjects with asthma	*Percentage of subjects with a maximum percentage fall in FEV_1 post-exercise challenge of <10%*

Safety Objective:	**Outcome Measure:**
To evaluate the safety and tolerability of BDA MDI relative to placebo MDI on EIB in adult and adolescent subjects with asthma	*Incidence of adverse events (AEs)/serious AEs (SAEs)*

Exploratory Objectives:	**Outcome Measures:**
To characterize the effect of BDA MDI 160/180 µg administered as a single-dose on bronchoconstriction compared with placebo	1. *Percentage of subjects with a maximum percentage fall in FEV_1 post-exercise challenge of <20%* 2. *Time to recovery, defined as the time from completion of the exercise challenge to the first measured post-exercise challenge FEV_1 value within 10% of the post-dose, pre-exercise challenge baseline FEV_1* 3. *The percentage fall from baseline in FEV_1 at each time point within 60 minutes post-exercise challenge* 4. *Post-exercise FEV_1 area under the curve from 0 to 30 minutes ($AUC_{0\text{-}30min}$)*

Target subject population

The target population will be outpatient subjects 12 to 70 years of age with asthma and EIB.

Two subgroups of equal size will be included in the study, 1 subgroup of subjects currently treated with short/rapid-acting β2-adrenoreceptor agonist (SABA) prn alone, and a second subgroup on low-to-medium-dose inhaled corticosteroid (ICS) maintenance therapy (according to Global Initiative for Asthma [GINA] guidelines) and SABA prn.

Duration of treatment

The randomized treatment phase will start after a 1 to 2-week screening period (Visits 1 and 2). The double-blind treatment will occur with single dosing of investigational product (IP) at Visits 3 and 4, which will be approximately 1 week apart. The overall study duration will take approximately 3 to 4 weeks.

Investigational product, dosage and mode of administration

Investigational Product will be BDA MDI and a matching placebo MDI, which will be used as the comparator. The IP will be administered as a single dose as follows:

- BDA MDI 160/180 µg (given as 2 inhalations of BDA MDI 80/90 µg per puff)
- Placebo MDI (given as 2 inhalations)

At Visit 3/Period 1 and Visit 4/Period 2, IP will be administered 30 (±5) minutes prior to the exercise challenge. During the study, subjects will not be allowed to use any asthma medication other than the SABA prn or ICS plus SABA prn that they were using before study entry. Subjects will be restricted from SABA within 6 hours before any lung function testing and/or exercise testing. Non-asthma medications which are necessary for the subject's safety and wellbeing, and which do not affect the participation in or results of the study, are allowed at the discretion of the investigator.

Statistical methods

Sample Size

Prior studies of a similar design have randomized subjects who experience exercise-induced symptoms without other generalized asthma symptoms. Other studies have permitted enrollment of those subjects experiencing exercise symptoms who may or may not be subjects with asthma (Bonini et al 2013). This study will only randomize subjects with asthma who are receiving background therapy for asthma (SABA prn alone; low-to-medium dose ICS plus SABA prn). Sub-analyses will be conducted on the primary endpoint for each of these subgroups of equal size.

Power calculations are based on the properties of the primary endpoint, the maximum percentage fall from post-dose, pre-exercise baseline in FEV_1 observed up to 60 minutes post-exercise challenge. A sample size of 30 subjects in each subgroup will provide a 92% probability to detect a difference of -9% between BDA MDI versus placebo MDI, within each of the 2 subgroups of interest (SABA prn alone; low-to-medium dose ICS plus SABA prn), assuming 2-sided, 5% level tests and a within-subject standard deviation of 10%. Randomization of 60 subjects in total will provide >99% overall probability to detect a difference of -9% between BDA MDI versus placebo MDI assuming a 2-sided, 5% level test and an estimated within-subject standard deviation of 10%. Since all subjects randomized in the study will be receiving background therapy for asthma, a more conservative estimate of variability and treatment effect has been assumed compared to studies of similar design (Ostrom et al 2015).

Primary Efficacy Analyses

The maximum percentage fall from post-dose, pre-exercise baseline in FEV_1 observed up to 60 minutes post-exercise challenge will be analyzed with a mixed effect model including categorical fixed effects for treatment, treatment period, treatment sequence, period-specific pre-dose baseline FEV_1 and average pre-dose baseline FEV_1, and a random subject within treatment sequence effect. Post-dose, pre-exercise baseline FEV_1 will be defined as the 30 minutes post-dose value, ie, 5 minutes before exercise challenge, at each visit for the respective treatment. The period-specific pre-dose baseline FEV_1 will be calculated separately at Visit 3 and Visit 4 as the pre-dose result, approximately 5 minutes prior to dosing. The average pre-dose baseline FEV_1 will be calculated as the mean of the period-specific pre-dose FEV_1 baselines. Estimated treatment differences and 95% confidence intervals (CIs) will be provided.

The primary analysis will be repeated on the subgroups on clinical interest (SABA prn alone; low-to-medium dose ICS plus SABA prn). To control the overall type-I error, a hierarchical testing strategy will be adopted. The treatment comparisons of BDA MDI 160/180 versus placebo MDI will be conducted on the subject populations in the sequence given below:

1. Overall population (SABA prn only OR low-to-medium dose ICS plus SABA prn background therapy)
2. Subjects taking SABA prn only for background therapy
3. Subjects taking low-to-medium dose ICS plus SABA prn for background therapy

If a comparison is significant (alpha=0.05, 2-sided), testing will proceed to the next comparison. Comparisons will stop if a non-statistically significant result occurs. All comparisons are of superiority.

Secondary/ Other Efficacy Analyses

The percentage of subjects with a maximum percentage fall in FEV_1 post-exercise challenge of <10% will be tabulated by treatment.

The odds of having a maximum percentage fall in FEV_1 post-exercise challenge of <10% will be analyzed using a generalized linear mixed model with logit link function to compare the treatments. The model will be adjusted for treatment, treatment period, treatment sequence, and a random subject within treatment sequence effect. The odds ratio and 95% CI will be reported for pairwise treatment comparisons. The odds of having a maximum percentage fall in FEV_1 post-exercise challenge of <20% will be separately analyzed in a similar manner.

Time to recovery at each of Visits 3 and 4 will be derived as the time (minutes) post-exercise challenge in which the FEV_1 result returns to within 10% of the value recorded at the post-dose, pre-exercise baseline. Only subjects who achieve a percentage fall in FEV_1 post-exercise challenge of >10% will have an event time derived; otherwise their value will be left censored. Subjects who have any rescue medication administered during the post-dose assessments will be censored at the time of receiving rescue medication. Subjects who do not recover to within 10% of the post-dose, pre-exercise baseline will be censored at 60 minutes. P-values will be calculated using a period-adjusted sign test, based on categorizing subjects into period preferences (Senn 1993).

The percentage fall in FEV_1 post-exercise challenge will be summarized descriptively by treatment group and planned time point within 60 minutes of the serial spirometry assessments conducted post-exercise challenge. An analysis of percentage fall in FEV_1 post-exercise challenge will be conducted using methods as per the primary analysis, with an additional adjustment for planned time point in the repeated measures model. The covariance within subject-periods will be unstructured over the time points.

The post-exercise FEV_1 $AUC_{0\text{-}30\ min}$ will be analyzed with a similar mixed effects model as described above using methods as per the primary analysis.

Analysis Sets

The following analysis sets are defined in this study:

The full analysis set is defined as all subjects who are randomized to treatment and have at least 1 post-dose, pre-exercise baseline and corresponding post-dose FEV_1 measure at Visits 3 and/or 4. Subjects will be analyzed according to the treatment they were assigned to as per the randomization scheme.

The safety analysis set is defined as all subjects receiving any amount of the IP. Subjects will be classified on the basis of treatment they actually received. Occurrences of safety events (ie,

AEs and use of concomitant medication) will be summarized under the actual treatment corresponding to the treatment period of which the event occurred. All safety summaries will be based on the safety analysis set.

The all subjects enrolled population will be defined as all subjects who provide informed consent. This subject population will be used for descriptive summaries of disposition.

There are no interim analyses planned for this study.

Estimands

The estimand of interest is the Efficacy Estimand, defined as the effect of the randomized treatments in all subjects in the absence of intercurrent events which may impact the interpretation of the treatment effect, such as use of rescue medication following the exercise challenge test. This estimand could be considered a while-on-treatment strategy or a hypothetical strategy as defined in the draft International Conference on Harmonisation (ICH) E9 Addendum.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation or special term	Explanation
AE	adverse event
ATS	American Thoracic Society
$AUC_{0\text{-}30min}$	area under the curve from 0 to 30 minutes
BDA MDI (PT027)	budesonide/albuterol metered-dose inhaler
β-hCG	β-human chorionic gonadotropin
BMI	body mass index
CI	confidence interval
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
ECG	electrocardiogram
eCRF	electronic case report form
ECT	exercise challenge test
EIB	exercise-induced bronchoconstriction
ERS	European Respiratory Society
[redacted]	[redacted]
FEV_1	forced expiratory volume in 1 second
FVC	forced vital capacity
GCP	Good Clinical Practice
GINA	Global Initiative for Asthma
GMP	Good Manufacturing Practice
HFA	hydrofluoroalkane
ICF	informed consent form
ICH	International Conference on Harmonisation
ICS	inhaled corticosteroid
Coordinating Investigator	The Coordinating Investigator is the investigator coordinating the investigators and/or activities in several study sites nationally.
IP	investigational product
IWRS	Interactive Web Response System
LABA	long-acting β2-agonist
PDV	premature discontinuation visit
PEF	peak expiratory flow
prn	as needed

Abbreviation or special term	Explanation
QTcF	QT interval corrected by Fridericia
SABA	short/rapid-acting β2-adrenoreceptor agonist
SAE	serious adverse event
SAP	statistical analysis plan
SMART	Symbicort Maintenance And Reliever Therapy
TC	telephone call
WBDC	web based data capture

1 INTRODUCTION

1.1 Background

Bond Avillion 2 Development LP (Sponsor) is developing budesonide/albuterol sulfate (PT027, a fixed-dose combination product; hereafter referred to as budesonide and albuterol metered-dose inhaler [BDA MDI]) pressurized inhalation suspension product in adults and children (≥4 years of age) with asthma. Please refer to the current Investigator Brochure for additional information.

Albuterol is a short/rapid-acting β2-adrenoreceptor agonist (SABA), inducing airway smooth muscle relaxation and reducing or preventing bronchoconstriction. Albuterol is approved in many countries in multiple formulations for treatment or prevention of bronchoconstriction, and is also known under the generic name of salbutamol. In clinical practice, albuterol is used as reliever therapy on an as-needed (prn) basis (Global Initiative for Asthma [GINA] guidelines).

Budesonide is a well-established anti-inflammatory corticosteroid that exhibits potent glucocorticoid and weak mineralocorticoid activity and is approved worldwide in inhaled formulations for the treatment of asthma and chronic obstructive pulmonary disease both as a mono-product and in combination with a long-acting β2-agonist (LABA), (ie, formoterol).

In vitro studies have demonstrated that inhaled corticosteroid (ICS) agents potentiate the effects of SABAs in reducing airway smooth muscle tone (Mendes et al 2008) and can reverse adrenergic receptor tolerance and desensitization (Cooper and Panettieri 2008). Clinically, similar functional potentiation with combined ICSs and albuterol has been observed in patients with asthma for functional measures of airway smooth muscle and airway blood flow (Mendes et al 2015).

Combining albuterol with budesonide in the proposed BDA MDI combination product should not only provide rapid bronchodilation, but also treat worsening airway inflammation by the addition of the budesonide component. Per current treatment guidelines (GINA 2019), ICS/formoterol maintenance and reliever can be used in patients with asthma. Studies of budesonide and a rapid-acting LABA (formoterol) as reliever therapy have demonstrated enhanced protection from severe exacerbations in patients already receiving combination therapy for maintenance without an increase in adverse effects (O'Byrne et al 2005, Rabe et al 2006). In addition, budesonide/formoterol as maintenance and reliever therapy or "Symbicort Maintenance And Reliever Therapy (SMART)" (available commercially as the Symbicort Turbuhaler [Symbicort] in the European Union and other markets) significantly reduced severe exacerbation risk in pediatric patients (O'Byrne 2007).

In some markets, Symbicort is approved for maintenance and reliever therapy. With SMART application, patients with asthma use Symbicort as maintenance inhalation medication and

also prn in response to symptoms. The simultaneous administration of budesonide with formoterol when symptoms occur ensures that patients with asthma receive both a rapid-acting bronchodilator for symptom relief and anti-inflammatory medication to treat their persistent airway inflammation.

The BDA MDI is proposed to be available prn to use in response to symptoms to all patients with asthma, regardless of maintenance therapy. BDA MDI would have added effect on improvement of lung function and achieving asthma improvement beyond what is seen with albuterol and budesonide alone. Current treatment guidelines (GINA 2019) recommend addition of low-dose ICS to SABA used as reliever medication as early as in GINA step 1 asthma (previously treated with SABA prn alone), broadening the range of asthma severity grades that would be treated by both ICS and β2-adrenoreceptor agonist. Anti-inflammatory and bronchodilation components used prn in a fixed-dose combination are expected to result in overall better asthma control and decreased risk of experiencing asthma symptoms than bronchodilation alone.

