

## VERSION HISTORY

Clinical Study Protocol	
<b>Bond Avillion 2 Development LP</b>	
Drug Substance	Budesonide/Albuterol Sulfate (BDA)
Study Code	AV004
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### **A 12-week, Randomized, Double-blind, Placebo-controlled, Multicenter, Parallel Group, Phase III Study Evaluating the Efficacy and Safety of PT027 Compared to PT008 and PT007 Administered QID in Adults and Children 4 Years of Age or Older with Asthma (DENALI)**

**Sponsor:** Bond Avillion 2 Development LP, [REDACTED]

**Version 3.0, Amendment 2, 06 July 2020**

Global Protocol Amendment 2

**Version 2.0, Amendment 1, 11 February 2019**

Global Protocol Amendment 1

**Version 1.0, 27 December 2018 FINAL/APPROVED**

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

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### **A 12-week, Randomized, Double-blind, Placebo-controlled, Multicenter, Parallel Group, Phase III Study Evaluating the Efficacy and Safety of PT027 Compared to PT008 and PT007 Administered QID in Adults and Children 4 Years of Age or Older with Asthma (DENALI)**

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#### **International coordinating investigators**



#### **Study site(s) and number of subjects planned**

Approximately 100 study sites are anticipated to randomize 1000 adult and adolescent subjects ( $\geq 12$  years of age) with asthma. Subjects will be randomized 1:1:1:1:1 to 1 of 5 treatment groups. Approximately 200 subjects per group: budesonide/albuterol metered-dose inhaler (BDA MDI) 80/180  $\mu$ g 4 times daily (QID), BDA MDI 160/180  $\mu$ g QID, budesonide metered-dose inhaler (BD MDI) 160  $\mu$ g QID, albuterol sulfate metered-dose inhaler (AS MDI) 180  $\mu$ g QID, or placebo MDI. In addition, up to 30 child subjects (aged 4 to 11 years) with asthma will be enrolled but will not receive high dose inhaled corticosteroid (ICS) and will be randomized 1:1:1 to receive low-dose BDA MDI 80/180  $\mu$ g QID, AS MDI 180  $\mu$ g QID or placebo MDI. Approximately 2000 subjects will need to be screened, assuming an estimated screen failure rate of 50% prior to randomization. This Phase III study is planned to be conducted globally.

#### **Study design**

This is a 12-week, randomized, double-blind, placebo-controlled, multicenter, parallel group, Phase III study. The purpose of this study is to compare 2 dose levels of BDA MDI compared

to its constitute components BD MDI and AS MDI on improvement in lung function and asthma symptoms after 12 weeks of treatment in adults, adolescents, and child subjects, aged 4 years and older, with symptomatic asthma currently being treated with short/rapid-acting  $\beta$ 2-adrenoreceptor agonist (SABA; eg, Ventolin) as needed (prn) alone or with low-dose ICS maintenance therapy plus SABA prn.

Subjects meeting all entry criteria at the screening visit (Visit 1) will enter a 14 to 28-day screening (run-in) period. Only Sponsor-provided investigational product (IP) and Sponsor-provided Ventolin to be used in response to asthma symptoms are allowed during the study. No other asthma medications are allowed during the study.

During the screening (run-in) period, subjects will self-administer single-blind placebo MDI QID and Ventolin prn for asthma symptoms only. Subjects will be trained and instructed in the use of an electronic diary (eDiary) and peak flow meter at Visit 1 to record protocol required data into the eDiary twice daily. Eligible subjects will be randomized at Visit 2.

## Objectives

Primary objective:	Primary endpoint:
<i>To demonstrate the contribution of budesonide and albuterol in BDA MDI 80/180 <math>\mu</math>g and 160/180 <math>\mu</math>g administered QID by comparing with mono-components (BD MDI 160 <math>\mu</math>g, AS MDI 180 <math>\mu</math>g) and placebo on lung function</i>	<i>Dual primary endpoints:</i> <ul style="list-style-type: none"><li>• Change from baseline in <math>FEV_1 AUC_{0-6 \text{ hours}}</math> over 12 weeks</li><li>• Change from baseline in trough <math>FEV_1</math> at Week 12</li></ul>
Secondary objective:	Secondary endpoint:
<i>To characterize the effect of BDA MDI 80/180 <math>\mu</math>g and 160/180 <math>\mu</math>g administered QID on bronchodilation and asthma symptoms compared to the mono-components (BD MDI 160 <math>\mu</math>g, AS MDI 180 <math>\mu</math>g) and placebo</i>	<ul style="list-style-type: none"><li>• The time to onset (defined as 15% increase in <math>FEV_1</math> over the pre-treatment value on Day 1), and duration of response on Day 1</li><li>• Number (%) of subjects who have an Asthma Control Questionnaire-7 (ACQ-7) score of <math>\geq 1.5</math> at baseline who achieve a clinically meaningful improvement (a decrease of at least 0.5 units from baseline) in ACQ-7 at Week 12</li><li>• Trough <math>FEV_1</math> at Week 1</li></ul>
Safety objective:	Safety endpoints:
<i>To evaluate the safety and tolerability of BDA MDI 80/180 <math>\mu</math>g and 160/180 <math>\mu</math>g administered QID compared to BD MDI (160 <math>\mu</math>g) and AS MDI (180 <math>\mu</math>g)</i>	<ul style="list-style-type: none"><li>• AE/SAEs</li><li>• Vital signs (ie, heart rate, blood pressure only)</li><li>• Clinical chemistry and hematology parameters</li><li>• Electrocardiogram (ECG)</li></ul>

Exploratory objective:	Exploratory endpoints:
<p><i>To characterize the effect of BDA MDI 80/180 µg and 160/180 µg administered QID on bronchodilation and asthma symptoms compared to the mono-components (BD MDI 160 µg, AS MDI 180 µg) and placebo</i></p>	<ul style="list-style-type: none"><li><i>Deteriorations of asthma</i></li><li><i>Incidence of severe exacerbations</i></li></ul> <p><i>Change from baseline in:</i></p> <ul style="list-style-type: none"><li><i>Trough FEV<sub>1</sub> at individual time points</i></li><li><i>FEV<sub>1</sub> AUC<sub>0-6 hours</sub> at individual time points</i></li><li><i>Peak change from baseline FEV<sub>1</sub> at Day 1 and Day 7</i></li><li><i>Morning and evening peak expiratory flow (PEF)</i></li><li><i>Use of Ventolin therapy in response to asthma symptoms</i></li><li><i>Asthma daytime/night-time symptoms</i></li><li><i>Asthma Control Questionnaire-5 (ACQ-5) and responder analysis at Week 12</i></li><li><i>Asthma Quality of Life Questionnaire +12 for 12 years and older (AQLQ+12)/Pediatric Asthma Quality of Life Questionnaire (PAQLQ) change from baseline at Week 12</i></li></ul>

## Target Subject Population

Male and female subjects  $\geq 4$  years of age, where approved,  $\geq 18$  years of age for all other countries, with a diagnosis of asthma as defined by Global Initiative for Asthma (GINA) criteria with pre-bronchodilator FEV<sub>1</sub> of  $\geq 50$  to  $<85\%$  predicted normal value (subjects  $\geq 18$  years of age) and  $\geq 50\%$  predicted normal value for subjects 4 to 17 years of age, where approved, with demonstrated in-clinic FEV<sub>1</sub> reversibility to Sponsor-provided SABA will be included.

Subjects must be taking a stable dosing of asthma therapies (only prn SABA or stable low-dose ICS in addition to prn SABA) for at least the last 30 days prior to Visit 1 may be eligible for this study.

## Duration of Study/treatment

The study will consist of 3 periods:

- A screening/run-in period (14 to 28 days).
- A 12-week treatment period.

- A safety follow-up period: where a safety follow-up telephone contact (TC) will occur 2 weeks ( $\pm 4$  days) after the subject's last dose of treatment (end-of-treatment [EOT]) or premature discontinuation visit (PDV).

The end-of-study is defined as the last visit of the last subject undergoing the study, therefore end-of-study will occur when the last subject has completed his or her post-study follow-up TC. Subjects who discontinue IP will complete a PDV, and adverse events (AEs)/serious adverse events (SAEs) will be followed up if medically indicated.

### **Investigational Product, Dosage, and Mode of Administration**

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

Only Sponsor-provided IP administered 4 times per day (QID) and Sponsor-provided Ventolin to be used in response to asthma symptoms are allowed during the study. No other asthma medications are allowed during the study.

At randomization (Visit 2), adult ( $\geq 18$  years of age) and adolescent subjects (aged 12 - 17 years, where approved) who meet the eligibility criteria will be randomly assigned to 1 of the following 5 treatment groups in a 1:1:1:1:1 ratio:

- BDA MDI 80/180  $\mu$ g QID (given as 2 actuations of BDA MDI 40/90  $\mu$ g per puff)
- BDA MDI 160/180  $\mu$ g QID (given as 2 actuations of BDA MDI 80/90  $\mu$ g per puff)
- BD MDI 160  $\mu$ g QID (given as 2 actuations of BD MDI 80  $\mu$ g per puff)
- AS MDI 180  $\mu$ g QID (given as 2 actuations of AS MDI 90  $\mu$ g per puff)
- Placebo MDI QID (given as 2 actuations)

The maximum daily dosage of IP should not exceed 12 puffs per day.