1.2 Exercise-induced bronchoconstriction

Exercise-induced bronchoconstriction (EIB) describes acute airway narrowing that occurs as a result of exercise. EIB occurs in a substantial proportion of patients with asthma, but may also occur in individuals without an asthma diagnosis. The quality of evidence supporting the recommendations for the treatment of EIB is variable. Recommendations include using an inhaled SABA at least 15 minutes before exercise in all patients with EIB. While for patients who continue to have symptoms of EIB despite the administration of an inhaled SABA before exercise, strong recommendations were made for a daily ICS, a daily leukotriene receptor antagonist, or a mast cell stabilizing agent before exercise (Parsons et al 2013). Inhaled disodium cromoglycate and β_2-agonists administered immediately before an exercise challenge test (ECT) also provide good protection (Molema et al 1989, Richter et al 2002).

1.3 Rationale for study design, doses and control groups

TYREE is a multicenter, randomized, double-blind, placebo-controlled, 2-period, single-dose, crossover study in adults and adolescents (12 to 70 years of age) with asthma and EIB. This Phase III study is conducted in addition to the AV003-MANDALA exacerbation and AV004-DENALI lung function studies.

Asthma patients with EIB, who use their SABA reliever therapy prophylactically before exercise to prevent EIB, may benefit from a fixed-dosed combination (BDA MDI), taken prior to exercise, to prevent asthma symptoms. The TYREE study will assess the efficacy and safety of single-dose BDA MDI as compared with placebo MDI in subjects with asthma and EIB. It is important to evaluate whether BDA MDI would prevent or reduce bronchoconstriction when used prophylactically.

Efficacy measures have been selected to demonstrate the therapeutic benefit of BDA MDI compared with placebo MDI:

1) The maximum percentage fall from post-dose, pre-exercise baseline in forced expiratory volume in 1 second (FEV_1) up to 60 minutes post-exercise challenge
2) The percentage of subjects with a maximum percentage fall in FEV_1 post-exercise challenge of <10%

1.4 Benefit/risk and ethical assessment

The study will be conducted in accordance with International Conference on Harmonisation (ICH) guidelines. Permission from the research ethics committee (EC) will be sought and the study will start only after authorization. In the study, single-dose treatment and a comparison with placebo is necessary, to show that the presumed protection against EIB is an effect of active treatment.

To mitigate any potential risks, all subjects will be closely monitored to ensure subject safety. At study visits, subjects will only be discharged from the clinic after satisfactory lung function based on the investigator's clinical judgment.

The study will be conducted in a similar design as previously published studies (eg, Ostrom et al 2015). When considering and assessing all non-clinical and clinical data available for study treatments, the Sponsor considers the risk and benefit profile of Study TYREE to be acceptable.

1.5 Study design

This will be a multicenter, double-blind, randomized, placebo-controlled, 2-period, single-dose, crossover study. The study will consist of a screening period (Visit 1 and Visit 2) and 2 treatment visits (Visit 3 and Visit 4). A final follow-up visit will be conducted via a telephone call (TC) 3 to 5 days after the final in-clinic visit.

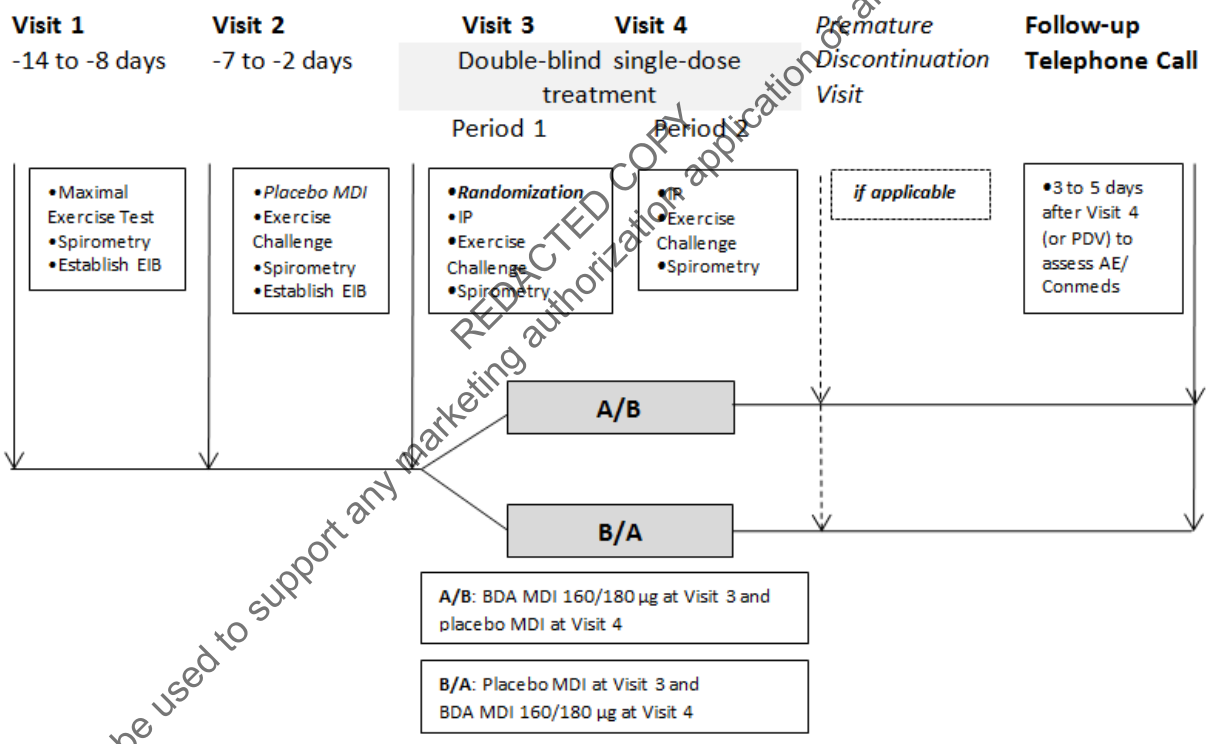
During the study, standardized ECTs will be conducted according to American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines (Crapo et al 2000). At each visit, standard FEV_1 spirometry assessments will be performed relative to ECT and dosing, (before and after) as applicable. All spirometry and testing procedures will be in accordance with current guidelines. A centralized spirometry data collection system incorporating a quality control program will be used to reduce FEV_1 variability between and within subjects, and between study sites.

To be eligible for the treatment phase of the study, subjects with asthma will be required to meet spirometry criteria and demonstrate EIB through standardized ECT. If any of the spirometry criteria are not met at Visit 1 (or Visit 2), subjects can be retested. See Sections 4.1.1 and 4.1.2 for specific details on retesting.

Visit 1 will include general screening procedures, spirometry, and demonstration of EIB through standardized ECT. Those subjects continuing to meet eligibility criteria will enter a 1 to 2-week screening period to Visit 2, at which they will be administered placebo MDI, undergo spirometry testing and confirmation of EIB. At Visit 3, eligible subjects will be randomized to 1 of 2 treatment sequences (ie, A/B or B/A), in which single doses of BDA MDI and placebo MDI will be administered in separate treatment periods (ie, Period 1 and Period 2). At Visit 4, subjects who received BDA MDI at Visit 3 will receive placebo, while those who received placebo at Visit 3 will receive BDA MDI.

Safety will be monitored by spontaneously reported adverse events (AEs)/serious AEs (SAEs) and physical examination findings. Further, heart rate will be monitored continuously during the ECTs and intermittently after ECT until 60 minutes after completion of the exercise challenge.

Figure 1 Study schema



Abbreviations: AE=adverse event; BDA=budesonide/albuterol; Conmeds=concomitant medication; EIB=exercise-induced bronchoconstriction; MDI=metered-dose inhaler; IP=investigational product; PDV=premature discontinuation visit.

2 STUDY OBJECTIVES

2.1 Primary objective

Primary Objective:	Outcome Measure:
To assess the efficacy of a single dose of BDA MDI (160/180 µg) compared with placebo MDI on EIB in adult and adolescent subjects with asthma	*The maximum percentage fall from post-dose, pre-exercise baseline in FEV_1 observed up to 60 minutes post-exercise challenge*

2.2 Secondary objectives

Secondary Objectives:	Outcome Measures:
To further assess the efficacy of a single dose of BDA MDI compared with placebo MDI on EIB in adult and adolescent subjects with asthma	*Percentage of subjects with a maximum percentage fall in FEV_1 post-exercise challenge of <10%*

2.3 Safety objective

Safety Objective:	Outcome Measures:
To evaluate the safety and tolerability of BDA MDI relative to placebo MDI on EIB in adult and adolescent subjects with asthma	*Incidence of AEs/SAEs*

2.4 Exploratory objectives

Exploratory Objective:	Outcome Measures:
To characterize the effect of BDA MDI 160/180 µg administered as a single-dose on bronchoconstriction compared with placebo	1. *Percentage of subjects with a maximum percentage fall in FEV_1 post-exercise challenge of <20%* 2. *Time to recovery, defined as the time from completion of the exercise challenge to the first measured post-exercise challenge FEV_1 value within 10% of the post-dose, pre-exercise challenge baseline FEV_1* 3. *The percentage fall from baseline in FEV_1 at each time point within 60 minutes post-exercise challenge* 4. *Post-exercise FEV_1 area under the curve from 0 to 30 minutes($AUC_{0\text{-}30min}$)*

3 SUBJECT SELECTION, ENROLLMENT, RANDOMIZATION, RESTRICTIONS, DISCONTINUATION AND WITHDRAWAL

Each subject must meet all inclusion criteria and none of the exclusion criteria for this study. Under no circumstances can there be exceptions to this rule.

3.1 Inclusion criteria

For inclusion in the study subjects should fulfill the following criteria:

1 Willing and able to provide/sign written informed consent or age-appropriate assent prior to any study-specific procedures; subjects below the legal age of consent must have parent(s) or guardian sign the informed consent form (ICF) before participation.

2 Female or male aged 12 to 70 years at the time of informed consent.

3 Documented history of asthma (as defined by GINA criteria) for at least 6 months prior to Visit 1.

4 Receiving 1 of the following asthma therapies with stable dosing for at least the 4 weeks before Visit 1; no other asthma therapies are permitted during the study:

   (a) SABA prn, or

   (b) Low-to-medium dose maintenance therapy with ICS and SABA prn.

5 Each pre-exercise challenge (and pre-dose at Visits 2 and 3) best FEV_1 determination from the beginning of screening and before randomization ≥70% of predicted normal value.

6 EIB as defined by a ≥20% decrease from pre-exercise challenge best FEV_1 observed within 60 minutes after an exercise challenge at Visit 1 and at Visit 2.

7 Demonstrate acceptable spirometry performance (ie, meet ATS/ERS acceptability/repeatability criteria). See Appendix D.

8 Demonstrate acceptable MDI administration technique.

   (a) Note: Use of a spacer device during the randomized treatment phase is not permitted.

9 Body mass index (BMI) <40 kg/m^2.

10 Females of childbearing potential must have a negative serum pregnancy test.

11 Females of childbearing potential who are sexually active and in heterosexual relationships, must agree to 1 of the following options to prevent pregnancy:

   (a) Practice complete abstinence defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. Periodic abstinence is not acceptable. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject. Therefore, complete abstinence is an acceptable method of

contraception only if it is consistent with the preferred and usual lifestyle of the subject.

(b) Use of 1 of the following methods of birth control from the date the ICF is signed until 2 weeks after the final dose of study drug is taken:

(i) Hormonal contraception (eg, oral contraceptive, contraceptive implant, or injectable hormonal contraceptive);

(ii) Double-barrier birth control (ie, a combination of male condom with either cap, diaphragm, or sponge with spermicide); or

(iii) Maintenance of a monogamous sexual relationship with a male partner who has been surgically sterilized by vasectomy provided that the male partner is the sole sexual partner of the female (of childbearing potential) participant and that the vasectomized partner has received medical assessment of the surgical success (ie, documented history of medical confirmation of success of vasectomy).

Note: Female subjects are considered to be of non-childbearing potential if they are physiologically incapable of becoming pregnant, including any female who is 2 years post-menopausal (a postmenopausal state is defined as no menses for 12 months without an alternative medical cause), or surgically sterile, defined as having a bilateral salpingectomy, bilateral oophorectomy, or hysterectomy. Tubal ligation will be considered an acceptable permanent birth control measure for this protocol. For purposes of this protocol, menopausal women are defined as women ≥50 years old who are amenorrheic for 12 consecutive months or more after cessation of all exogenous hormonal treatment.

Adolescent-specific recommendations: If the subject is female and has reached menarche, or has reached Tanner stage 3 breast development (even if not having reached menarche), the subject will be considered a female of childbearing potential. Contraceptive methods may be recommended for adolescent females only if they are already sexually active. Use of hormonal contraceptives in adolescent females must always be in consultation with a gynecologist.

12 Male subjects who are sexually active in heterosexual relationships must be surgically sterile or agree to use a double-barrier method of contraception (ie, a combination of male condom with either cap, diaphragm, or sponge with spermicide) from the first dose of randomized study drug until 2 weeks after their last dose. Male subjects must not donate sperm during their study participation period.

13 Willingness and ability to comply with all required study procedures including completion of all study visit assessments.