Subjects will be recommended not to take more than 8 puffs of Ventolin per day and advised to contact the investigator if their symptoms necessitate more than 8 puffs of Ventolin in a day.

### **Statistical Methods**

#### **Sample Size Calculation**

A preliminary sample size calculation was based on historical trial data. A sample size of 600 subjects was initially proposed to provide 93% power to detect a difference in change

from baseline in trough FEV<sub>1</sub> at week 12 of 100 mL for comparisons of BD MDI versus placebo MDI, BDA MDI versus placebo MDI, or BDA MDI versus AS MDI. This calculation was based on a standard deviation of 210 mL obtained from the placebo MDI group of Study PT008001 and an assumed dropout rate of 10% and 15% for active and placebo treatment group, respectively, prior to Week 12.

Because the assumed variability from the lung function data has a large impact on the estimated sample size necessary to achieve a stated power, a blinded estimate of the variability of pre-dose trough FEV<sub>1</sub> at Week 12 was calculated. The review was performed once 44% of subjects had completed Week 12, and prior to the 600<sup>th</sup> subject being randomized. The pooled estimate of variability across treatment groups was used to re-calculate the projected power.

### Decisions following the blinded sample size re-estimation

The blinded sample size re-estimation was performed once 44% of subjects had completed Week 12. Based on the blinded estimate of variability, approximately 1000 subjects are required in order to demonstrate 90% power. Consequently, the total number of randomized adult and adolescent subjects has been increased by 400 to 1000.

Randomization of approximately 200 subjects to each treatment group will provide 90% probability to detect a 100 mL difference in the change from baseline in trough FEV<sub>1</sub> at Week 12 for comparison of BD MDI versus placebo MDI, BDA MDI versus placebo MDI, or BDA MDI versus AS MDI. This calculation is based on a standard deviation of 290 mL obtained from the blinded sample size re-estimation performed after 44% of subjects completed week 12 and an estimated overall dropout rate of 11% prior to Week 12.

The sample size of 200 subjects per treatment group will also provide >99% probability to detect a 130 mL difference in FEV<sub>1</sub> AUC<sub>0-6 hours</sub> over 12 weeks for comparison of BDA MDI versus BD MDI (effect sizes for AS MDI or BDA MDI versus placebo MDI should be considerably larger). This calculation assumes 2% dropout prior to Week 1 and an effective standard deviation of 290 mL obtained from the blinded sample size re-estimation performed after 44% of subjects completed Week 12.

Approximately 1000 adults ( $\geq 18$  years of age) and adolescent subjects (12 - 17 years of age, where approved) with asthma will be randomized 1:1:1:1:1 to 1 of 5 treatment groups (approximately 200 subjects per group: BDA MDI 80/180  $\mu$ g QID, BDA MDI 160/180  $\mu$ g QID, BD MDI 160  $\mu$ g QID, AS MDI 180  $\mu$ g QID, or placebo MDI). In addition, where approved, up to 30 child subjects (aged 4 to 11 years) with asthma will be enrolled but will not receive high dose ICS and will be randomized 1:1:1 to receive low-dose BDA MDI 80/180  $\mu$ g QID, AS MDI 180  $\mu$ g QID, or placebo MDI. Approximately 2000 subjects will need to be screened, assuming an estimated screen failure rate of approximately 50% prior to randomization. This Phase III study is planned to be conducted globally.

A second blinded sample size re-estimation will be performed once approximately 65% of the revised sample has completed 12 weeks and prior to the last subject being randomized. This will allow the re-assessment of variability in a larger sample and at a point where any impact on COVID-19 with respect to lung function variability and dropout rates can be quantified more accurately. Final total enrollment in the study will be confirmed following the second blinded sample size re-calculation in order to ensure 90% power.

The potential increase in sample size will be capped at 1300, a 30% increase above the revised number of 1000 subjects.

### Primary Efficacy Analysis

The first and second dual-primary variables, change from baseline in  $FEV_1 AUC_{0-6\text{ hours}}$ , and change from baseline in trough  $FEV_1$  will each be analyzed using a repeated measures (RM) linear model to compare treatment groups. The model will include baseline  $FEV_1$ , percentage reversibility to Ventolin, and age as continuous covariates, and visit, treatment, the treatment-by-visit interaction, and prior ICS use (Yes/No) as categorical covariates. Baseline will be defined as the average of the pre-dose assessments collected on randomization (Visit 2).

An unstructured variance-covariance matrix will be implemented. If this model fails to converge, a heterogeneous Toeplitz (TOEPH) will be fit.

### Secondary Efficacy Analyses

The median time to onset (defined as 15% increase in  $FEV_1$ ) over the pre-treatment value at randomization (Visit 2) will be compared among treatment groups using a Wilcoxon rank sum test. Confidence intervals for the median treatment difference will be calculated using the Hodges-Lehmann method. Descriptive statistics for duration of response will be reported by treatment group. Only the subjects who achieve the 15% increase in  $FEV_1$  within 30 minutes post-dose will be included in these calculations.

The treatment effect for change from baseline in ACQ-7 will be estimated using a mixed model RM (MMRM) analysis. All data up to Week 12 will be included in the model, with terms for age, treatment, visit, treatment\* visit, prior ICS use (Yes/No), baseline ACQ-7 score and baseline post-dose percent predicted  $FEV_1$ . Visit will be fitted as a categorical variable, and the variance-covariance matrix will be assumed to be unstructured. If the procedure does not converge, then a heterogeneous Toeplitz (TOEPH) will be used instead. This model will be used to give an overall assessment of the treatment effect as well as 95% confidence intervals.

## Estimands

The primary estimand of interest is the efficacy estimand, defined as the effect of the randomized treatment in all subjects assuming continuation of randomized treatment for the duration of the study, regardless of actual compliance. This estimand could be considered as a while-on-treatment strategy or a hypothetical strategy as defined in the draft International Conference on Harmonization (ICH) E9 Addendum.

The second estimand of interest is the attributable estimand, defined as the effect of treatment in subjects attributable to the randomized treatment. For this estimand, discontinuation of randomized treatment for reasons such as tolerability or lack of efficacy is considered a negative outcome. This estimand is a mixture of composite and hypothetical strategies as defined in the draft ICH E9 addendum.

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## LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation or special term	Explanation
ACQ-5	Asthma Control Questionnaire-5
ACQ-7	Asthma Control Questionnaire-7
ACQ-IA	Asthma Control Questionnaire-Interviewer-Administered
AE	adverse event
AIT	allergy immunotherapy
ALT	alanine aminotransferase
AQLQ+12	Asthma Quality of Life Questionnaire for 12 years and older
AS MDI (PT007)	albuterol sulfate metered-dose inhaler
AST	aspartate aminotransferase
ATS/ERS	American Thoracic Society/European Respiratory Society
AUC <sub>0-6</sub> hours	area under the concentration curve from 0 to 6 hours
BD MDI (PT008)	budesonide metered-dose inhaler
BDA MDI (PT027)	budesonide/albuterol metered-dose inhaler
β-hCG	β-human chorionic gonadotropin
BMI	body mass index
CFC	chlorofluorocarbon propellant
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
ECG	electrocardiogram
eCRF	electronic case report form
eDiary	electronic diary
EOT	end-of-treatment
ePRO	electronic patient reported outcome
FEV <sub>1</sub>	forced expiratory volume in 1 second
FVC	forced vital capacity
GCP	Good Clinical Practice
GINA	Global Initiative for Asthma
GMP	Good Manufacturing Practice
HL	Hy's Law
ICF	informed consent form
ICH	International Conference on Harmonization
ICS	inhaled corticosteroid

Abbreviation or special term	Explanation
IDMC	Independent Data Monitoring Committee
International Coordinating investigator	If a study is conducted in several countries, the International Coordinating investigator is the investigator coordinating the investigators and/or activities internationally.
IP	investigational product
IWRS	Interactive Web Response System
LABA	long-acting $\beta$ 2-agonist
MDI	metered-dose inhaler
MID	minimal important difference
MMRM	mixed model repeated measures
PAQLQ	Pediatric Asthma Quality of Life Questionnaire
PDV	premature discontinuation visit
PEF	peak expiratory flow
PFT	pulmonary function test
PHL	potential Hy's Law
prn	as needed
QID	four times daily
RM	repeated measures
SABA	short/rapid-acting $\beta$ 2-adrenoreceptor agonist
SAE	serious adverse events
SAP	Statistical Analysis Plan
SCS	systemic corticosteroids
SMART	budesonide/formoterol (Symbicort); approved for maintenance and reliever therapy
TBL	total bilirubin
TC	telephone contact
ULN	upper limit of normal
WBDC	Web Based Data Capture

## 1 INTRODUCTION

### 1.1 Background

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

Albuterol is a short/rapid-acting  $\beta_2$ -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. In clinical practice, albuterol is used as an as needed (prn) reliever therapy (Global Initiative for Asthma [[GINA](#)] 2018). Albuterol is approved in many countries as salbutamol in multiple formulations for the treatment or prevention of bronchoconstriction.

Budesonide is a well-established anti-inflammatory corticosteroid that exhibits potent glucocorticoid and weak mineralocorticoid activity and is approved worldwide in orally inhaled formulations for the treatment of asthma and chronic obstructive pulmonary disease both as a mono-product and in combination with a long/rapid-acting  $\beta_2$ -agonist (LABA, formoterol).

In vitro studies have demonstrated that inhaled corticosteroid (ICS) agents potentiate the effects of SABAs in reducing airway smooth muscle tone ([Mendes 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 2015](#)). An analysis of 425 asthma exacerbations in patients from the Formoterol and Corticosteroids Establishing Therapy International Study Group study ([Tattersfield 1999](#)) revealed that asthma symptoms use were noted over several days before the start of an asthma exacerbation; increased reliever therapy (ie, albuterol) followed a similar pattern, providing rapid bronchodilation to treat the symptoms. 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 2018](#)), 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 ([Rabe 2006; O'Byrne 2005](#)). In addition, budesonide/formoterol as maintenance and reliever therapy or '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](#)).

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. 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 2018](#)) recommend considering 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  $\beta$ 2-adrenoreceptor agonist. Anti-inflammatory and bronchodilation component in combination is expected to result with superior control and decreased risk of experiencing asthma symptoms.

## 1.2 Rationale for study design, doses, and control groups

This is a 12-week, randomized, double-blind, placebo-controlled, multicenter, parallel group, Phase III study in adults, adolescents, and child subjects, aged 4 years and older, with symptomatic asthma currently being treated with SABA prn alone or with low-dose ICS maintenance therapy plus SABA prn.

This 12-week Phase III study is a pivotal efficacy and safety study for approval of BDA MDI fixed dose combination product. This study is designed to investigate the benefit of 2 dose levels of BDA MDI compared to its constituent components budesonide metered-dose inhaler (BD MDI [PT008]) and albuterol sulfate metered-dose inhaler (AS MDI [PT007]) based on improvement in lung function and asthma symptoms after 12 weeks of treatment. This study will demonstrate the combination rule required by the Food and Drug Administration according to the 21 Code of Federal Regulations 300.50.

Two dosage levels, of BDA MDI administered 4 times daily (QID), 80/180  $\mu$ g (given as 2 actuations of BDA MDI 40/90  $\mu$ g per puff) and 160/180  $\mu$ g (given as 2 actuations of BDA MDI 80/90  $\mu$ g per puff), are included in this study to support final dose selection for approval. Children aged 4 to 11 years will only be randomized to the lower dosage level of BDA MDI (80/180  $\mu$ g QID, or AS MDI [180  $\mu$ g QID], or placebo MDI).

The treatment duration of 12 weeks for each subject, is considered to be an appropriate duration to evaluate lung function benefit in asthma subjects. This is supported by a 12-week standard treatment duration being assessed in Symbicort<sup>®</sup> (budesonide/formoterol fumarate dihydrate), Breo Ellipta (fluticasone/furoate and vilanterol), and Advair<sup>®</sup> (fluticasone/propionate/salmeterol) lung function studies (Symbicort [[Corren 2007](#) and [Noonan 2006](#)], Breo [[Kerwin 2017](#)], Advair [[Kavuru 2000](#)]).

Two dose levels of BDA MDI will be used to evaluate the dual-primary efficacy measures versus the mono-components BD MDI 160 µg QID and AS MDI 180 µg QID as active control groups in order to demonstrate the combination rule and to compare efficacy outcomes.

Dual-primary efficacy measures have been selected to demonstrate the therapeutic contribution of each component of the combination to the overall bronchodilator efficacy:

- Change from baseline in forced expiratory volume in 1 second (FEV<sub>1</sub>) area under the curve from 0 to 6 hours (AUC<sub>0-6 hours</sub>) over 12 weeks
- Change from baseline in trough FEV<sub>1</sub> at Week 12

### **1.3 Benefit/risk and ethical assessment**

This study consists of 12 weeks of treatment and 2 weeks of safety follow-up designed to evaluate the effect of BDA MDI on asthma symptoms and lung function. This study with its typical design for lung function studies is complementary to the AV003 MANDALA study evaluating the effect of BDA MDI on the occurrence of severe asthma exacerbations and is part of the regulatory requirements for US registration of BDA MDI for an asthma indication. This study has 2 active control groups (BD MDI and AS MDI), and a placebo MDI control group, designed. SABA (Ventolin®) will also be provided to each subject prn in response to asthma symptoms.

It should be noted that as part of this study design, some of the subjects who have not received ICS before may be assigned to treatment with BD MDI or BDA MDI. In addition, some subjects who have been receiving low-dose ICS may be randomized to either placebo MDI or AS MDI (ie, they will no longer be receiving ICS treatment).

To mitigate potential risks, all subjects will be closely monitored to ensure subject safety throughout the study through a range of mechanisms including:

- Frequently evaluated by investigator during clinic visits at Weeks 1, 4, 8, and 12.
- Subjects will provide information to the electronic diary (eDiary) including; asthma symptoms score, use of Ventolin prn in response to asthma symptoms, dosing of Sponsor-provided investigational product (IP, captured in eDiary in evenings only), and peak expiratory flow (PEF) twice daily. In the situation where the subject's symptoms and/or Ventolin prn use has increased and/or PEF decreased over 2 days, an eDiary alert is created and sent to the subject, the investigator site, and the Sponsor's medical monitoring team. This alert should initiate contact between the subject and the investigator site to determine the well-being of the subject.
- The eDiary will be programmed to alert both the subject and study center to assess the well-being of the subject and any possible asthma exacerbation.
- An Independent Data Monitoring Committee (IDMC) will be established to assess the ongoing safety of the study.

- The Sponsor's medical team will have medical oversight of blinded data for continuous subject safety evaluations.

The Sponsor considers the risk and benefit profile of Study AV004-DENALI to be acceptable when considering and assessing all non-clinical and clinical data available for study treatments.

## **COVID-19**

Recent information from the American Academy of Allergy Asthma and Immunology (AAAAI) published on their website (<https://www.aaaai.org/>) on June 4, 2020 indicates that currently there is no evidence of increased infection rates in subjects with asthma and that it is best to get and keep their asthma under control." In the DENALI study, subjects are provided Ventolin for as needed use and have their asthma symptoms closely monitored through daily eDiary symptom alerts provided to the investigator and medical monitors. The Sponsor believes that the benefit-risk assessment for trial participants to enroll and continue in the study remains positive.

## **1.4 Study design**

This is a 12-week, randomized, double-blind, placebo-controlled, multicenter, parallel group, Phase III study. The purpose of this study is to compare 2 dose levels of BDA MDI compared to its constitute components BD MDI and AS MDI on improvement in lung function and asthma symptoms after 12 weeks of treatment (Section 5.1.1) in adults, adolescents, and child subjects, aged 4 years and older, with symptomatic asthma currently being treated with SABA prn alone or with low-dose ICS maintenance therapy plus SABA prn.

Subjects meeting all entry criteria at the screening visit (Visit 1) will enter a 14 to 28-day screening (run-in) period.

Only Sponsor-provided IP administered 4 times per day (QID) and Sponsor-provided Ventolin to be used in response to asthma symptoms are allowed during the study. No other asthma medications are allowed during the study.

During the screening (run-in) period, subjects will self-administer single-blind placebo MDI QID and Ventolin prn to be used in response to asthma symptoms only. Subjects will be trained and instructed in the use of an eDiary and peak flow meter at Visit 1 to record protocol required data into the eDiary twice daily (Section 5.1.6).

Eligible subjects will be randomized at Visit 2.

At randomization (Visit 2), adult and adolescent subjects (age  $\geq 12$  years) who meet the eligibility criteria will be randomly assigned to 1 of the following 5 treatment groups in a 1:1:1:1:1 ratio:

- BDA MDI 80/180 µg QID (given as 2 actuations of BDA MDI 40/90 µg per puff)
- BDA MDI 160/180 µg QID (given as 2 actuations of BDA MDI 80/90 µg per puff)
- BD MDI 160 µg QID (given as 2 actuations of BD MDI 80 µg per puff)
- AS MDI 180 µg QID (given as 2 actuations of AS MDI 90 µg per puff)
- Placebo MDI QID (given as 2 actuations)

Children aged 4 to 11 will be randomized in a 1:1:1 ratio only to the lower BDA MDI QID dosage, AS MDI QID, or placebo MDI QID.