3.2 Exclusion criteria

Subjects should not enter the study if any of the following exclusion criteria are fulfilled:

1 Chronic obstructive pulmonary disease or other significant lung disease (eg, chronic bronchitis, emphysema, bronchiectasis with the need of treatment, cystic fibrosis, bronchopulmonary dysplasia), including regular or occasional use of oxygen.

2 Systemic corticosteroids use (any dose and any indication) within 3 months before Visit 1.

3 Subject has a history of life-threatening asthma, defined by past intubations for asthma, or intensive care unit admission for asthma within the prior 24 months.

4 Subjects receiving regular maintenance treatment with prohibited anti-inflammatory or long-acting bronchodilator asthma medication (inhaled, nebulized, oral, or systemic) within 1 month prior to Visit 1. **Note**: During the treatment phase, subjects are not allowed to use any asthma treatments/medications (of any class) other than the IP and the permitted SABA or ICS treatment that was started before screening. No subject can be on other asthma maintenance therapies. See Section 7.8.2 for details.

5 Subjects unable to tolerate the lung function testing performed after ECT at Visit 1 or 2 without use of rescue medication.

6 Current smokers, former smokers with >10 pack-years history, or former smokers who stopped smoking <6 months (including all forms of tobacco, e-cigarettes [vaping], and marijuana).

7 Subjects with contraindications to ECT according to ATS/ERS guidelines.

8 Completed treatment for lower respiratory infection within 6 weeks prior to Visit 1, regardless if resulting in accompanying asthma symptoms aggravation or not.

9 Upper respiratory infection involving antibiotic treatment not resolved within 7 days prior to Visit 1.

10 Subjects with a known or suspected hypersensitivity to albuterol/salbutamol, or budesonide and/or their excipients.

11 Having received any marketed (eg, omalizumab, mepolizumab, reslizumab, benralizumab, dupilumab) or investigational biologic within 3 months or 5 half-lives before Visit 1, whichever is longer, or any other prohibited medication.

12 Treatment with any IP within the last 30 days (or 5 half-lives, whichever is longer) of Visit 1.

13 Any of the following results at Visit 1:

(a) an abnormal electrocardiogram (ECG) that is, in the investigator's opinion, clinically significant
(b) a QT interval corrected by Fridericia (QTcF) interval >480 ms

14 Historical or current evidence of a clinically significant disease including, but not limited to: cardiovascular (eg, congestive heart failure, known aortic aneurysm, clinically

significant cardiac arrhythmia, coronary heart disease), hepatic, renal, hematological, neuropsychological, endocrine (eg, uncontrolled diabetes mellitus, uncontrolled thyroid disorder, Addison's disease, Cushing's syndrome), or gastrointestinal (eg, poorly controlled peptic ulcer, gastroesophageal reflux disease) disorders. Significant is defined as any disease that, in the opinion of the investigator, would put the safety of the subject at risk through study participation, or that could affect the efficacy or safety analysis if the disease/condition exacerbated during the study.

15 Cancer not in complete remission for at least 5 years before Visit 1.

Note: Subjects with squamous cell carcinoma of the skin, basal cell carcinoma of the skin, in situ carcinoma of the cervix, or localized prostate cancer are eligible, if in the opinion of the investigator, the condition has been clinically controlled and the subject's participation in the study would not represent a safety concern.

16 Hospitalization for psychiatric disorder or attempted suicide within 1 year of Visit 1.

17 History of psychiatric disease, intellectual deficiency, poor motivation, or other conditions if their magnitude is limiting informed consent validity.

18 Having a scheduled/planned hospitalization during the study.

19 Inability (and/or unwillingness) to abstain from protocol-defined prohibited medications during the study.

20 Use of any herbal products by inhalation or nebulizer within 2 weeks of Visit 1 and/or the unwillingness to stop during the study duration.

21 Significant abuse of alcohol or drugs, in the opinion of the investigator.

22 For females only: currently pregnant (confirmed with positive serum pregnancy test), planning a pregnancy during the study, or breastfeeding.

23 Current participation in any interventional study.

24 Previous enrollment in the present study or randomization in any other BDA MDI (budesonide/albuterol) clinical study.

25 Involvement in the planning and/or conduct of the study (applies to both Sponsor's staff and/or staff at the study site, including investigators and immediate family members).

For procedures for withdrawal of incorrectly enrolled subjects, see Section 3.4.

3.3 Subject enrollment and randomization

Approximately 6 study sites in the United States are anticipated to be included.

Approximately 120 adult and adolescent subjects (12 to 70 years of age) will need to be screened for asthma and EIB, assuming an estimated screen failure rate of 50% prior to randomization.

Approximately 60 adult and adolescent subjects (12 to 70 years of age) will be randomized 1:1 to 1 of 2 treatment sequences (ie, A/B or B/A) as described in Table 1.

Randomization will be centralized and stratified by age (adults: 18 to 70; adolescents: 12 to 17) and background ICS therapy (ICS or no ICS).

Investigator(s) should keep a record, ie, the subject screening log, of subjects who entered pre-study screening.

The investigator(s) will:

1 Obtain signed informed consent/assent (as applicable) from the potential subject and/or their guardian/legal representative before any study-specific procedures are performed.
2 Enter the subject data into the enrollment module in Rave Web Based Data Capture (WBDC) electronic case report form (eCRF) to enable the allocation of subject identification code (Ecode).
3 Determine subject eligibility. See Sections 3.1 and 3.2.
4 Enter the information required to enable the Interactive Web Response System (IWRS) to initiate randomization and generate the randomization code.

Randomization codes will be assigned through IWRS strictly sequentially to subjects eligible for randomization. If a subject withdraws from participation in the study, then his/her enrollment/randomization code cannot be reused.

3.4 Procedures for handling incorrectly enrolled or randomized subjects

Subjects who fail to meet the eligibility criteria should not, under any circumstances, be enrolled, randomized, or receive IP. There can be no exceptions to this rule. There can be no waivers granted from the Sponsor for any subject not meeting inclusion or exclusion criteria.

Where a subject does not meet all the eligibility criteria but is randomized in error, or incorrectly started on treatment, the investigator should inform the medical monitor immediately, and a discussion should occur between the medical monitor and the investigator regarding whether to continue or withdraw the subject in the study. The medical monitor must ensure all decisions are appropriately documented.

3.5 Methods for assigning treatment groups

A randomization schedule will be generated by a designated statistical representative performing statistical support for the study. This schedule will be prepared before the start of the treatment phase. The designated statistical representative will follow their established standard operating procedures regarding generation, security, and distribution of the randomization schedule.

Upon enrollment, subjects will be assigned a unique subject identification code (Ecode) which is automatically generated by the electronic data capture system (Rave WBDC) based on the order of entry. Once it has been determined that a subject meets all eligibility criteria, the subject information will be integrated into the IWRS (Randomization and Trial Supply Management) for randomization.

3.6 Methods for ensuring blinding

The study blind is to be maintained until all subjects have completed the treatment phase and until after the database has been locked. The study site receives documentation of subject study identification and kit allocation through the IWRS. The randomization code will not be available, with the exception of unblinding procedures described in Section 3.7, to the study team, study center personnel, Sponsor monitors, Sponsor project statisticians, or any other personnel employed or affiliated with the Sponsor, as well as investigators and subjects until after the database has been locked.

The 2 different kit types of study IP and placebo are visually identical, protecting the blind through their similarity in appearance.

3.7 Methods for unblinding

The treatment blind should not be broken except in medical emergencies and based on the investigator's clinical judgment, when the appropriate management and welfare of the subject requires knowledge of the treatment allocation. Individual treatment details, for each subject, will be available to the investigator(s) or pharmacists from the IWRS, if needed. If unblinding occurs, the investigator must notify the Sponsor as soon as possible, but *without* revealing the treatment assignment of the unblinded subject. Routines for this will be described in the IWRS user manual that will be provided to each center. The IWRS provides unblinding procedures, if needed.

The designated representative retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an IP and that potentially require expedited reporting to regulatory authorities. Treatment codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual subject have been made and documented.

With the exception of emergency unblinding as described above, all members of the study team, investigators, and site staff will be blinded.

3.8 Restrictions

During the study, subjects are not allowed to use any asthma medication other than the IP and their background treatment (ie, SABA prn alone or ICS with SABA) that was started before screening and continued as part of their asthma treatment (see inclusion criteria). Non-asthma medications which are necessary for the subject's wellbeing and which do not affect the participation or results of the study are allowed at the investigator's discretion. All such medication should be recorded in the subject's eCRF.

3.9 Criteria for study withdrawal

At any time, subjects may withdraw from the study (ie, study procedures/visits) at their own request (or their parent/legal representative's request, as applicable) for any reason, without prejudice. Subjects may also be withdrawn from the study upon request of the investigator, or by the Sponsor at any time or for any reason. Some reasons for study withdrawal include:

- An AE or other unacceptable toxicity considered to jeopardize the safety of a subject participating in the study.
- Subjects who suffer 1 severe exacerbation or worsening of asthma that in the investigator's opinion could affect short-term disease course or stability of lung function will be discontinued if the Sponsor and the investigator decide that it is in the best interest of the subject to withdraw from the study.
- General or specific change(s) in the subject's condition that render(s) him/her ineligible for further participation according to the inclusion/exclusion criteria.
- Non-compliance: in the opinion of the investigator, the subject is non-compliant with the requirements of the Clinical Study Protocol (eg, post-enrollment eligibility violation).
- Lost to Follow-up: the subject is lost to follow-up and no alternative contact information is available (this implies that at least 2 documented attempts have been made to contact the subject).
- Intercurrent illness: a condition, injury, or disease unrelated to the primary diagnosis that became apparent during treatment and necessitated the subject's termination from the study, eg, a symptomatic lower respiratory tract infection that puts the subjects at potential risk and interferes with the subject's ability to carry out the required procedures.
- Pregnancy; if a female subject becomes pregnant, she will be immediately withdrawn from the study.

If a subject is withdrawn from the study for any reason, the study site must immediately notify the medical monitor. The date and the reason for study withdrawal must be recorded on the eCRF. The subject will be asked to complete a premature discontinuation visit (PDV) and the

follow-up TC. The safety follow-up TC contact will occur 3 to 5 days after the last study visit or PDV, as indicated in the Schedule of Assessments (Table 2).

In the event that a subject withdraws prematurely from the study because of an AE or SAE, the AE/SAE will be followed up until it resolves (returns to normal or baseline values) or stabilizes, or until it is judged by the investigator to no longer be clinically significant.

Once a subject is withdrawn from the study, the subject may not re-enter the study. If a subject withdraws from participation in the study, then his/her enrollment/randomization code cannot be reused. Withdrawn subjects will not be replaced.

3.9.1 Screen failures

Screening failures are subjects who do not fulfill the eligibility criteria for the study, and therefore must not be randomized. These subjects should have the reason for study withdrawal recorded as "Screen failure" (the potential subject who does not meet 1 or more criteria required for participation in a trial, this reason for study withdrawal is only valid for non-randomized subjects). Subjects who are screen failures will not be rescreened.

Subjects who fail to meet Visit 1/Visit 2 criteria will be considered for retesting. See Section 4.1.2 for specific details on all retesting.

3.10 Discontinuation of the study

The study may be stopped if, in the judgment of the Sponsor, trial subjects are placed at undue risk because of clinically significant findings that:

- meet individual stopping criteria or are otherwise considered significant
- are assessed as causally related to study drug
- are not considered to be consistent with continuation of the study

Regardless of the reason for termination, all data available for the subject at the time of discontinuation of follow-up must be recorded in the eCRF. All reasons for discontinuation of treatment must be documented.

In terminating the study, the Sponsor will ensure that adequate consideration is given to the protection of the subjects' interests.

4 STUDY PLAN AND TIMING OF PROCEDURES

Table 2 presents study assessments and procedures; Table 3 and Table 4 presents timed spirometry assessments relative to the ECT (and dosing, as applicable) at Visit 1 through Visit 4. Repeat assessments, if needed, will be captured in unscheduled visits. Details on study assessments are presented in Section 5.

General Considerations

To ensure standardization, it is recommended that sites review and remind/discuss the following with the subject on at least the day before a scheduled visit, as applicable:

- Site personnel will remind/instruct subjects not to take any prohibited asthma medications during the study. Non-asthma medications which are necessary for the subject's wellbeing and which do not affect the participation in or results of the study, are allowed. All such medication should be recorded in the subject's eCRF.
  - At every visit during which lung function testing will be performed, subjects must withhold SABA for at least 6 hours prior to start of test day procedures. If subjects have taken SABA within 6 hours before the planned lung function test, the test should not be carried out and the visit should be rescheduled.
- Subjects are not allowed to perform physical exercise during the 24 hours prior to the visits.
- Subjects must not ingest/consume xanthine and/or xanthine analogue (caffeine)-containing foods and beverages for at least 6 hours prior to each study visit and for the duration of each study visit. Examples of such products include coffee, tea, chocolate, and cola. Decaffeinated beverages are acceptable.
- Subjects should avoid having a large meal at least 2 hours prior to a study visit.
- Subjects will be required to return to the clinic at approximately the same time beginning at Visit 2 for all visits (±2 hours of timing of Visit 1). Therefore, all subjects appointments must be scheduled with careful attention to the following criteria:
  - The first spirometry assessment each at Visits 2, 3, and 4 should be completed prior to 11:00 AM and within ±1 hour of the timing of the first spirometry measurement done at Visit 1.
  - After Visit 1, every attempt should be made to have subsequent ECTs done ±2 hours of the timing of the exercise challenge done at Visit 1.
  - Subjects will be required to remain at clinic until completion of all protocol-defined assessments. To minimize diurnal variance, sites should make every effort to assess subjects at the same time throughout the study.