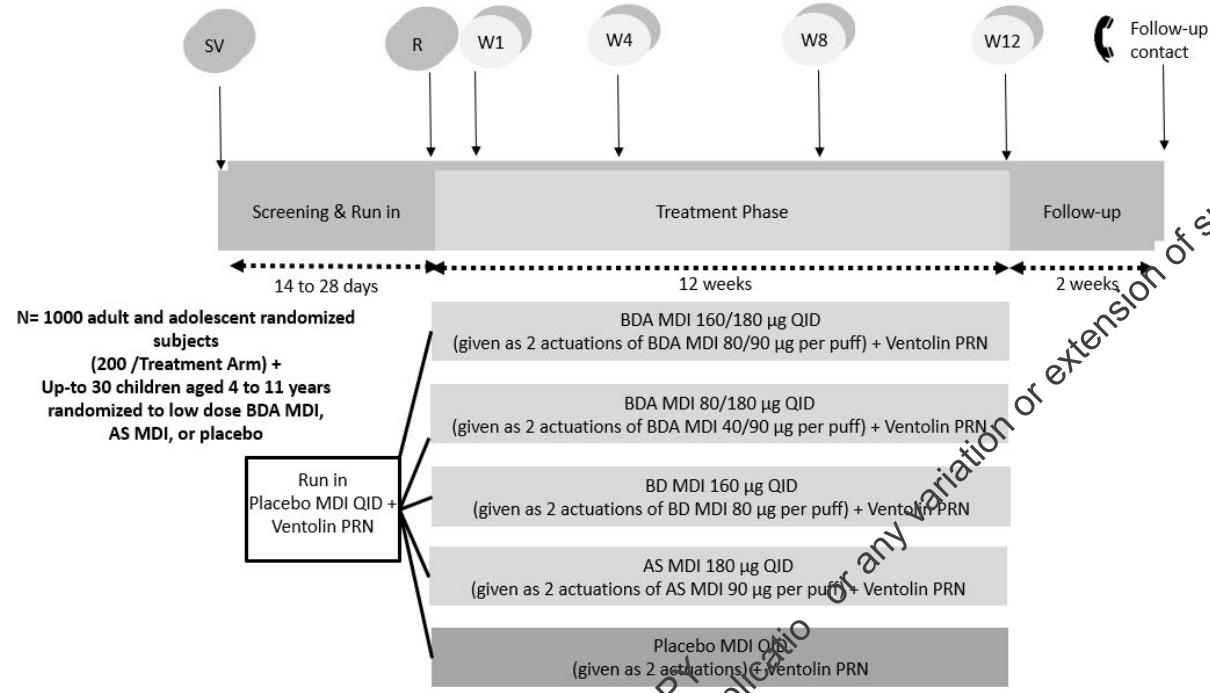
Ventolin will be provided to all subjects for prn use in response to asthma symptoms with a daily dosing recommendation not to exceed 8 puffs per day. See [Figure 1](#) for a graphical presentation of the study schema and [Table 1](#) for a list of study assessments and [Table 2](#) for timed assessments at Visit 2 through Visit 6.

The study will consist of 3 periods:

- A screening/run-in period (14 to 28 days).
- A 12-week treatment period.
- A safety follow-up period: where a safety follow-up TC will occur 2 weeks ( $\pm 4$  days) after the subject's last dose of treatment (end-of-treatment [EOT]) or premature discontinuation visit (PDV).

The study will be completed when the last subject has completed his or her safety follow-up telephone contact. Subjects who discontinue IP prior to the end of the 12-week treatment period will be withdrawn from the study and will be asked to complete a PDV, and adverse events (AEs)/serious AEs (SAEs) will be followed up if medically indicated.

**Figure 1** **Study design**



Abbreviations: AS MDI=albuterol metered-dose inhaler; BD MDI=budesonide metered-dose inhaler; BDA MDI=budesonide/albuterol metered-dose inhaler; N=number; placebo MDI=placebo metered-dose inhaler; PRN=as needed; QID=four time daily; R=randomization; SV=screening visit; W=week.

## 1.5 Study governance and oversight

### 1.5.1 Independent data monitoring committee

An IDMC will be established to assess the ongoing safety of the study. The IDMC will review blinded data (open session) and unblinded safety data (closed session) to assess any safety related reasons why the study should continue, be modified, or stopped. Closed sessions will be supported by the unblinded statistician and responsibilities of the IDMC will be clarified within a charter before initiation of the study.

The IDMC chair and all committee members will be independent investigators/specialists separate from the study team or contract research organization.

All decisions made by the IDMC will be documented within written records of meetings and recommendation made to the Sponsor.

## 2 STUDY OBJECTIVES

### 2.1 Primary objectives

Primary objective:	Primary endpoints:
<p><i>To demonstrate the contribution of budesonide and albuterol in BDA MDI 80/180 µg and 160/180 µg administered QID by comparing with mono-components (BD MDI 160 µg, AS MDI 180 µg) and placebo on lung function</i></p>	<p><i>Dual-primary endpoints:</i></p> <ul style="list-style-type: none"><li><i>Change from baseline in FEV<sub>1</sub> AUC<sub>0-6 hours</sub> over 12 weeks</i></li><li><i>Change from baseline in trough FEV<sub>1</sub> at Week 12</i></li></ul>

### 2.2 Secondary objectives

Secondary objective:	Secondary endpoints:
<p><i>To characterize the effect of BDA MDI 80/180 µg and 160/180 µg administered QID on bronchodilation and asthma symptoms compared to the mono-components (BD MDI 160 µg, AS MDI 180 µg) and placebo</i></p>	<ul style="list-style-type: none"><li><i>The time to onset (defined as 15% increase in FEV<sub>1</sub> over the pre-treatment value on Day 1), and duration of response on Day 1</i></li><li><i>Number (%) of subjects who have an Asthma Control Questionnaire-7 (ACQ-7) score of <math>\geq 1.5</math> at baseline who achieve a clinically meaningful improvement (a decrease of at least 0.5 units from baseline) in ACQ-7 at Week 12</i></li><li><i>Trough FEV<sub>1</sub> at Week 1</i></li></ul>

### 2.3 Safety objectives

Safety objective:	Safety endpoints:
<p><i>To evaluate the safety and tolerability of BDA MDI 80/180 µg and 160/180 µg administered QID compared to BD MDI (160 µg) and AS MDI (180 µg)</i></p>	<ul style="list-style-type: none"><li><i>AE/SAEs</i></li><li><i>Vital signs (ie, heart rate, blood pressure only)</i></li><li><i>Clinical chemistry and hematology parameters</i></li><li><i>Electrocardiogram (ECG)</i></li></ul>

## 2.4 Exploratory objectives

Exploratory objective:	Exploratory endpoints:
<p><i>To characterize the effect of BDA MDI 80/180 µg and 160/180 µg administered QID on bronchodilation and asthma symptoms compared to the mono-components (BD MDI 160 µg, AS MDI 180 µg) and placebo</i></p>	<ul style="list-style-type: none"><li><i>Deteriorations of asthma</i></li><li><i>Incidence of severe exacerbations</i></li></ul> <p><i>Change from baseline in:</i></p> <ul style="list-style-type: none"><li><i>Trough FEV<sub>1</sub> at individual time points</i></li><li><i>FEV<sub>1</sub> AUC<sub>0-6 hours</sub> at individual time points</i></li><li><i>Peak change from baseline FEV<sub>1</sub> at Day 1 and Day 7</i></li><li><i>Morning and evening PEF</i></li><li><i>Use of Ventolin therapy in response to asthma symptoms</i></li><li><i>Asthma daytime/nighttime symptoms</i></li><li><i>Asthma Control Questionnaire-5 (ACQ-5) and responder analysis at Week 12</i></li><li><i>Asthma Quality of Life Questionnaire +12 for 12 years and older (AQLQ+12)/Pediatric Asthma Quality of Life Questionnaire (PAQLQ) change from baseline at Week 12</i></li></ul>

## 3 SUBJECT SELECTION, ENROLLMENT, RANDOMIZATION, RESTRICTIONS, TREATMENT DISCONTINUATION, AND STUDY TERMINATION

Each subject must meet all of the inclusion criteria and none of the exclusion criteria for this study.

No study-related procedures may be performed before the subject has signed the Ethics Committee (EC) approved Informed Consent Form (ICF)/assent form.

### 3.1 Inclusion criteria

For inclusion in the study, subjects must fulfill the following criteria within the screening period:

- 1 Able and willing to provide written informed consent or sign age-appropriate forms; subjects below legal age of consent must have parent(s) or guardian sign the ICF before participation
- 2 Female or male aged  $\geq 4$  years at the time of informed consent. In the Czech Republic, Germany, Serbia, Slovakia, and Ukraine only subjects  $\geq 18$  years will be included.

- 3 Diagnosis of asthma as defined by GINA criteria with a documented history of the last 6 months prior to Visit 1
- 4 Receiving 1 of the following inhaled asthma medications with stable dosing for at least 30 days prior to Visit 1:
  - (a) Only SABA used prn
  - (b) Stable low-dose ICS ([Appendix C, GINA 2018](#)) in addition to prn use of SABA

The following defines the minimally acceptable documentation required to support inclusion criterion 4:

- Signed and dated notes from a referring physician, including name, dose, and duration of the SABA or SABA with low-dose ICS (or names and doses, if used as separate inhalers), if applicable, and/or
- Evidence of prescriptions for SABA or SABA with low-dose ICS, if applicable, medications that demonstrate coverage for the duration specified in inclusion criteria

- 5 Pre-bronchodilator FEV<sub>1</sub> of  $\geq 50$  to  $< 85\%$  predicted normal value for adults ( $\geq 18$  years of age) and  $\geq 50\%$  predicted normal value for subjects aged 4 to 17 years after withholding SABA  $\geq 6$  hours at Visit 1. If subject took SABA or any bronchodilator in the morning of Visit 1, either the entire visit must be rescheduled or just PFT assessment rescheduled. Subjects 4 to 17 years of age who previously failed inclusion criteria 5 due to the upper FEV<sub>1</sub> limit will be permitted to re-screen once and will be required to meet all eligibility criteria upon re-screening.
- 6 Demonstrate reversibility of airflow limitation defined as a  $\geq 15\%$  increase in FEV<sub>1</sub> relative to baseline after administration of Sponsor-provided SABA (Ventolin) at either Visit 1 or Visit 1a. One re-test for reversibility testing is allowed within the screening period prior to Visit 2
- 7 Demonstrate acceptable spirometry performance (ie, meet American Thoracic Society/European Respiratory Society [ATS/ERS]) acceptability/repeatability criteria ([Appendix K, Spirometry Assessment Criteria](#)). Subjects 4 to 11 years will be eligible if they provide 2 acceptable / repeatable measurements.
- 8 Taken Ventolin on  $\geq 2$  days out of 7 days prior to Visit 2
- 9 Willing and, in the opinion of the investigator, able to adjust current asthma therapy, as required by the protocol
- 10 Demonstrate acceptable metered-dose-inhaler (MDI) administration technique as assessed by the investigator. Note: spacer use is not allowed throughout the screening and randomized treatment periods
- 11 Able to perform acceptable and reproducible PEF measurements as assessed by the investigator
- 12 Body mass index (BMI)  $< 40 \text{ kg/m}^2$

- 13 Willing to remain at the study site as required per protocol and complete all visit assessments
- 14 Negative pregnancy test (serum at Visit 1) for female subjects of childbearing potential
- 15 Women of childbearing potential and sexually active 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) If a female of childbearing potential agrees to prevent pregnancy by using 1 of the following effective methods of birth control from the date the ICF is signed until 2 weeks after the final dose of IP is taken:
    - i. Hormonal contraception (eg, oral contraceptive, contraceptive implant, or injectable hormonal contraceptive)
    - ii. Double-barrier birth control (eg, a combination of male condom with either cap, diaphragm, or sponge with spermicide)
    - iii. Maintenance of a monogamous sexual relationship with a male partner who has been surgically sterilized by vasectomy
  - (c) Note: Women are considered to be of nonchildbearing potential if they are physiologically incapable of becoming pregnant, including any female who is 2 years postmenopausal, or surgically sterile, defined as having a bilateral oophorectomy, hysterectomy, tubal ligation, or other permanent birth control measures. For purposes of this protocol, menopausal women are defined as women that are amenorrheic for 12 consecutive months or more after cessation of all exogenous hormonal treatment. Adolescent specific recommendations: if subject is female and has reached menarche or has reached Tanner stage 3 breast developments (even if not having reached menarche), the subject will be considered a female of child-bearing potential.
- 16 Male subjects who are sexually active in heterosexual relationships must be surgically sterile or agree to use a double-barrier effective method of contraception (condom with spermicide) from the first dose of randomized IP until 2 weeks after their last dose. Male subjects must not donate sperm during their study participation period.

### **3.2      Exclusion criteria**

Subjects must not enter the study if any of the following exclusion criteria are fulfilled within the screening period:

- 1 Chronic obstructive pulmonary disease or other significant lung disease (eg, chronic bronchitis, emphysema, bronchiectasis with the need of treatment, cystic fibrosis, or bronchopulmonary dysplasia)
- 2 Systemic corticosteroids (SCS) use (any dose and any indication) within 3 months before Visit 1
- 3 Chronic ( $\geq 3$  weeks) use of SCS within 6 months prior to Visit 1
- 4 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
- 5 Current smokers, former smokers with  $>10$  pack-years history, or former smokers who stopped smoking  $<6$  months before Visit 1 (including all forms of tobacco e-cigarettes [vaping], and marijuana)
- 6 Life-threatening asthma defined as any history of significant asthma episode(s) requiring admission to an intensive care unit, intubation associated with hypercapnia, respiratory arrest, hypoxic seizures, or asthma-related syncopal episode(s) within 5 years of Visit 1
- 7 Completed treatment for lower respiratory infection within 6 weeks prior to Visit 1
- 8 Upper respiratory infection involving antibiotic treatment not resolved within 7 days prior to Visit 1
- 9 Hospitalizations due to asthma within 6 months prior to Visit 1
- 10 Have taken  $\geq 12$  actuations per day of Sponsor-provided Ventolin during the run-in period prior to Visit 2 according to the following criteria:
  - (a)  $\geq 2$  days out of 14 days of run-in
  - (b)  $\geq 3$  days out of 15 to 21 days of run-in
  - (c)  $\geq 4$  days out of 22 or more days of run-in
- 11 Unable to comply with study procedures including non-compliance with diary completion (ie,  $<70\%$  subject completion of diary assessments in the last 7 days preceding Visit 2 or QID dosing,  $<80\%$  compliance during the placebo run-in period)
- 12 Clinically significant laboratory abnormalities, in the opinion of the investigator, or having any of the following results at Visit 1:
  - (a) a serum creatinine value  $>1.5$  times the upper limit of the reference range
  - (b) a serum total bilirubin value (TBL)  $>1.5$  times the upper limit of the reference range
  - (c) a serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) value  $>2.5$  times the upper limit of the reference range
- 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 QTcF interval  $>480$  ms (subjects aged  $\geq 12$  years)  $/\geq 460$  ms (subjects aged 4 to 11 years, based on the Fridericia correction where  $QT_{cF}=QT/RR^{0.33}$ )

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

19 A known or suspected hypersensitivity to albuterol/salbutamol, or budesonide and/or their excipients

20 A scheduled/planned hospitalization during the study

21 Inability to abstain from protocol-defined prohibited medications during the study

22 Using any herbal products by inhalation or nebulizer within 2 weeks of Visit 1 and not agreeing to stop during the study duration

23 Received a live attenuated vaccination within 7 days of Visit 1

24 Currently pregnant or breastfeeding

25 Study investigators, sub investigators, coordinators, and their employees or immediate family members, or employees of the Sponsor

26 Treatment with any investigational treatment or device in another clinical study within the last 30 days (or 5 half-lives, whichever is longer) of Visit 1

27 Currently participating in any interventional study

28 Previously been randomized in this study or any other PT007 or PT027 clinical study. For pediatrics, see inclusion criterion 4.

Procedures for withdrawal of incorrectly enrolled subjects are described in [Section 3.4](#).

### **3.3 Subject enrollment and randomization**

Approximately 1000 adults and adolescent subjects ( $\geq 12$  years of age) with asthma will be randomized 1:1:1:1:1 to 1 of 5 treatment groups (approximately 200 subjects per group: BDA MDI 80/180  $\mu\text{g}$  QID, BDA MDI 160/180  $\mu\text{g}$  QID, BD MDI 160  $\mu\text{g}$  QID, or AS MDI 180  $\mu\text{g}$  QID or placebo MDI). In addition, up to 30 child subjects (4 to 11 years of age) with asthma will be enrolled but will not receive high dose ICS and will be randomized 1:1:1 to receive low-dose BDA MDI 80/180  $\mu\text{g}$  QID, AS MDI 180  $\mu\text{g}$  QID, or placebo MDI. Approximately 2000 subjects will need to be screened, assuming an estimated screen failure rate of 50% prior to randomization. This Phase III study is planned to be conducted globally.

The investigator(s) and/or study personnel 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 (Ecode)
- 3 Determine subject eligibility ([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 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 randomized or receive IP. 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 assigned to the project immediately, and a discussion should occur between the medical monitor assigned to the project and the investigator regarding whether to continue or discontinue the subject from treatment. The Sponsor's medical monitor assigned to the project must ensure all decisions and protocol deviations, if any, 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 period. The designated statistical representative will follow their established standard operating procedures regarding generation, security, and distribution of the randomization schedule. Randomization will be centralized.

Randomization for adults and adolescents will be centralized and stratified by pre-study background therapy consisting of either ICS or non-ICS (subjects not previously treated with ICS), by Asthma Control Questionnaire-7 (ACQ-7;  $\leq 1.5$ ,  $> 1.5$ ), and by age ( $\geq 12$  to  $< 17$ ,  $\geq 18$ ). Children aged 4 to 11 years will not be stratified.

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 period 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 5 different kit types of study IP 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 judgement 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. The only individuals who will have access to unblinded information during the conduct of the study in advance of the primary outcome database lock will be the unblinded statistician supporting the IDMC closed session review which will be performed in accordance with the IDMC charter.

### 3.8 Restrictions

Subjects should be advised that marketed (eg, omalizumab, mepolizumab, reslizumab, benralizumab) or investigational biologic treatments are not allowed during the treatment period. Subjects requiring chronic SCS are excluded.

Only Sponsor-provided IP and Sponsor-provided Ventolin to be used in response to asthma symptoms are allowed during the study. No other asthma medications are allowed during the study. Restrictions regarding concomitant medications are described in [Section 7.8](#).

Subjects should not take Sponsor-provided Ventolin  $\leq$  6 hours before a study visit (if Ventolin is needed in the morning of a study visit, either the entire visit must be rescheduled or just PFT assessment rescheduled).

Subjects should avoid strenuous exercise for at least 30 minutes prior to a study visit.