Table 2 Schedule of assessments

Visit	Screening [a]		Double-blind Treatment Phase		Unscheduled Visit or PDV (if applicable)	Follow up
	1	2	3	4		TC (3 to 5 days after V4 or PDV)
			Period 1	Period 2		
Day	-14 to -8 [a]	-7 to -2 [a]	1	8(±6)		
Informed consent/assent	X					
Eligibility criteria	X [c]	X [c]				
Verify randomization criteria			X [d]			
Routine clinical procedures						
Medical/surgical history	X					
Demography	X					
Alcohol consumption and smoking history	X					
Physical examination	X			X	X	
Height and BMI	X					
Weight	X			X	X	
Concomitant medications	X	X	X	X	X	X
Routine safety measurements						
Pregnancy test [e]	X		X	X	X	
Laboratory assessments [f]	X					
Adverse events	X	X	X	X	X	X
Seated vital signs (blood pressure and heart rate) [g]	X	X	X	X		
12-lead ECG [g, h]	X	X	X	X		
Efficacy measurements						
Spirometry (FEV_1) [g]	X	X	X	X		
Maximal exercise test [h]	X					
ECT with Treadmill [h]		X [i, j]	X [i, j]	X [i, j]		
Confirm FEV_1 stability [k]		X [k]	X [k]	X [k]		
Study treatment						
Randomization			X [d]			
IP		(placebo MDI)	X	X		

Abbreviations: *β-hCG=beta-human chorionic gonadotropin; BMI=body mass index; ECG=Electrocardiogram; ECT=Exercise Challenge Test; EIB=exercise-induced bronchoconstriction; FEV_1=Forced expiratory volume in 1 second; IP=Investigational Product; PDV=Premature discontinuation visit; TC=Telephone call; V=Visit.*

Notes:

[a] *The run-in periods at Screening are suggestions which can be shortened; the Screening and Double-blind Treatment Phase period must include at least 1 non-exercise test day between visit days.*

[b] *Subjects who prematurely withdraw from the study will undergo a PDV.*

[c] *Eligibility criteria: At V2 pre-dose FEV_1 best value not exceeding ±20% of the best value measured at V1 pre-exercise; pre-exercise FEV_1 ≥70% of predicted at V1 and V2; demonstration of EIB (at both V1 and V2). One retest will also be allowed for a lack of FEV_1 drop (ie, negative EIB outcome) at V1 only if the FEV_1 drop is between 15% and <20%. Those subjects not meeting criteria will be considered screen failed. See Sections 4.1.1 and 4.1.2 for specific details.*

[d] *Subjects will be randomized at V3 to treatment if they demonstrate (at V3) a pre-exercise challenge FEV_1 ≥70% of predicted and a best pre-dose, pre-exercise challenge FEV_1 that does not exceed ±20% of the best pre-exercise challenge FEV_1 at V1. See Section 4.2.1 for details.*

[e] *A serum pregnancy test (β-hCG) will be performed at V1, V4 and PDV; and a urine β-hCG test will be performed at V3 (for women of childbearing potential only).*

[f] *Laboratory assessments (clinical chemistry, hematology and urinalysis) to be performed according to Section 5.2.1.*

[g] *The spirometry (and related safety) assessments to be performed in association with the exercise challenge at V1 to V4 are described in detail in Table 3 and Table 4.*

[h] *Heart rate to be monitored continuously during the exercise challenge and until 60 minutes after completion.*

[i] *After V1, every attempt should be made to have subsequent ECTs started ±2 hours of the timing of the maximal exercise test done at V1.*

[j] *At V2, V3, and V4, an ECT will be conducted 30 (±5) minutes after IP administration.*

[k] *The pre-dose, pre-exercise challenge best FEV_1 value measured at each denoted visit (performed before exercise challenge) should not exceed ±20% of the pre-dose, pre-exercise challenge best FEV_1 value measured at V1.*

Table 3 Spirometry assessments relative to the maximal exercise test at Visit 1

	Pre-exercise challenge			***Maximal exercise test***	***Post-exercise challenge***							
Time (minutes) / *Assessments*	*-50 (±15)*	*-35 (±5)*	*-5 (±3)*	*0*	*5 (±3)*	*10 (±3)*	*15 (±3)*	*20 (±5)*	*30 (±5)*	*40 (±5)*	*45 (±5)*	*60 (±5)*
Seated vital signs (BP and HR)	*X* [a]							*X*		*X*		*X* [b]
12-lead ECG	*X* [c]										*X*	
Spirometry [d]		*X*	*X*		*X*	*X*	*X*		*X*			*X*
Exercise challenge [e]				*X*								
HR monitoring [f]				*X* ----------								----------*X*
Concomitant medication monitoring	*X* ----------											----------*X*
AE monitoring	*X* ----------											----------*X*

Abbreviations*: AE=adverse event; BP=blood pressure; ECG=electrocardiogram; ECT=exercise challenge test; HR=heart rate; PFT=pulmonary function test.*

Notes*:*

[a] *Vital signs should be recorded with the subject in the seated position and after 10 minutes of rest.*

[b] *Seated vital signs at the 60-minutes post-exercise challenge time point should be recorded 5-10 minutes AFTER the last PFT (ie, 65 minutes [±5 minutes]).*

[c] *12-lead ECG recording at the pre-exercise challenge time point should be conducted after 10 minutes of rest.*

[d] *Every attempt should be made to perform the first pre-exercise (and pre-dose at Visits 2 to 4) spirometry measurement prior to 11:00 AM consistently across Visits 1 through 4 visit (ie, ±1 hour of the timing of the initial assessment at Visit 1).*

[e] *After Visit 1, every attempt should be made to have the subsequent ECTs done ±2 hours of the timing of the maximal exercise test done at Visit 1.*

[f] *Heart rate will be monitored continuously during the maximal exercise test and intermittently after maximal exercise test until 60 minutes after completion of the exercise challenge (ie, intermittently during PFTs).*

Table 4 Spirometry assessments relative to the exercise challenge test and dosing at Visits 2, 3, and 4

	Pre-dose		***Dose***	***Post-dose***		***Post-exercise challenge***							
Time (minutes) / *Assessments*	*-50 (±15)*	*-5 (±3)*	*0*	*30 (±5)*	***ECT***	*5 (±3)*	*10 (±3)*	*15 (±3)*	*20 (±5)*	*30 (±5)*	*40 (±5)*	*45 (±5)*	*60 (±5)*
Seated vital signs (BP and HR)	*X* [a]								*X*		*X*		*X* [b]
12-lead ECG	*X* [c]											*X*	
Spirometry [d, e]		*X* [d, e]		*X*		*X*	*X*	*X*		*X*			*X*
Administer study drug [f]			*X*										
Exercise challenge [g]					*X*								
HR monitoring [h]				*X*----------*X*									
Concomitant medication monitoring	*X*----------*X*												
AE monitoring	*X*----------*X*												

Abbreviations: *AE=adverse event; BDA=budesonide/albuterol; BP=blood pressure; ECG=electrocardiogram; ECT=exercise challenge test; HR=heart rate; FEV_1=forced expiratory volume in 1 second; IP=investigational product; MDI=metered dose inhaler; PFT=pulmonary function test.*

Notes:

[a] *Vital signs should be recorded with the subject in the seated position and after 10 minutes of rest.*

[b] *Seated vital signs at the 60-minutes post-exercise challenge time point should be recorded 5-10 minutes AFTER the last PFT (ie, 65 minutes [±5 minutes]).*

[c] *12-lead ECG recording at pre-dose time point should be conducted after 10 minutes of rest.*

[d] *At Visits 2 through 4, if the FEV_1 criteria are not met in the first spirometry measurement (ie, 5 minutes pre-dose), 1 optional pre-dose spirometry measurement can be repeated after 30 minutes of the initial attempt. If first pre-dose FEV_1 fulfill all criteria, then the subject can proceed to dosing.*

[e] *Every attempt should be made to perform the first pre-exercise spirometry measurement prior to 11:00 AM consistently across Visits 1 through 4 visit (ie, ±1 hour of the timing of the initial spirometry performed at Visit 1).*

[f] *At Visit 2, subjects will receive placebo, while at Visit 3 and Visit 4 they will receive IP (BDA MDI or placebo MDI) depending on their randomization assignment.*

[g] *After Visit 1, every attempt should be made to have the subsequent ECTs done ±2 hours of the timing of the maximal exercise test done at Visit 1.*

[h] *Heart rate will be monitored continuously during the ECT and intermittently after ECT until 60 minutes after completion of the exercise challenge (ie, intermittently during PFTs).*

4.1 Screening period

Procedures will be performed according to study assessments and procedures presented in Table 2, Table 3, and Table 4. At Visit 1, consenting subjects are assessed to ensure that they meet eligibility criteria. Subjects who do not meet the criteria must not be enrolled in the study. Subjects meeting all eligibility criteria will enter a screening period.

4.1.1 Visit 1

Standard demographic data and other characteristics will be recorded and will include age and year of birth; gender, race, and/or ethnicity according to local regulations; alcohol consumption, and smoking history.

A standard medical, disease, and surgical history will be obtained with review of the inclusion and exclusion criteria with the subject. Other study procedures carried out during this period will include physical examination (with weight, height, and BMI), concomitant medications review, seated vital signs (blood pressure and heart rate), 12-lead ECG, AEs assessment/review, serum pregnancy test for women of childbearing potential, blood samples for hematology and clinical chemistry, and urine samples for urinalysis. See Sections 5.2 and 5.3 for details on assessments.

Visit 1 will also include spirometry (lung function testing and baseline FEV_1 determination) and subjects suitable for the study will perform a maximal exercise test on a treadmill in which maximal aerobic capacity is defined. Heart rate will be monitored continuously during the maximal exercise test and heart rate will be noted when the test is stopped and at specific time points as per Table 3.

Spirometry FEV_1 determinations will be made as per Table 3. To be eligible for the treatment phase of the study, subjects will be required to meet the following criteria at Visit 1:

- Pre-exercise challenge best FEV_1 ≥70% of predicted value
- EIB as demonstrated by a ≥20% decrease from the 5-minute pre-exercise challenge absolute FEV_1

If any of the spirometry criteria are not met at Visit 1, subjects can be retested within 2 to 10 days of the initial visit. Only 1 retest will be permitted for reasons related to technical issues (ie, acceptability) and/or pre-exercise FEV_1 ≥70% predicted, prior to randomization. The 1 retest will also be permitted for a lack of FEV_1 drop (ie, negative EIB outcome) at Visit 1 only if the FEV_1 drop is between 15% and <20%. Those subjects not meeting criteria will be considered screen failed.

4.1.2 Visit 2

At Visit 2, a standardized ECT with spirometry FEV_1 determinations will be performed according to Table 4 for continuing eligibility determination. The first spirometry assessment will be performed beginning at approximately the same time as the subject's initial assessment at Visit 1 (±1 hour) and before 11:00 AM. Subjects will be administered placebo MDI, with an ECT conducted 30 (±5) minutes after placebo administration.

Subjects will be required to meet the following criteria:

- The pre-dose, pre-exercise challenge best FEV_1 ≥70% of predicted value
- The pre-dose, pre-exercise challenge best FEV_1 value measured not exceeding ±20% of the pre-exercise challenge best FEV_1 value measured at Visit 1
- The post-dose, pre-exercise challenge best FEV_1 ≥70% of predicted value
- EIB as demonstrated by a ≥20% decrease from the post-dose, pre-exercise challenge FEV_1
- No development of a respiratory tract infection or asthma exacerbation between Visit 1 and 2. The visit can be rescheduled once within 7 to 10 days for an upper respiratory tract infection (eg, common cold) that resolves and does not interfere with the subject's ability to perform the study procedures.

If any of the spirometry criteria are not met at Visit 2, subjects can be retested within 2 to 10 days of the initial visit. Only 1 retest will be permitted for reasons related to technical issues (ie, acceptability) and/or pre-exercise FEV_1 ≥70% predicted and/or exceeding ±20%, prior to randomization. No retest will be allowed for a lack of FEV_1 drop (ie, negative EIB outcome). Those subjects not meeting criteria will be considered screen failed.

4.2 Randomization/Treatment phase

Procedures will be performed according to study visit assessments presented in Table 2, and Table 4. The treatment phase consists of 2 visits (Visit 3 and Visit 4). Subjects meeting eligibility criteria will be randomized at Visit 3.

4.2.1 Visit 3 and 4

At Visit 3, eligible subjects will be randomized (1:1) to receive 1 of 2 treatment sequences (A/B or B/A). Randomization will be centralized and stratified by age (adults: 18 to 70; adolescents: 12 to 17) and background ICS therapy (ICS or no ICS).

At Visits 3 and 4, subjects will also be required to continue to meet the following criteria:

- The pre-dose, pre-exercise challenge best FEV_1 ≥70% of predicted value
- The pre-dose, pre-exercise challenge best FEV1 value measured did not exceed ±20% of the pre-exercise challenge best FEV_1 value measured at Visit 1

- The post-dose, pre-exercise challenge best FEV_1 ≥70% of predicted value. (This is for safety reasons; however, if this criterion is not met, it is at the investigator's discretion to proceed if it is considered that there is no safety risk for the subject to proceed to the ECT.)