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

Subjects must not ingest xanthine and/or xanthine analogue (caffeine)-containing foods and beverages for at least 6 hours prior to and for the duration of each in-clinic study visit.

Examples of such products include coffee, tea, chocolate, and cola. Decaffeinated beverages are acceptable.

Illicit drugs or drugs of abuse will not be allowed from Visit 1 to the end of the follow-up telephone contact or to whenever the subject withdraws from the study. If any illicit drugs or drugs of abuse are used by the subject during the study, the dates of use and the amount will be documented, and the subject will be discontinued at the discretion of the Investigator.

Medical marijuana is not an exclusionary drug if used for medical purposes, and there is no change in the dose or frequency of consumption.

### 3.9 Treatment discontinuation by subject and/or Sponsor

Subjects may be withdrawn from the study at any time at their own request, upon request of the investigator, or by the Sponsor at any time or for any reason. The subject or his/her parent/legal representative is free to discontinue treatment at any time, without prejudice to further treatment. Other reasons for IP discontinuation may include:

- An AE considered to jeopardize the safety of a subject participating in the study
- Subjects who suffer 1 severe exacerbation should be considered for discontinuation if Sponsor and the investigator decide that it is in the best interest of the subject to discontinue randomized treatment and withdraw from the study
- In the opinion of the investigator, the subject is non-compliant with the Clinical Study Protocol (eg, post-enrollment eligibility violation, failure to adhere to dosing compliance) or 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)
- If female subject becomes pregnant, the subject will automatically be discontinued from IP
- In subjects who have elevated liver enzymes AST and/or ALT  $\geq 3$  times the upper limit of normal ( $\times$ ULN) and total bilirubin  $\geq 2 \times$ ULN (ie, meeting the criteria of at least potential Hy's Law), IP will be suspended until the liver test values return to the normal range. If the AST, ALT, or total bilirubin reach these elevated levels again, after recommencement of IP, the subject will be discontinued from IP and withdrawn from the study.

Subjects who discontinue IP prior to the end of the 12-week treatment period will be withdrawn from the study and will be asked to complete a PDV, and AEs/SAEs will be followed up if medically indicated.

A subject that decides to discontinue IP will always be asked about the reason(s) and the presence of any AEs. If possible, they will be seen and assessed by an investigator(s). AEs and SAEs will be followed up ([Section 6](#)); eDiary and all IPs should be returned by the subject.

### 3.10 Study termination

If the Sponsor, investigator, study monitor, IDMC, or regulatory officials discover conditions arising during the study that indicate that the subject's safety and/or scientific value of the study and/or quality of the IPs have been compromised, the study may be halted or the study center's participation may be terminated. Ongoing subjects will be discontinued from the study and assigned to receive treatment as per local standard of care.

Conditions that may warrant termination of the study include, but are not limited to, the following list:

- The study may be stopped if, in the judgement of the Sponsor, study subjects are placed at undue risk because of findings that:
  - are considered significant
  - are assessed as causally related to IP
  - are not considered to be consistent with continuation of the study
- The discovery of an unexpected, serious, or unacceptable risk to the subjects enrolled in the study
- A decision on the part of the Sponsor to suspend or discontinue testing, evaluation, or development of the IP for any reason

Conditions that may warrant termination of a study center's participation include, but are not limited to, the following list:

- Failure of the investigator to enroll subjects into the study at an acceptable rate or within an agreed timeline
- Failure of the investigator to comply with pertinent governing body regulations
- Submission of knowingly false information from the research facility to the Sponsor, study monitor, medical officer, or regulatory official
- Insufficient adherence to protocol requirements

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.

Study termination and follow-up will be performed in compliance with applicable governing body regulations.

### **3.11 Screen failures**

Screening failures are subjects who do not fulfill the eligibility criteria for the study, and therefore must not be randomized. These subjects, who have a reason for not enrolling to the study, should be recorded as 'Screen failure'. Subjects who are screen failures will not be re-screened with the exception of children and adolescents who screen-failed because they did not meet the now obsolete upper FEV1 % predicted limit. Children and adolescents who previously failed to meet the upper FEV1 % predicted threshold, but who met all other eligibility requirements, may re-screen once. Upon re-screening, these subjects must meet all eligibility requirements in order to be randomized.

## 4 STUDY PLAN AND TIMING OF PROCEDURES

**Table 1** presents study assessments and procedures and **Table 2** presents timed assessments at Visit 2 through Visit 6. Repeat assessments, if needed, will be captured in unscheduled visits.

### General Considerations

- For subjects who inadvertently took IP, SABA, or any bronchodilator in the morning of any study visit, either the entire visit must be rescheduled or just PFT assessment rescheduled.
- Subjects must not ingest 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 at Visit 2 for all treatment visits ( $\pm 2$  hours) and dosing time should not exceed 10:00 AM and pulmonary function tests (PFTs) should be completed within  $\pm 1$  hour of Visit 2. Subjects will be required to remain at clinic until completion of all protocol-defined assessments. In order to minimize diurnal variance, sites should make every effort to assess subjects at the same time throughout the study.
- IP should be taken in the morning upon waking, and then distributed equally throughout the day with the final dose taken before going to sleep. The evening before clinic visits, subjects should be advised to take the last dose at 22:00  $\pm 2$  hours.
- To ensure dosing time standardization, it is recommended that sites encourage subjects to maintain a dosing schedule consistent with their in-clinic dosing time and that sites call the subjects on the day before a scheduled visit to remind the subject of the following:
  - To take their last dose the evening before the scheduled visit
  - To withhold all inhaled medications (oral and intranasal) for at least 6 hours prior to PFTs
  - To bring their study medications and eDiary with them to the clinic

Site personnel will instruct subjects not to take any inhaled medications, without site personnel permission, during a visit until all study procedures have been completed, and the subject is discharged. Site personnel should take every precaution to prevent subject use of asthma medications during the test day. Site personnel may request the subject to surrender all IP and Ventolin prior to the visit start before performing any study procedures and return the IP and Ventolin to the subject at the end of the visit when all study procedures are completed. Subjects will be asked to abstain wherever possible from using Ventolin during study visits. If a subject is experiencing severe symptoms and requires Ventolin in response to asthma symptoms at any time during a test day, site personnel must note the time and justification of

use in the subject's chart and all subsequent spirometry assessments should be stopped.  
However, safety assessments should be continued at the discretion of the investigator.

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**Table 1** Study assessments and procedures

	Screening (run-in) <sup>b</sup>	Double-blind Treatment Period						PDV <sup>d</sup> (if applicable)	Safety Follow-up TC (2 weeks [ $\pm 4$ days] after treatment discontinuation)
		1 (1/1a)	2	3	4	5	6 <sup>c</sup>		
<i>Visit<sup>a</sup></i>	1 (1/1a)	2		3	4	5	6 <sup>c</sup>		
<i>Week</i>	-4 to -2	0		1	4	8	12		
<i>Day</i>	-28 to -14	1		7 $\pm$ 2	28 $\pm$ 2	56 $\pm$ 2	84 $\pm$ 2		
<i>Informed consent</i>	X								
<i>Eligibility criteria</i>	X	X							
<b>Routine clinical procedures</b>									
Medical/surgical history (including any on-study medical/surgical procedures) <sup>e</sup>	X	X	X	X	X	X	X		
Demography	X								
Physical examination <sup>f</sup>	X						X	X	
Concomitant medications	X	X			X	X	X	X	X
SABA reversibility test <sup>g</sup>	X								
<b>Safety measurements</b>									
Vital signs (HR and BP only)	X	X	X	X	X	X	X		
12-lead ECG	X	X				X	X		
Adverse events	X	X	X	X	X	X	X		X
Pregnancy test <sup>h</sup>	X	X	X	X	X	X	X		
Safety laboratory assessments (clinical chemistry, hematology)	X					X	X		

	<i>Screening (run-in)<sup>b</sup></i>	<i>Double-blind Treatment Period</i>					<i>PDV<sup>d</sup> (if applicable)</i>	<i>Safety Follow-up TC (2 weeks [<math>\pm 4</math> days] after treatment discontinuation)</i>
<i>Visit<sup>a</sup></i>	<i>1 (1/1a)</i>	<i>2</i>	<i>3</i>	<i>4</i>	<i>5</i>	<i>6<sup>c</sup></i>		
<i>Week</i>	<i>-4 to -2</i>	<i>0</i>	<i>1</i>	<i>4</i>	<i>8</i>	<i>12</i>		
<i>Day</i>	<i>-28 to -14</i>	<i>1</i>	<i>7<math>\pm 2</math></i>	<i>28<math>\pm 2</math></i>	<i>56<math>\pm 2</math></i>	<i>84<math>\pm 2</math></i>		
<b><i>Efficacy measurements</i></b>								
<i>Spirometry (FEV<sub>1</sub>)<sup>i</sup></i>	X	X	X	X	X	X	X	
<i>ACQ-5</i>	X	X	X	X	X	X	X	
<i>ACQ-7</i>	X	X	X	X	X	X	X	
<i>AQLQ+12/PAQLQ</i>		X		X		X	X	
<i>Review of PEF, use of Ventolin therapy, asthma daytime/night-time symptoms, night-time awakenings due to asthma symptoms<sup>j</sup></i>		X	X	X	X	X	X	
<i>Dispense/collect eDiary (AM3+)</i>	X						X	
<i>Review compliance with eDiary</i>		X		X	X	X	X	
<b><i>Investigational product administration</i></b>								
<i>IP compliance</i>		X	X	X	X	X	X	
<i>Randomization</i>								
<i>IP (dispense/collect)<sup>k</sup></i>	d	c/d <sup>k</sup>	c/d	c/d	c/d	c/d <sup>n</sup>	c/d <sup>n</sup>	
<i>Ventolin (collect/dispense)</i>	d <sup>l</sup> X	c/d <sup>l</sup>	c/d <sup>l</sup>	c/d <sup>l</sup>	c/d <sup>l</sup>	c	c	
<i>Ventolin administration (recorded in MasterScope)</i>								
<i>IP administration (recorded in MasterScope)<sup>m</sup></i>	X	X	X	X	X	X	X	