If any of the spirometry criteria are not met at Visit 3 or 4, subjects can be retested. Those subjects not meeting criteria will be withdrawn. See Sections 4.1.1 and 4.1.2 for specific details on retesting.

Investigational product will be administered to eligible subjects at Visit 3 and Visit 4. To allow for proper preparation of IP, it is recommended that the seal around the study-day treatment box is opened with sufficient time prior to dosing and the instructions for administration of IP followed:

- After IP is primed (see the separate manual for instructions on MDI handling and cleaning) and ready for use, provide assigned IP to the subject
- IP will be administered in the clinic
- Complete post-dose assessments presented in Table 2 and Table 4 (in particular, standardized ECT with spirometry FEV_1 determinations will be made according to Table 4)

4.3 Study withdrawal

Planned end of study will occur on completion of Visit 4. Subjects who prematurely withdraw from the study (ie, withdrawal prior to Visit 4) will be asked to undergo a PDV. The assessments for Visit 4 and PDV will be performed according to the study visits and procedures presented in Table 2.

See Sections 3.9 and 3.10 for details on study withdrawal procedures.

4.4 Unscheduled visit

Repeat assessments/visits, if needed, will be captured in unscheduled visits and the procedures carried out during an unscheduled visit will be determined by the investigator.

4.5 Follow-up period

Procedures will be performed according to study visits and procedures presented in Table 2. The safety follow-up TC contact will occur 3 to 5 days after Visit 4 or PDV.

The study procedures carried out during the follow-up period will include recording of concomitant medications and AEs.

5 STUDY ASSESSMENTS

The Rave WBDC system will be used for data collection and query handling. The investigator will ensure that data are recorded on the eCRFs and in accordance with the instructions provided.

The investigator ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Trial Agreement. The investigator will sign the completed eCRF. A copy of the completed eCRF will be archived at the study site.

The laboratory assessments will be sent for analysis to a central laboratory.

The spirometry and ECG assessments will be performed at each site using MasterScope equipment provided by [redacted]

5.1 Efficacy assessments

Efficacy assessments include ECTs with spirometry (FEV_1) measurements.

5.1.1 Lung function measurement by spirometry (FEV_1)

Lung function will be measured by spirometry at the study site using equipment provided by [redacted]. Spirometry will be performed according to ATS/ERS guidelines (Miller et al 2005). Spirometry calibration will be detailed in a separate spirometry procedures manual.

The vendor providing central spirometry services will be responsible for assuring that the spirometer used by each site meets ATS/ERS recommendations, and that the study site personnel who will be performing the testing are properly certified. Preferably, the same study personnel should oversee the ECT procedure throughout the study to reach optimal performance and to enhance reproducibility. A centralized spirometry data collection system incorporating a quality control program will be used to reduce FEV_1 variability between and within subjects and between study sites.

Spirometry should be performed as specified in Table 3 and Table 4. The measurements are to be made with the subject seated in an upright position (preferably), or if not comfortable, a standing position is also acceptable. The same position should be used for all spirometry measures during the entire study. The head must not be tilted during measurements. During the breathing maneuvers, the thorax should be able to move freely; hence tight clothing should be loosened.

The subject should rest for at least 15 minutes prior to the initial test. Multiple maneuvers are necessary. For each pre-dose and/or pre-exercise challenge spirometry, a maximum of 8 maneuvers can be performed, and the highest value obtained from 3 acceptable and 2

repeatable spirometry maneuvers will be used. (For the pre-dose PFTs, FEV_1 and forced vital capacity repeatability will be required [Appendix D].) For each post-exercise challenge spirometry, the highest value of 2 acceptable spirograms will be used (Appendix D).

Pre- and post-exercise FEV_1 will be performed at Visit 1 and pre-dose, post-dose, and post-exercise at Visits 2 through Visit 4. The 5-minute pre-exercise post-dose spirometry assessment at Visits 2 through 4 is crucial to accurately measure baseline FEV_1 prior to exercise testing. The subject and site personnel should be adequately prepared for this assessment prior to the exercise test.

5.1.1.1 Demonstration of exercise-induced bronchoconstriction

Subjects will be required to meet the following criteria at Visit 1 (Section 4.1.1) and Visit 2 (Section 4.1.2):

- EIB as demonstrated by a ≥20% decrease from the 5-minute pre-exercise challenge absolute FEV_1

5.1.2 Exercise challenge testing

A standardized maximal exercise test on a treadmill in which maximal aerobic capacity is defined will be completed at Visit 1. At Visits 2 through 4, an ECT, with duration of 6 to 8 minutes, at approximately 80% to 95% of maximal aerobic capacity will be performed on a treadmill as specified in Table 2, Table 3, and Table 4. The subjects will have a face mask during exercise and will breathe dry air.

Details on exercise testing will be provided in a separate manual. (Measurement procedures should be performed in accordance with the manual.)

Subjects will also be reminded that they are not allowed to perform physical exercise during the 24 hours prior to the visits.

Subjects will be reminded to avoid having a large meal at least 2 hours prior to a study visit, and that they must not ingest/consume xanthine and/or xanthine analogue (caffeine)-containing foods and beverages for at least 6 hours prior to each study visit and for the duration of each study visit. Examples of such products include coffee, tea, chocolate, and cola. Decaffeinated beverages are acceptable.

The ECT should be done at approximately the same time (±2 hours of the timing of exercise challenge done at Visit 1) at each subsequent visit. Before any procedure is done the subject should rest for at least 15 minutes. The subject needs to be stable before the test.

During the maximal exercise challenge, the subject's heart rate will be monitored continuously. Maximal heart rate should be noted when the test is stopped at Visit 1. After the

establishment of exercise challenge criteria at Visit 1, subjects will undergo standardized ECTs at Visit 2 for eligibility determination and at Visit 3 and Visit 4 (30 [±5] minutes after IP administration). Heart rate will be monitored continuously during the ECTs until 60 minutes after ECT completion. See Section 4.1.2 for details on spirometry assessments and timing relative to ECTs (and dosing).

If the subject has been diagnosed with an intercurrent illness or suffers a severe asthma exacerbation before a visit, the subject will be withdrawn from the study, depending on the reason. See Section 3.9 for details. The visit can be rescheduled once within 7 to 10 days for an upper respiratory tract infection (eg, common cold) that resolves and does not interfere with the subject's ability to perform the study procedures.

If at any visit an exercise test and/or the post-exercise lung function tests need to be stopped prematurely (ie, the FEV_1 drops > 40% [which requires treatment with SABA]), or the subject has asthma symptoms that require treatment with SABA as judged by the investigator, the subject's visit will be stopped. After an appropriate observation period, if the subject's condition has stabilized as judged by the investigator, the subject's visit will end.

5.2 Safety assessments

Safety assessments include 12-lead ECG readings and the collection of AEs.

5.2.1 Laboratory assessments

Samples for determination of clinical chemistry, hematology, and urinalysis will be taken at the times indicated in Table 2.

A serum pregnancy test (β-human chorionic gonadotropin [β-hCG]) will be performed at Visit 1, 4 and PDV; urine β-hCG test will be performed at Visit 3 (for women of childbearing potential only).

Additional safety samples may be collected if clinically indicated at the discretion of the investigator.

The clinical chemistry, hematology, and urinalysis assessments will be performed using a centralized laboratory. Sample tubes and sample sizes may vary depending on laboratory method used and routine practice at each site.

The following laboratory variables in Table 5 will be measured:

Table 5 Laboratory variables

Hematology/Hemostasis (whole blood)	***Clinical Chemistry (serum or plasma)***
Basophils (%)	*Albumin*
Basophils Abs	*Alanine transaminase*
Eosinophils (%)	*Alkaline phosphatase*
Eosinophils Abs	*Aspartate transaminase*
Hemoglobin	*Bilirubin, total*
Hematocrit	*Calcium, total*
Mean Corpuscular Hemoglobin	*Chloride*
Mean Corpuscular Hemoglobin Concentration	*Cholesterol, total*
Mean Corpuscular Volume	*Creatinine*
Monocytes (%)	*Creatine kinase*
Monocytes Abs	*Gamma-glutamyl transpeptidase*
Neutrophils (%)	*Glucose (random)*
Neutrophils Abs	*Magnesium*
Red blood cells (erythrocytes)	*Phosphate*
White blood cells (leukocytes)	*Potassium*
Platelet count	*Protein, total*
Lymphocytes Abs	*Sodium*
Lymphocytes (%)	*Triglycerides*
Urine	*Urea*
Urine β-hCG pregnancy (at Visit 3) [a]	*Serum β-hCG pregnancy (Visit 1, 4 and PDV)* [a]
Urine hemoglobin	
Urine erythrocytes	
Urine protein	
Urine albumin	
Urine glucose	

Abbreviations: Abs=absolute; β-hCG=β-human chorionic gonadotropin; PDV=premature discontinuation visit
[a] β-hCG pregnancy testing for women of childbearing potential only

5.2.2 Physical examination

A complete physical examination will be performed at Visit 1, Visit 4, and PDV (if applicable) as detailed in Table 2. This will include an assessment of the following items: height in centimeters and BMI (both at Visit 1 only), weight, 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.

5.2.3 ECG

Twelve-lead ECGs will be obtained using a centralized laboratory. A standardized ECG machine should be used and the subject should be examined using the same machine throughout the study.

5.2.3.1 Resting 12-lead ECG

A resting 12-lead ECG will be performed at Visit 1 (Table 2). The 12-lead ECG will be obtained using a centralized laboratory after the subject has been resting semi-supine for at least 10 minutes.

The ECG should be recorded with the subject in the same physical position, using a standardized ECG machine. The subject should be examined using the same machine throughout the study, where feasible.

After ECGs have been recorded, the investigator or designated physician will review each of the ECGs and may refer to a local cardiologist, if appropriate. A paper copy should be filed in the subject's medical records. If an abnormal ECG finding at screening/baseline is considered to be clinically significant by the investigator, it should be reported as an AE. For all ECGs, details of rhythm, PR, RR, QRS, and QT intervals, as well as an overall evaluation will be recorded.

5.2.4 Heart rate monitoring during exercise challenge testing

During the exercise challenge at Visit 1, the subject's heart rate will be monitored continuously for 60 minutes as detailed in Table 3. At Visit 1, Maximal heart rate should be noted when the maximal exercise test is stopped at Visit 1.

At Visits 2 through Visit 4 standardized ECTs will be conducted and the subject's heart rate will be monitored continuously for 60 minutes as detailed in Table 4.

5.2.5 Vital signs

Vital signs will include measurements of blood pressure and heart rate, while the subject is seated, as detailed in Table 2, Table 3, and Table 4.

Blood pressure measurements should be taken in the sitting position after at least 10 minutes of rest.

Any clinically significant values in vital signs should be recorded as an AE if applicable.

5.2.6 Adverse event assessments

Adverse events will be collected from time of signature of informed consent/assent through to the follow-up time point, as described in Section 6.

5.3 Other assessments

5.3.1 Concomitant medications

The collection and recording of all concomitant medications, including all pre-enrollment asthma therapies will be performed as detailed in Table 2. Permitted and restricted concomitant medications are further described in Sections 7.8.2, 7.8.3, and 7.8.4.

All prescription drugs, herbal products, vitamins, minerals, and over-the-counter medications taken within 3 months before screening will be recorded as previous medications. All medications taken after screening and through the follow-up TC will be recorded as concomitant therapy.

For restrictions relating to concomitant medications, see Sections 3.1 and 3.2.

6 SAFETY REPORTING AND MEDICAL MANAGEMENT

The investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

Serious AEs will be reported as per standard reporting guidance. Associated symptoms of asthma are considered as symptoms of disease under study and will not be recorded as AEs unless considered an SAE.

6.1 Definition of adverse events

An AE is the development of any untoward medical occurrence in a subject or clinical study subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom (eg, nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including the screening period, even if no IP has been administered.

6.2 Definitions of serious adverse event

An SAE is an AE occurring during any study phase (ie, after the signing of the informed consent/assent through to the safety follow-up TC), that fulfills 1 or more of the following criteria:

- Results in death
- Is immediately life-threatening

- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent 1 of the outcomes listed above

For further guidance on the definition of an SAE, see Appendix C.

6.3 Recording of adverse events

6.3.1 Period for collection of adverse events

Adverse events (including SAEs) will be collected from the time of signature of informed consent/assent through the safety follow-up TC.

6.3.2 Follow-up of unresolved adverse events

Any AEs that are unresolved at the subject's last assessment visit in the study are followed up by the investigator for as long as medically indicated, but without further recording in the eCRF. The Sponsor or a [redacted] Safety and Pharmacovigilance Department representative retains the right to request additional information for any subject with ongoing AE(s)/SAE(s) at the end of the study (after the subject's follow-up telephone call) and capture that information in the eCRF, if judged necessary.

6.3.3 Variables

The following variables will be collected for each AE:

- AE (verbatim)
- Dates when the AE started and stopped
- Maximum severity
- Seriousness
- Investigator causality rating against the IP (yes or no)
- Action taken with regard to the IP
- Outcome

In addition, the following variables will be collected for SAEs, when applicable:

- Date AE met criteria for SAE
- Date the investigator became aware of SAE
- Reason why the AE is considered serious
- Treatment given for the SAE
- Date of hospitalization

- Date of discharge
- Probable cause of death
- Date of death
- Whether an autopsy is performed
- Causality assessment in relation to study procedure(s)
- Causality assessment to other medication
- Description of AE

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not an SAE unless it meets the criteria shown in Section 6.2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE when it satisfies the criteria shown in Section 6.2.