Abbreviations: ACQ-5=Asthma Control Questionnaire-5; ACQ-7=Asthma Control Questionnaire-7; AQLQ+12= Asthma Quality of Life Questionnaire for 12 years and older;  $\beta$ -hCG=  $\beta$  -human chorionic gonadotropin; BP=blood pressure; c= collect; d=dispense; eDiary=electronic diary; ECG=electrocardiogram; FEV<sub>1</sub>=forced expiratory volume in 1 second; HR=heart rate; IP=investigational product; PAQLQ=Pediatric Asthma Quality of Life Questionnaire; PDV= premature discontinuation visit; PEF= peak expiratory flow; QID=4 times daily; SABA=short/rapid-acting  $\beta$ 2-adrenoreceptor agonist; TC=telephone contact; V=visit

<sup>a</sup> Repeat assessments/visits, if needed, will be captured in unscheduled visits.

<sup>b</sup> Screening (run-in) Period may be 14 to 28 days. Visit 1 may be split (used for repeated assessments, if needed) for the repeat assessment of SABA reversibility test, if applicable.

<sup>c</sup> Planned end-of-treatment (EOT) will occur at Visit 6.

<sup>d</sup> Subjects who prematurely withdraw (withdraw pre-week 12) from study treatment will undergo a PDV.

<sup>e</sup> Details of any surgical procedures occurring during randomization and the treatment period will be also recorded.

<sup>f</sup> Includes evaluation of height, body mass index, and weight at Visit 1 and weight only for Visit 6 or PDV.

<sup>g</sup> Demonstrate reversibility at Visit 1, with an increase in FEV<sub>1</sub>  $\geq$ 15% relative to baseline after administration of Sponsor-provided Ventolin via central spirometry at either Visit 1 (reversibility must be demonstrated at either Visit 1 or Visit 1a); Visit 1a will be used for re-testing, if needed; with only 1 reversibility re-test permitted prior to randomization (Visit 2).

<sup>h</sup> A serum pregnancy test ( $\beta$ -hCG) will be performed at Visits 1 and treatment discontinuation (EOT) or PDV; urine  $\beta$ -hCG test will be performed at all other visits (for women of childbearing potential only).

<sup>i</sup> Pre-bronchodilator (Visit 1/Visit 1a)/ Pre-dose (Visit 2 onwards) FEV<sub>1</sub> will be measured in the morning between 06:00 and 10:00 AM at the designated visits in Table 1, and within 1 hour of FEV<sub>1</sub> measured at Visit 2. Pre-bronchodilator FEV<sub>1</sub> of  $\geq$ 50 to  $<$ 85% predicted normal value for adults ( $\geq$ 18 years of age) and  $\geq$ 50% predicted normal value for subjects aged 4 to 17 years after withholding SABA  $\geq$ 6 hours (at Visit 1 or Visit 1a, if applicable). If subject took SABA within 6 hours in the morning of Visit 1, either the entire visit must be rescheduled or just PFT assessment rescheduled. At Visit 1, pre- and post- dose will be with respect to administration of Sponsor-provided bronchodilator (Ventolin). From Visit 2 onwards, pre- and post- dose measurements will be with respect to administration of IP.

<sup>j</sup> The eDiary (AM3+) will be dispensed at screening.

<sup>k</sup> All subjects will be assigned placebo during the run-in period for dosing QID. Compliance to dosing should be reviewed prior to randomization.

<sup>l</sup> Ventolin usage to be reviewed at each collection/dispensing visit using eDiary. Replacement kit dispensed as required. The actuator should be cleaned once per week if used in the last 7 days according to instruction summarized in [Appendix J, Metered-dose Inhaler Handling and Cleaning](#).

<sup>m</sup> IP should be taken in the morning upon waking, and then distributed equally throughout the day with the final dose taken before going to sleep. The evening before clinic visits, subjects should be advised to take the last dose at 22:00 (10:00 PM)  $\pm$ 2 hours. For all on-treatment visits, IP should be administered before 10:00 AM in the clinic using newly dispensed IP. The actuator should be cleaned once per week if used in the last 7 days according to instruction summarized in [Appendix J, Metered-dose Inhaler Handling and Cleaning](#).

<sup>n</sup> IP will be dispensed at Visit 6 and PDV for performance of FEV<sub>1</sub> measurements only, this will not be taken home by the subjects. IP dispensed at these visits will be retained at the site following the visit and reconciled for IP accountability.

**Table 2** Timed assessments at Visit 2 through Visit 6 and Premature Discontinuation Visit

Clinical Variable	Pre-Dose		IP Dose	Post-Dose										
	-60 min	-30 min		0 min	5 min	15 min	30 min	45 min	60 min	120 min	180 min	240 min	300 min	360 min
IP Collection <sup>h</sup>	X <sup>a</sup>													
IP Dispensing <sup>i</sup>	X <sup>a</sup>													
IP Dosing <sup>i</sup>			X											
Questionnaires														
ACQ-5														
ACQ-7														
AQLQ+12/PAQLQ														
Review of Electronic Diary	X <sup>a</sup>													
Vital Signs <sup>c</sup>	X <sup>a,d</sup>													
12-Lead ECG	X <sup>a,e</sup>													
Clinical Laboratory Testing	X <sup>a,f</sup>													
Spirometry (FEV <sub>1</sub> ) <sup>g</sup>	X	X		X	X	X	X	X	X	X	X	X	X	X

Abbreviations: ACQ-7=Asthma Control Questionnaire 7, AQLQ+12=Asthma Quality of Life Questionnaire for 12 years and older; ECG=electrocardiogram; FEV<sub>1</sub>= forced expiratory volume in 1 second; IP=investigational product; min=minute; PAQLQ=Pediatric Asthma Quality of Life Questionnaire; PDV= premature discontinuation visit

**Note:** Time point for dosing is regarded as “0 minutes”. When data collection time-points are concurrent, variables should be collected in the following order: Questionnaires, vital signs, ECG, clinical laboratory assessments, and spirometry.

- a. This is not a timed assessment. Sites should plan to perform these activities to allow for collection of timed spirometry.
- b. Questionnaires (ACQ-5, ACQ-7, AQLQ+12, and PAQLQ) are collected at all visits (except Visit 3 AQLQ+12, and PAQLQ).
- c. Vital signs should be started (approximately 5 to 10 minutes) ahead of the specified time point to ensure spirometry will be conducted as close to the specified time points as possible.
- d. Pre-dose vital signs (heart rate, blood pressure) will be collected twice, at least 5 minutes apart.
- e. Pre-dose ECG will be collected at Visit 2, Visit 6, and PDV only, or as clinically indicated.
- f. All clinical laboratory tests (hematology and chemistry) will be assessed approximately 60 minutes prior to dosing at Visit 6 in advance of first spirometry measurement. Laboratory tests may be performed at all other visits as clinically indicated.
- g. Every effort should be made to assess subjects' trough pre-dose and post-dose FEV<sub>1</sub> at the same time throughout the study. Pre-dose FEV<sub>1</sub> will be measured in the mornings between 06:00 and 10:00 AM, and within 1 hour of FEV<sub>1</sub> measured at Visit 2. From Visit 2 onwards, pre- and post-dose measurements will be with respect to administration of IP (Table 3).

- h. At the start of each treatment visit, subjects must withhold all asthma medications, including Sponsor-provided Ventolin for at least 6 hours prior to start of test day procedures.*
- i. Dispense new IP to subjects for on-site dosing after trough pre-dose FEV<sub>1</sub> measurement and for subsequent at-home use following the completion of all post-dose assessments. IP will be dosed before 10:00 AM following pre-dose FEV<sub>1</sub> measurements at each visit.*

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## 4.1 Screening and enrollment period

Procedures will be performed according to study assessments and procedures presented in [Table 1](#) and [Table 2](#) for timed assessments at Visit 2 through Visit 6. The screening period will be 14 to 28 days. At screening, consenting subjects are assessed to ensure that they meet eligibility criteria. Subjects who do not meet these criteria must not be enrolled in the study.

Subjects meeting all entry criteria at the screening visit (Visit 1) will enter a 14- to 28-day screening (run-in) period. Subjects will discontinue their usual asthma medications at Visit 1.