The severity of the event should be assessed as mild, moderate, or severe.

6.3.4 Causality collection

The investigator and the Sponsor will assess causal relationship between IP and each AE, and answer "yes" or "no" to the question "Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?"

For SAEs causal relationship will also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as "yes".

A guide to the interpretation of the causality question is found in Appendix C.

6.3.5 Adverse events based on signs and symptoms

All AEs spontaneously reported by the subject or care provider or reported in response to the open question from the study site staff: *"Have you/your child had any health problems since the previous visit/you (or your child) were last asked?"*, or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, recording a diagnosis is preferred (when possible) to the recording of a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

Asthma symptoms or signs, such as wheeze, cough, chest tightness, dyspnea, breathlessness, and phlegm, will be recorded as AEs only when:

- The sign or symptom is serious
- The subject discontinues the study because of the sign or symptom
- The sign or symptom is new to the subject or not consistent with the subject's pre-existing asthma history (defined as within 1 year of Visit 1) as judged by the investigator

6.3.6 Adverse events based on examinations and tests

The results from the Clinical Study Protocol mandated laboratory tests, ECGs, vital signs (ie, blood pressure and heart rate) and other assessments will be summarized in the Clinical Study Report. Deterioration from baseline in these parameters should therefore only be reported as AEs if they fulfill any of the AE criteria or are the reason for discontinuation from the study or are considered "clinically significant."

The criteria for determining whether the mandated laboratory tests, ECGs, vital signs, and other assessments are clinically significant and should be reported as AEs are generally:

- Test result is associated with accompanying symptoms or signs, and/or
- Test result requires additional diagnostic testing or medical/surgical intervention, and/or
- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy, and/or
- Test result is considered to be an AE by the investigator or Sponsor.

If deterioration in a laboratory value, ECG, vital sign, or other assessment is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated parameter will be considered as additional information. Wherever possible the reporting investigator uses the clinical, rather than the laboratory term (eg, anemia versus low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

6.4 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the IP, or to the study procedure(s). All SAEs will be recorded in the eCRF.

If any SAE occurs during the course of the study, then investigators or other site personnel should inform the [redacted] Safety and Pharmacovigilance Department within 1 day ie, immediately but **no later than 24 hours** of when he/she becomes aware of it.

Should the eCRF system become non-operational, SAEs shall be sent in paper form to:

[redacted] Safety and Pharmacovigilance Department

[redacted]

[redacted] Safety and Pharmacovigilance Department will work with the investigator to ensure that all the necessary information is provided.

For fatal or life-threatening SAEs where important or relevant information is missing, active follow-up is undertaken immediately.

Investigators or other site personnel should inform the [redacted] Safety and Pharmacovigilance Department of any follow-up information on a previously reported SAE within 1 calendar day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The Sponsor will also report to all applicable health authorities **within 7 days** of awareness for a fatal or life-threatening reaction or **within 15 days** for a reaction neither fatal nor life-threatening of any serious unexpected adverse drug reaction related to the drug which occurred during the study.

6.5 Overdose

For the purpose of this study, an accidental or deliberate intake of blinded treatment of more than 2 actuations during Visits 3 and 4 is defined as an overdose and must be reported as such as described below.

An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose/Medication Error eCRF module. An overdose without associated symptoms is only reported on the Overdose/Medication Error eCRF module.

The maximum daily dosage of IP should not exceed 2 actuations per visit. If an overdose of IP occurs in the course of the study which has an associated SAE, then the investigator or other site personnel will inform the [redacted] Safety and Pharmacovigilance Department immediately, or **no later than 24 hours** of when he or she becomes aware of it.

The [redacted] Safety and Pharmacovigilance Department works with the investigator to ensure that all relevant information is provided to the [redacted] Safety and Pharmacovigilance Department representative.

For overdoses associated with an SAE, the standard SAE reporting timelines apply, see Section 6.4.

6.6 Pregnancy

All pregnancies and outcomes of a pregnancy should be reported to the [redacted] Safety and Pharmacovigilance Department representative except if the pregnancy is discovered before the study subject has received any IP.

6.6.1 Maternal exposure

If a subject becomes pregnant during the course of the study, IP should be discontinued immediately and "Pregnancy" recorded as the reason for discontinuation on the eCRF. The subject will be withdrawn from the study.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IP under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the subject was discontinued from the study.

If any pregnancy occurs in the course of the study, then the investigator or other site personnel will inform the [redacted] Safety and Pharmacovigilance Department within 1 day; ie, immediately but **no later than 24 hours** of when he/she becomes aware of it. Any conception occurring from the date of dosing through the safety follow-up TC should be reported.

The [redacted] Safety and Pharmacovigilance Department will work with the investigator to ensure that all relevant information is provided.

The same timelines apply when outcome information is available.

6.6.2 Paternal exposure

Pregnancy of a subject's partner is not considered to be an AE. However, any conception occurring from the date of dosing through the safety follow-up TC should be reported to the [redacted] Safety and Pharmacovigilance Department representative and followed up for its outcome.

6.7 Medication error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for the Sponsor's IP that either causes harm to the subject or has the potential to cause harm to the subject.

A medication error is not lack of efficacy of the drug, but rather a human or process-related failure while the drug is in control of the study site staff or subject.

A medication error includes situations where an error:

- occurred
- was identified and intercepted before the subject received the drug
- did not occur, but circumstances were recognized that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion
- Preparation error, eg, medication prepared incorrectly, even if it was not actually given to the subject
- Drug not administered as indicated, eg, wrong route or wrong site of administration
- Drug not taken as indicated
- Drug not stored as instructed, eg, kept in the refrigerator when it should be at room temperature
- Wrong subject received the medication (excluding IWRS errors)
- Wrong drug administered to subject (excluding IWRS errors)
- Subject received the medication in the wrong order (excluding IWRS errors)

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Errors related to or resulting from IWRS , including those which lead to 1 of the above listed events that would otherwise have been a medication error
- Accidental overdose (will be captured as an overdose)

Medication errors are not regarded as AEs but AEs may occur as a consequence of the medication error.

All medication errors must be recorded in the Overdose/Medication Error eCRF. Any associated AEs should also be recorded as the AE diagnosis/symptoms on the relevant AE/SAE modules in the eCRF.

If a medication error occurs during the course of the study which has an associated SAE, then the investigator or other site personnel will inform the [redacted] Safety and Pharmacovigilance Department **immediately, or no later than 24 hours** of when he or she becomes aware of the medication error.

The [redacted] Safety and Pharmacovigilance Department will work with the investigator to ensure that all relevant information is provided to [redacted] Safety and Pharmacovigilance Department representative. For medication errors associated with an SAE, the standard SAE reporting timelines apply, (see Section 6.4).

6.8 Management of investigational product-related toxicities

In the absence of a specific antidote, management of toxicities can be dealt with on the basis of the symptoms.

7 INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

7.1 Identity of investigational product(s)

BDA MDI is formulated (Table 6) as both micronized budesonide and micronized albuterol co-suspended with spray-dried porous particles in an HFA propellant. The co-suspension formulation ensures that subjects receive a consistent delivery of the drug from each actuation of the MDI.

Table 6 Investigational product strength and dosage form

Investigational product name and dose	*Product strength*	*Dosage form/ Fill count*	*Administration*	*Manufacturer*
BDA MDI 160/180 µg	*BDA MDI 80 µg budesonide and 90 µg albuterol[a] per puff*	*MDI/120 actuations*	*Taken as 2 actuations*	*AstraZeneca*
Placebo MDI	*0 µg of active product[b]*	*MDI/120 actuations*	*Taken as 2 actuations*	*AstraZeneca*

Abbreviations: BDA MDI=budesonide/albuterol metered-dose inhaler; HFA=hydrofluoroalkane.

[a] Each puff contains 108 µg albuterol sulfate corresponding to 90 µg albuterol base per actuation.

[b] Each puff contains 183 µg of porous particles and 63 µg of HFA-134a propellant made to be identical in appearance to BDA MDI.

7.2 Dose and treatment regimens

At Visit 2, subjects will be administered placebo MDI.

At Visit 3, eligible subjects will be randomized (1:1) to 1 of the following 2 sequences of double-blind single-dose treatment phase (Table 7):

Table 7 Treatment sequences

Treatment sequences	*Visit 3/Period 1*	*Visit 4/Period 2*
A/B	*BDA MDI 160/180 µg (given as 2 actuations of BDA MDI 80/90 µg)*	*Placebo MDI (given as 2 actuations)*
B/A	*Placebo MDI (given as 2 actuations)*	*BDA MDI 160/180 µg (given as 2 actuations of BDA MDI 80/90 µg)*

Abbreviations: BDA=budesonide/albuterol; MDI metered-dose inhaler.

Handling instructions for the MDI device will be available for each site throughout the study (Section 7.7).

7.3 Labelling

Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels will fulfill GMP Annex 13 requirements for labelling. Label text will be translated into local language.

Each kit will contain an MDI device, wrapped in a foil bag held within a carton. The MDI devices provided in this study and the packaging and labelling of the kits are visually identical to maintain the blind.

Each kit will contain the following blinded labels:

- Single panel canister label (English only)
- Single panel actuator label or multilanguage actuator booklet label
- MDI device shield label (single panel, English only)
- Foil bag label (single panel, English only) or multilanguage booklet label
- Single panel carton label or multilanguage carton booklet label

The labels will include the following information:

- Name of Sponsor (Bond Avillion 2 Development LP – Clinical Development Company: Avillion LLP)
- IP dosage form, route of administration, and quantity of dosage units (blinded across all treatment groups)
- Storage conditions
- Study Trial Reference
- Medication ID number
- Directions for use
- The name of the investigator, where applicable (this will be added on the label manually when the IP is administered)
- The period of use, eg, expiry date

The label will include the following standard statements:

- "Caution: New Drug –Limited by Federal law to investigational use."
- "Keep out of reach of children"

7.4 Storage

All IP should be kept in a secure place under appropriate storage conditions. The IP label specifies the appropriate storage.

Blinded supplies: BDA MDI 80/90 µg per puff and placebo should be stored below 25°C (77°F) in a dry place. Excursions permitted up to 30°C (86°F).

7.5 Compliance

The administration of all IP will be captured and recorded in the appropriate sections of the eCRF, as applicable, with the exception of the details of any interruptions for which the dates and reason for interruption will be recorded. The IP accountability will be recorded in the eCRF.

7.6 Accountability

The IP provided for this study will be used only as directed in the Clinical Study Protocol.

All IP will be returned to the approved study returns vendor for destruction after accountability and reconciliation is complete.

7.7 Metered-dose inhaler handling

Detailed handling instructions will be provided to the site in the form of a "Site Manual" document, which will cover all aspects of the study with regards to IP.

The importance of the device priming requirements should be emphasized. Priming of the IP MDI must occur. Device priming should *not* be conducted in the same room as spirometry assessments are being conducted.

7.8 Concomitant and other treatments

7.8.1 Investigational product

In addition to the Sponsor-provided IP, the only other asthma treatments/medications (of any class) allowed during the study are the asthma medications (ie, SABA prn alone or ICS with SABA, as applicable) that were started before screening and continued as part of maintenance treatment. See the inclusion criteria for details.

7.8.2 Permitted asthma therapies

SABA prn or low-to-medium dose ICS plus SABA prn are the only permitted therapies to be used as asthma therapy on-study as specified in the inclusion criteria. No subject can be on any other asthma maintenance therapies.

During the study, subjects should maintain stable dosing of their maintenance and/or prn therapy as presented at screening. Dose changes to maintenance therapy are discouraged unless clinically indicated in accordance with GINA guidelines. Investigators should notify the study medical monitors of any change to maintenance therapy for study subjects; considerations should be made to subject drug compliance and other factors in advance of making changes to maintenance therapy.

If, following the ECT, the investigator considers that the subject is experiencing asthma symptoms which are not tolerable, then rescue SABA can be administered.

7.8.3 Medication that may affect FEV_1 testing

Investigators should notify the study medical monitors of any change to maintenance therapy for study subjects. At the start of each treatment visit, subjects must withhold SABA for at least 6 hours prior to start of test day procedures. If a subject has taken SABA within 6 hours before the planned FEV_1 test, the test should not be carried out and the subject's visit should be rescheduled.

7.8.4 Prohibited medications

Prohibited concomitant medications during and at least 1 month prior to the study include the following, with specified timeframes where needed:

- Oral, parenteral, or rectal corticosteroids (except if required to treat severe asthma exacerbation) during and at least 3 months prior to Visit 1
- Any other asthma medication except Sponsor-provided IP during Visits 3 and 4 and the permitted SABA prn alone or ICS with SABA treatment that was started before screening and continued as part of maintenance treatment (see inclusion criteria), regular SABA use (eg, four times a day [QID]) is not permitted)
- Inhaled disodium cromoglycate or inhaled nedocromil sodium
- 5-lipoxygenase inhibitors (ie, zileuton)
- Inhaled short-acting anticholinergics (or short-acting muscarinic antagonists [SAMA], ie, ipratropium)
- Inhaled long-acting muscarinic antagonists (LAMA)
- Phosphodiesterase-4 inhibitors (ie, roflumilast)
- Leukotriene receptor antagonists (ie, montelukast, zafirlukast), also for the treatment of other allergic conditions
- Xanthine and theophylline
- Omalizumab, benralizumab, mepolizumab, reslizumab, dupilumab, or any other monoclonal or polyclonal therapy for any reason during the study or within 3 months or 5 half-lives before Visit 1, whichever is longer; (locally administered biologics, eg, intra-ocular, are allowed)
- Beta-2-adrenergic blockers, including eye-drops; (For the purpose of this study, metoprolol is considered to have beta-2-adrenergic receptor blocking ability.)

7.8.5 Food and beverage restrictions

Subjects must *not* ingest/consume xanthine and/or xanthine analogue (*caffeine*)-containing foods and beverages for at least 6 hours prior to each study visit and for the duration of each study visit. Examples of such products include coffee, tea, chocolate, and cola.

Decaffeinated beverages are acceptable.

Subjects should avoid having a large meal at least 2 hours prior to a study visit.

7.8.6 Other concomitant treatment

Non-asthma medication other than those described above, which is/are considered necessary for the subject's safety and wellbeing, may be given at the discretion of the investigator and recorded in the appropriate sections of the eCRF.

8 STATISTICAL ANALYSES

8.1 Statistical considerations

All personnel involved with the analysis of the study will remain blinded until database lock and identification of Clinical Study Protocol violators are identified.

Analyses will be performed by the Sponsor or its representatives.

A comprehensive statistical analysis plan (SAP) will be prepared and any subsequent amendments will be documented, with final amendments completed before the unblinding of the data.

8.1.1 Estimands

The estimand of interest is the Efficacy Estimand, defined as the effect of the randomized treatments in all subjects and in the absence of intercurrent events which may impact the interpretation of the treatment effect, such as use of SABA medication following the exercise challenge test. This estimand could be considered a while-on-treatment strategy or a hypothetical strategy as defined in the draft ICH E9 Addendum.

8.2 Sample size estimate

Power calculations are based on the properties of the primary endpoint, the maximum percentage fall from post-dose, pre-exercise baseline in FEV_1 observed up to 60 minutes post-exercise challenge. A sample size of 30 subjects in each subgroup will provide a 92% probability to detect a difference of -9% between BDA MDI versus placebo MDI, within each of the 2 subgroups of interest (SABA prn alone; low-to-medium dose ICS plus SABA prn), assuming 2-sided, 5% level tests and a within-subject standard deviation of 10%. Randomization of 60 subjects in total will provide >99% overall probability to detect a

difference of -9% between BDA MDI versus placebo MDI assuming a 2-sided, 5% level test and an estimated within-subject standard deviation of 10%. Since all subjects randomized in the study will be receiving background therapy for asthma, a more conservative estimate of variability and treatment effect has been assumed compared to studies of similar design (Ostrom et al 2015).

8.3 Definitions of analysis sets

8.3.1 Full analysis set

The full analysis set is defined as all subjects who are randomized to treatment and have at least 1 baseline and corresponding post-dose FEV_1 measure. Subjects will be analyzed according to the treatment they were assigned as per the randomization scheme.

All efficacy analyses will be conducted on the full analysis set.

8.3.2 Safety analysis set

The safety analysis set is defined as all subjects receiving any amount of the IP. Subjects will be classified on the basis of treatment they actually received within each treatment period. Occurrences of safety events (ie, AEs and use of concomitant medication) will be summarized under the actual treatment corresponding to the treatment period of which the event occurred. All safety summaries will be based on the safety analysis set.

8.3.3 All subjects enrolled

The all subjects enrolled analysis set will be defined as all subjects who provide informed consent. This analysis set will be used for descriptive summaries of disposition.

8.4 Violations and deviations

Important protocol deviations will be listed and summarized by randomized treatment group. A per protocol analysis excluding subjects with significant protocol deviations is not planned.

All subjects who failed any inclusion/exclusion criteria will be listed along with details of the failed criteria. This information will also be summarized in terms of the number and percentage of subjects failing any of the inclusion/exclusion criteria and will be based on the full analysis set.

8.5 Outcome measures for analyses

8.5.1 Primary efficacy analysis

The primary analysis will include all data obtained before subjects withdraw from the study and will use the full analysis set, in accordance with the Efficacy Estimand (Section 8.1.1).

8.5.1.1 Derivation of primary efficacy endpoint

The fall from post-dose, pre-exercise baseline in FEV_1 will be calculated at each post-exercise FEV_1 assessment time point at Visit 3 and Visit 4. The post-dose, pre-exercise baseline FEV_1 assessment is expected to occur 30 minutes after administration of IP and 5 minutes prior to the exercise challenge. The percentage fall in FEV_1 will be calculated proportional to the post-dose, pre-exercise FEV_1 value at each visit. The maximum percentage fall available in the 60-minute assessment period, prior to the use of rescue medication, will be calculated at Visit 3 and Visit 4.

8.5.2 Secondary efficacy analysis

The secondary analysis will include all data obtained before subjects withdraw from the study and will use the full analysis set, in accordance with the Efficacy Estimand (Section 8.1.1).

8.5.2.1 Derivation of secondary efficacy endpoints

The fall in FEV_1 will be calculated at Visit 3 and Visit 4 as the difference in the baseline post-dose, pre-exercise FEV_1 assessment and each post-exercise assessment at the respective visit, as per the serial spirometry timings detailed in Table 3 and Table 4. The percentage fall will be calculated relative to the pre-exercise FEV_1 assessment at the respective visit. The post-dose, pre-exercise baseline FEV_1 is defined as per Section 8.5.1.1.

A binary response variable will be assigned to identify subjects with a maximum percentage fall in FEV_1 post-exercise of <10% separately at Visit 3 and Visit 4:

- Protected: Maximum percentage fall from post-dose, pre-exercise baseline in FEV_1 up to 60 minutes post-exercise challenge <10%
- Not Protected: Maximum percentage fall from post-dose, pre-exercise baseline in FEV_1 up to 60 minutes post-exercise challenge ≥10%

As with the primary efficacy endpoint specified in Section 8.5.1.1, the maximum percentage fall will be calculated based on post-dose FEV_1 measures prior to use of rescue medication. Subjects who have no post-exercise FEV_1 measure prior to rescue medication will have a missing responder status at the given visit.

8.5.3 Exploratory efficacy analysis

The exploratory analysis will include all data obtained before subjects discontinue the study and will use the full analysis set, in accordance with the Efficacy Estimand (Section 8.1.1).

8.5.3.1 Derivation of exploratory efficacy endpoints

The binary response variable specified in Section 8.5.2.1 will be replicated to identify subjects with a maximum percentage fall in FEV_1 post-exercise of <20% at each of Visits 3 and 4.

Time to recovery at each of Visits 3 and 4 will be derived as the time (minutes) post-exercise challenge in which the FEV_1 result returns to within 10% of the value recorded at the post-dose, pre-exercise baseline. Only subjects who achieve a percentage fall in FEV_1 post-exercise challenge of >10% will have an event time derived; otherwise their value will be left censored. Subjects who have any rescue medication administered during the post-dose assessments will be censored at the time of receiving rescue medication. Subjects who do not recover to within 10% of the post-dose, pre-exercise baseline will be censored at 60 minutes. The fall from post-dose, pre-exercise baseline in FEV_1 will be calculated at each of the post-exercise assessment time points at Visit 3 and Visit 4. The post-dose, pre-exercise baseline FEV_1 assessment is expected to occur 30 minutes after administration of IP and 5 minutes prior to the exercise challenge. The percentage fall in FEV_1 will be calculated proportional to the post-dose, pre-exercise FEV_1 value at each visit.

FEV_1 $AUC_{0\text{-}30min}$ will be derived for the changes from the post-dose, pre-exercise baseline using the trapezoidal rule and will be normalized by dividing by the actual time (in minutes) from dosing to the last included measurement, scheduled at 30 minutes post-exercise challenge at each of Visits 3 and 4. Only FEV_1 results prior to the use of rescue medication will be considered when calculating FEV_1 $AUC_{0\text{-}30min}$.

8.6 Methods for statistical analyses

All tests will be 2-sided and at 5% level of significance unless otherwise stated.

In addition to the analyses described below, all variables will be summarized descriptively where appropriate. All descriptive and formal analyses will be described in accordance with the Efficacy Estimand.

8.6.1 Analysis of the primary variable(s)

The maximum percentage fall from post-dose, pre-exercise baseline in FEV_1 observed up to 60 minutes post-exercise challenge will be analyzed with a mixed effect model including categorical fixed effects for treatment, treatment period, treatment sequence, period-specific pre-dose baseline FEV_1 and average pre-dose baseline FEV_1, and a random subject within treatment sequence effect. Post-dose, pre-exercise baseline FEV_1 will be defined as the post-dose value measured 5 minutes before exercise challenge, at each visit for the respective treatment. The period-specific pre-dose baseline FEV_1 will be at the respective Visit 3 or Visit 4 pre-dose result, approximately 5 minutes prior to dosing. The average pre-dose baseline FEV_1 will be calculated as the mean of the period-specific baselines. Estimated treatment differences and 95% confidence intervals (CIs) will be provided.

The corresponding hypotheses for the primary analysis are as follows:

H_{01}: Difference between treatments =0,

H_{A1}: Difference between treatments ≠0.

The primary treatment comparison of BDA MDI 160/180 versus placebo MDI for the maximum percentage fall from post-dose, pre-exercise baseline in FEV_1 observed up to 60 minutes post-exercise challenge will be conducted on the full analysis set and include all data up to study withdrawal as per the Efficacy Estimand (Section 8.1.1). Missing results for maximum percentage fall in FEV_1 is unlikely (ie, rescue medication prior to the collection of the 5 minutes measure) and will be assumed to be missing at random. Sensitivity analyses will be conducted to explore the robustness of the primary analysis with respect to this missing data assumption (Section 8.6.6).

The primary analysis will be repeated on the subgroups on clinical interest (SABA prn alone; low-to-medium dose ICS plus SABA prn). To control the overall type-I error, a hierarchical testing strategy will be adopted. The treatment comparisons of BDA MDI 160/180 versus placebo MDI will be conducted on the subject populations in the sequence given below:

1. Overall population (SABA prn only OR low-to-medium dose ICS plus SABA prn background therapy)
2. Subjects taking SABA prn only for background therapy
3. Subjects taking low-to-medium dose ICS plus SABA prn for background therapy

If a comparison is significant (alpha=0.05, 2-sided), testing will proceed to the next comparison. Comparisons will stop if a non-statistically significant result occurs. All comparisons are of superiority.

8.6.2 Analysis of the secondary variable(s)

In addition to the analyses described below, all variables will be summarized descriptively where appropriate. All descriptive and formal analyses will be described in accordance with the Efficacy Estimand.

8.6.2.1 Responder analysis in post-exercise FEV_1

The odds of being protected against EIB (ie, having a maximum percentage fall in FEV_1 post-exercise challenge of <10%) will be analyzed using a generalized linear mixed model with logit link function to compare the treatments. The model will be adjusted with fixed effects for treatment, treatment period and treatment sequence, and a random subject within treatment sequence effect. The odds ratio and 95% CI will be reported for pairwise treatment comparisons. The analysis will only include maximum percentage falls in FEV_1 prior to study discontinuation. The data considered missing under the primary Efficacy Estimand will be assumed to be missing at random in the analysis.

8.6.3 Analysis of the exploratory variables

In addition to the analyses described below, all variables will be summarized descriptively where appropriate. All descriptive and formal analyses will be described in accordance with the Efficacy Estimand.

8.6.3.1 Responder analysis in post-exercise FEV_1 (20% threshold)

The odds of having a maximum percentage fall in FEV_1 post-exercise challenge of <20% will be separately analyzed using a generalized linear mixed model to compare treatments as specified in Section 8.6.2.1.

8.6.3.2 Time to recovery

The median time to recovery will be reported descriptively by treatment. P-values will be calculated using a period-adjusted sign test, based on categorizing subjects into period preferences (Senn 1993). Further details will be clarified in the SAP.

8.6.3.3 Fall in post-exercise FEV_1 at individual time points

The percentage fall in FEV_1 post-exercise challenge will be summarized descriptively by treatment group and planned time point within 60 minutes of the serial spirometry assessments conducted post-exercise challenge. An analysis of percentage fall in FEV_1 post-exercise challenge will be conducted using methods as per the primary analysis, with an additional adjustment for planned time point in the repeated measures model. The covariance within subject-periods will be unstructured over the time points. Only FEV_1 results prior to administration of rescue therapy (within the study visit) will be included in the analyses, as per the Efficacy Estimand.

8.6.3.4 Post-exercise FEV_1 $AUC_{0\text{-}30min}$

The post-exercise FEV_1 $AUC_{0\text{-}30\ min}$ will be analyzed with a similar mixed effects model as described in Section 8.6.1 for the change from post-dose, pre-exercise baseline in the maximum percentage fall in FEV_1 without exercise pre-treatment. Only the FEV_1 $AUC_{0\text{-}30\ min}$ measurements prior to administration of rescue SABA therapy will be included in the analyses.

8.6.4 Subgroup analysis

Two subgroups of equal size will be included in the study, 1 subgroup of subjects on SABA prn only and the other subgroup on low-dose ICS maintenance therapy according to GINA guidelines. All primary, secondary and exploratory analyses will be repeated on each of these subgroups of interest. Please refer to the testing strategy in Section 8.6.1 for analyzing the primary endpoint in these subgroups of interest.

The assessment of treatment effect will be investigated in other clinically important subgroups and will be defined in more detail in the SAP.

8.6.5 Interim analysis

There are no interim analyses planned for this study.

8.6.6 Sensitivity analysis

If there are missing data, sensitivity analyses on the impact of such data will be conducted on the primary endpoint of maximum percentage fall from post-dose, pre-exercise baseline FEV_1 observed up to 60 minutes post-exercise challenge. Under the Efficacy Estimand, missing data are assumed missing at random. The sensitivity analysis will explore the robustness of conclusions when data are considered missing not at random. Further details will be given in the SAP.

9 STUDY AND DATA MANAGEMENT

9.1 Training of study site staff

Before the first subject is entered into the study, a designated representative will review and discuss the requirements of the Clinical Study Protocol and related documents with the investigational staff and also train them in any study specific procedures and the Rave WBDC system(s) utilized.

The investigator(s) will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

The investigator(s) will maintain a record of all individuals involved in the study (medical, nursing, and other staff).

9.2 Monitoring of the study

During the study, the Sponsor or a designated representative will have regular contacts with the study site, including visits to:

- Provide information and support to the investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the Clinical Study Protocol, that data are being accurately and timely recorded in the eCRFs, that biological samples are handled in accordance with the Laboratory Manual and that IP accountability checks are being performed
- Perform source data verification (a comparison of the data in the eCRFs with the subject's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent/assent of participating subjects. This will require direct access to all original records for each subject (eg, clinic charts)

- Ensure all SAEs and AEs have been captured and reported correctly, providing oversight of subject safety while on-study
- Verify the correct storage, handling, administration, and return of all IP

The designated representative will be available between visits if the investigator(s) or other staff at the center needs information and advice about the study conduct.

9.2.1 Source data

Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records. Also, current medical records must be available.

Definition of what constitutes source data can be found in the Source Data Agreement, agreed with each investigator before site initiation.

9.2.2 Study agreements

The investigator(s)/the participating center(s) should comply with all the terms, conditions, and obligations of the Clinical Study Protocol, or equivalent, for this study.

Clinical Trial Agreements with the investigator(s)/the participating center(s) should be in place before any study-related procedures can take place, or subjects are enrolled.

9.2.3 Archiving of study documents

The investigator follows the principles outlined in the Clinical Trial Agreement.

9.3 Study timetable and end of study

The end of the study is defined as "the last visit of the last subject undergoing the study".

The study may be terminated at individual centers if the study procedures are not being performed according to Good Clinical Practice (GCP), or if recruitment is slow. The Sponsor may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with the IP.

9.4 Data management

Data management will be performed by the Data Management Team at [redacted] according to the Data Management Plan.

The data collected through third party sources will be obtained and reconciled against study data. Data from third parties will be transferred in accordance with data transfer specifications and reconciled in accordance with the Data Management Plan.

Adverse events and medical/surgical history will be classified according to the terminology of the latest version of the Medical Dictionary for Regulatory Activities at the time of database lock.

Medications will be classified according to the World Health Organization Drug Dictionary. All coding will be performed by the Medical Coding Team at [redacted]

Data queries will be raised for inconsistent, impossible or missing data. All entries to the study database will be available in an audit trail.

The data will be validated as defined in the Data Management Plan. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. The Data Management Plan will also clarify the roles and responsibilities of the various functions and personnel involved in the data management process.

Serious adverse event (SAE) reconciliation

SAE reconciliation reports are produced and reconciled with the applicable [redacted] Safety and Pharmacovigilance Department safety database and/or the investigational site.

Management of external data

[redacted] Data Management will set up import agreements with third party data sources, to ensure external data is integrated in line with applicable data standards.

Final database lock

Database lock will occur once "the last visit of the last subject participating in the study has been completed" and all data have been coded, validated, signed, and locked, and clean file has been declared.

10 ETHICAL AND REGULATORY REQUIREMENTS

10.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/GCP, and applicable regulatory requirements.

10.2 Subject data protection

The ICF/assent will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

Subjects will be assigned a unique identifier by the Sponsor. Any subject records or datasets that are transferred to the Sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred. Subjects must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law(s). The level of disclosure must also be explained to the subject. Subjects must also be informed that his/her medical records may be examined by study monitors, clinical quality assurance auditors, or other authorized personnel appointed by the Sponsor, by appropriate EC members, and by inspectors from regulatory authorities.

10.3 Ethics and regulatory review

An EC should approve the final Clinical Study Protocol, including the final version of the ICF/assent and any other written information and/or materials to be provided to the subjects. The investigator will ensure the distribution of these documents to the applicable EC, and to the study site staff.

The opinion of the EC should be given in writing. The investigator should submit the written approval to the Sponsor or designated representative before enrollment of any subject into the study.

The EC should approve all advertising used to recruit subjects for the study.

The Sponsor or designated representative should approve any modifications to the ICF/assent that are needed to meet local requirements.

If required by local regulations, the Clinical Study Protocol should be re-approved by the EC annually.

Before enrollment of any subject into the study, the final Clinical Study Protocol, including the final version of the ICF/assent, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

The Sponsor or designated representative will handle the distribution of any of these documents to the national regulatory authorities.

The Sponsor or designated representative will provide regulatory authorities, ECs and investigator(s) with safety updates/reports according to local requirements.

10.4 Informed consent/assent

The investigator(s) at each center will:

- Ensure each subject (and/or parent/legal representative, as applicable) is given full and adequate oral and written information about the nature, purpose, possible risk(s) and benefit(s) of the study.
- Ensure each subject (and/or parent/legal representative, as applicable) is notified that they are free to discontinue from the study at any time.
- Ensure that each subject (and/or parent/legal representative, as applicable) is given the opportunity to ask questions and allowed time to consider the information provided.
- Ensure each subject (and/or parent/legal representative, as applicable) provides signed and dated informed consent/assent before conducting any procedure specifically for the study.
- Ensure the original, signed ICF/assent(s) is/are stored in the Investigator's Study File.
- Ensure a copy of the signed ICF/assent is given to the subject (and/or parent/legal representative, as applicable).
- Ensure that any incentives for subjects who participate in the study as well as any provisions for subjects harmed as a consequence of study participation are described in the ICF/assent that is approved by an EC.

10.5 Changes to the clinical study protocol and informed consent form/assent

Study procedures will not be changed without the mutual agreement of the international coordinating investigator and the Sponsor.

If there are any substantial changes to the Clinical Study Protocol, then these changes will be documented in a new version of the study protocol.

The new version of the Clinical Study Protocol is to be approved by the relevant EC and if applicable, also the national regulatory authority, before implementation. Local requirements are to be followed for new versions of Clinical Study Protocols.

The Sponsor will distribute any new versions of the Clinical Study Protocol to each investigator for distribution to EC, see Section 10.3.

If a change to a Clinical Study Protocol requires a change to a center's ICF/assent, the Sponsor and the center's EC are to approve (or submit a notification to the national regulatory authority, where applicable for) the revised ICF/assent before the revised form is used.

10.6 Audits and inspections

Authorized representatives of the Sponsor, a regulatory authority, or an EC may perform audits or inspections at the center, including source data verification. The purpose of an audit

or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, data were recorded, analyzed, and accurately reported according to the Clinical Study Protocol, GCP, guidelines of the ICH, and any applicable regulatory requirements. The investigator will contact the Sponsor immediately if contacted by a regulatory agency about an inspection at the center.

11 LIST OF REFERENCES

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12. Ostrom NK, Taveras H, Iverson H, Pearlman DS. Novel albuterol multidose dry powder inhaler in patients with exercise-induced bronchoconstriction: a single-dose, double-blind, randomized, 2-way crossover study. *Respir Med*. 2015;109(11):1410-1415.

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APPENDIX A AVILLION PROTOCOL SIGNATURE PAGE

[redacted]

APPENDIX B PRIMARY INVESTIGATOR SIGNATURE PAGE

I agree to conduct the study in accordance with the current protocol.

Principal Investigator's Name (print)

Principal Investigator's Signature

Date

Please keep the signed original form in your study files, and return a copy to your local study monitor.

APPENDIX C ADDITIONAL SAFETY INFORMATION

Further guidance on the definition of a Serious Adverse Event (SAE)

Life-threatening
"Life-threatening" means that the subject was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the subject's death. "Life-threatening" does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalization
Out-patient treatment in an emergency room is not in itself an SAE, although the reasons for it may be (eg, bronchospasm, laryngeal edema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important medical event or medical intervention
Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life-threatening or result in death, hospitalization, disability or incapacity but may jeopardize the subject or may require medical intervention to prevent 1 or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used. Examples of important medical events include but are not limited to:

- Angioedema not severe enough to require intubation but requiring intravenous hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalization
- Development of drug dependency or drug abuse

A guide to interpreting the causality question
When making an assessment of causality, consider the following factors when deciding if there is a "reasonable possibility" that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the subject actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another cause/etiology such as, the underlying disease, other drugs, and other host or environmental factors.
- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? The Sponsor would not normally recommend or support a re-challenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the drug?
- Is there a known mechanism?

Causality of "related" is made if following a review of the relevant data, there is evidence for a "reasonable possibility" of a causal relationship for the individual case. The expression "reasonable possibility" of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed on the basis of the available data including enough information to make an informed judgment. With limited or insufficient information in the case, it is highly encouraged for the reporting investigator to express his/her clinical opinion. If (despite all efforts) the causality assessment cannot be made, these SAEs will be considered to be "related."

Causal relationship in cases where the disease under study has deteriorated because of lack of effect should be classified as "no reasonable possibility."

APPENDIX D SPIROMETRY ASSESSMENT CRITERIA

Acceptable Versus Usable Tests

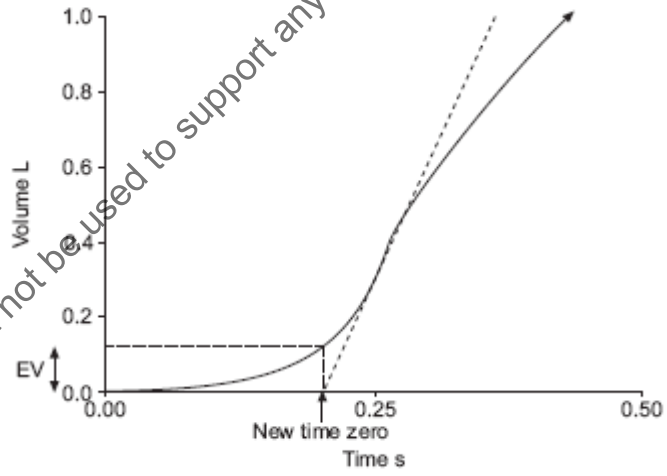
Acceptable **Tests must meet the following criteria:**

1. Acceptable start of exhalation with brisk upstroke, no hesitation or false start, and back extrapolation volume <5% of forced vital capacity (FVC) or 0.150 L, whichever is the greater (see example in Figure 1)
2. No cough during the first second
3. No Valsalva maneuver
4. No leak
5. No obstruction of mouthpiece
6. No extra breaths
7. Plateau achieved: ie, the volume-time curve shows no change in volume (<0.025 L) for ≥ 1 second, and the subject has tried to exhale for at least 6 seconds

An acceptable test meets all 7 criteria listed. This is to be considered the "gold standard."

Usable spirometry tracings are those that only meet criteria 1 and 2. When this occurs, repeat testing up to 8 attempts for pre-dose and 5 attempts for post-dose assessments, in an effort to obtain 3 acceptable spirograms. If only usable tests are obtained, report results based on the 3 best usable trials with observed limitations.

Figure 1 Example of a Usable Spirogram



EV=back extrapolation volume

The expanded version of the early part of a subject's volume-time spirogram, illustrating back extrapolation through the steepest part of the curve, where flow is peak expiratory flow (PEF) rate, to determine the new "time zero". Forced vital capacity -4.291 L; extrapolated volume (EV) – 0.123 L (2.9% FVC): back extrapolation line through PEF.

Between-Manoeuver Reproducibility Criteria

Pre-dose assessments

After **3** acceptable spirograms have been obtained, apply the following tests:

- The 2 largest values of FVC must be within 0.150 L of each other
- The 2 largest values of FEV_1 must be within 0.150 L of each other

If these criteria are met, the spirometry testing for that time point may conclude, however, if possible, please continue collecting additional spirograms to a maximum of 8 pre-dose and 5 post-dose attempts. The highest FEV_1 and the highest FVC obtained at each testing time point (even if from different reproducible tracings), will be collected.

If acceptability criteria are not met, continue testing until they are met or the subject cannot/ should not continue (maximum of 8 attempts).

Post-dose assessments

After **2** acceptable spirograms have been obtained, apply the following tests:

- The 2 largest values of FVC are within 0.150 L of each other and/or
- The 2 largest values of FEV_1 are within 0.150 L of each other

If these criteria are met, the spirometry testing for that time point may conclude. The highest FEV_1 and the highest FVC obtained at each testing time point (even if from different reproducible tracings), will be collected.

If acceptability/reproducibility criteria are not met, continue testing until they are met or the subject cannot/ should not continue (maximum of 5 attempts).