The study procedures carried out during this period will include medical and surgical history, demographics, physical examination (including height, BMI, and weight), concomitant medications review, Sponsor-provided Ventolin reversibility test (reversibility must be demonstrated at either Visit 1 or Visit 1a; Visit 1a will be used for re-testing if needed; with only 1 reversibility re-test permitted prior to randomization [Visit 2]), vital signs (heart rate, blood pressure only), 12-lead ECG, AEs, serum pregnancy test, blood samples for hematology and clinical chemistry, FEV<sub>1</sub> determination, Asthma Control Questionnaire-5 (ACQ-5), Asthma Control Questionnaire-7 (ACQ-7), dispensing/collecting eDiary, dispensing Ventolin, and administration of single-blind placebo MDI.

At Visit 1, placebo MDI and Sponsor-provided Ventolin prn to be used in response to asthma symptoms will be dispensed; during the screening (run-in) period, these will be the subject's only asthma medications. At Visit 2, compliance to placebo MDI dosing in screening (run-in) will be assessed by review eDiary completion as specified in the exclusion criteria. Ventolin usage will be assessed at Visit 2 and subjects using prohibitively high Ventolin usage as specified in the exclusion criteria will be screen-failed.

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

A standard medical history, medication, and surgical history will be obtained with review of the selection criteria with the subject.

## 4.2 Randomization/treatment period

Procedures will be performed according to study assessments and procedures presented in [Table 1](#) and [Table 2](#) for timed assessments.

Only Sponsor-provided IP administered QID and Ventolin prn to be used in response to asthma symptoms are allowed during the treatment period. IP should be taken in the morning upon waking, and then distributed equally throughout the day with the final dose taken before going to sleep. The evening before clinic visits, subjects should be advised to take the last dose at 22:00 (10:00 PM) ±2 hours.

At Visit 2 onwards, both IP and Sponsor-provided Ventolin should not be administered  $\leq 6$  hours prior to lung function testing (if Ventolin is needed within 6 hours of a study visit, either the entire visit must be rescheduled or just PFT assessment rescheduled).

At randomization (Visit 2), eligible subjects will enter a 12-week double-blind treatment period. The planned end-of-treatment will occur at Visit 6, the end of the 12-week treatment period.

Dispensation of IP:

New IP will be dispensed to subjects at each visit where FEV<sub>1</sub> measurements are taken and the new IP should be used in advance of all post-dose measurements. To allow for proper preparation of IP, it is recommended that the seal around the study day treatment box is opened 15 to 30 minutes prior to dosing and the instructions for administration of IP followed:

- After IP is primed and ready for use, provide assigned IP to subject
- Administer IP at the clinic
- Complete post-dose assessments

The study procedures carried out during this period will include: medical and surgical procedures, physical examination (includes weight at Visit 6 only), concomitant medications review, vital signs (heart rate, blood pressure only), 12-lead ECG at Visits 2 and 6, AEs, urine pregnancy test at Visits 2 and 4 (additionally Visits 3 and 5 in the Czech Republic and also for the safety follow up visit in Argentina), serum pregnancy test at treatment discontinuation (Visit 6 or the PDV), blood samples for hematology and clinical chemistry, spirometry, ACQ-5, ACQ-7, Asthma Quality of Life Questionnaire for 12 years and older (AQLQ+12)/Pediatric Asthma Quality of Life Questionnaire (PAQLQ), PEF, use of Ventolin therapy, asthma daytime/night-time symptoms, night-time awakenings due to asthma symptom, dispensing/collecting eDiary, review compliance with eDiary, dispensing and/or collection of IP, dispensing and/or collection of Ventolin, recording in eDiary of IP use, IP compliance, and randomization.

#### 4.3 Treatment discontinuation visit

Planned end-of-treatment (EOT) will occur at Visit 6 (Week 12).

Subjects who prematurely withdraw from study treatment (withdraw pre-week 12) will undergo a PDV. Procedures for planned EOT and PDV will be performed according to study assessments and procedures presented in [Table 1](#).

The study procedures carried out during the PDV visit will include: details of any surgical procedures will be recorded, physical examination (including weight), concomitant medications review, vital signs (heart rate, blood pressure only), 12-lead ECG, AEs, serum pregnancy test (at treatment discontinuation or PDV), blood samples for hematology and clinical chemistry, dispensation of IP (for spirometry only), dosing, spirometry, ACQ-5, ACQ-7,

AQLQ+12/PAQLQ, review of PEF, use of IP and Ventolin therapy, asthma daytime/night-time symptoms, night-time awakenings due to asthma symptoms, collecting eDiary, review compliance with eDiary, collection and final reconciliation of the IP and Ventolin, and IP compliance.

#### **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 decided by the investigator.

#### **4.5 Safety Follow-up period**

Procedures will be performed according to study assessments and procedures presented in [Table 1](#). The safety follow-up telephone contact will occur 2 weeks ( $\pm 4$  days) after treatment discontinuation (Visit 6/EOT or PDV).

The study procedures carried out during this period will include: recording of concomitant medications and AEs.

### **5 STUDY ASSESSMENTS**

The Rave WBDC system and the electronic patient reported outcome (ePRO; hereafter called eDiary) eDiary will be used for data collection and query handling. The investigator will ensure that data are recorded on the eCRF 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 safety assessments will be sent for analysis to a central laboratory.

The spirometry and ECG assessments will be performed at site using MasterScope equipment provided by eResearch Technology. The eDiary (AM3+) will be dispensed at screening which will also be used to collect PEF measurements, use of IP or Ventolin therapy, asthma daytime/night-time symptoms, night-time awakenings due to asthma symptoms, ACQ-5, and ACQ-7 data. In addition to this, a tablet will be used to collect the AQLQ+12 data using the StudyWorks software. This data will be recorded in the vendor's central database and transferred/reconciled with the eCRF data as summarized in [Section 9.4](#).

#### **5.1 Efficacy assessments**

Efficacy assessments include spirometry, ACQ-7, AQLQ+12/PAQLQ, PEF, use of Ventolin therapy, asthma daytime/night-time symptoms, and night-time awakenings due to asthma symptoms.

### 5.1.1 Lung function measurement by spirometry

Lung function will be measured by spirometry at the study site using equipment provided by a central vendor. Spirometry will be performed by the investigator or authorized delegate according to ATS/ERS guidelines ([Miller 2005](#)).

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. Spirometry calibration will be detailed in a separate spirometry procedures manual.

Subjects should not take Ventolin (or IP during the treatment phase)  $\leq 6$  hours before a study visit. This restriction is particularly critical for efficacy measures taken during the treatment period but should also facilitate meeting the run-in FEV<sub>1</sub> and reversibility eligibility criteria.

Trough pre-dose and post-dose FEV<sub>1</sub> will be performed on a MasterScope provided for the study by the central reader at Visit 1 (screening), Visit 2 (baseline), and through Visit 6/PDV (endpoint measurements). For Visit 1/Visit 1a, pre- and post-dose measurements will be with respect to Sponsor-provided bronchodilator (Ventolin) and from Visit 2 onwards, will be with respect to IP.

It is important that all in-clinic dosing occurs prior to 10:00 AM and that in-clinic dosing at Visits 3 through 6 is administered  $\pm 1$  hour in relation to the time of dosing at Visit 2.

Preferably, the same study personnel should test the subject's lung function throughout the study to reach optimal performance and to enhance reproducibility. The subject should rest at least 15 minutes prior to the test. For repeated measurements, eg, to assess best of at least 5, a pause of at least 1 minute between measurements is recommended.

The timing of FEV<sub>1</sub> assessment is presented in [Table 3](#). Please note: the 5 minute post-IP dosing spirometry assessment at Visit 2 is crucial to accurately measure time of onset. The subject and site personnel should be adequately prepared for this assessment at the time of dosing.

The measurements are to be made with the subject seated in an upright position (preferably), or if not comfortable 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.

Measurement procedures should be performed in accordance with the user manual for the study.

#### Timing of FEV<sub>1</sub> assessments

- Visit 1: If a subject has not taken SABA or any bronchodilator  $\leq 6$  hours before lung function tests at Visit 1, they may proceed to pre-bronchodilator FEV<sub>1</sub> measurement and

reversibility eligibility assessments. If they have dosed with SABA or any bronchodilator  $\leq$  6 hours before study visit lung function tests, either the entire visit must be rescheduled or just PFT assessment rescheduled. Reversibility assessment will be performed in accordance with [Section 5.1.1.1](#). Considerations for medications that may impact reversibility testing are stated in [Section 7.8.2](#).

- Visit 2: Subjects should withhold administration of Sponsor-provided Ventolin or any bronchodilator for at least 6 hours before lung function tests at Visit 2. Trough pre-dose measurements should be taken at -60 and -30 minutes before administration of IP. Post-dose measurements will commence at 5 minutes after administration of IP followed by measurements at all subsequent times as listed in [Table 3](#). If a subject has taken Sponsor-provided Ventolin before Visit 2, either the entire visit must be rescheduled or just PFT assessment rescheduled.
- Visit 3 onwards: Subjects should withhold administration of Sponsor-provided Ventolin and IP for at least 6 hours before lung function tests at Visit 3 through 6. On-clinic dosing will be administered prior to 10:00 AM and within 1 hour of the dosing at Visit 2. Trough pre-dose measurements should be taken at -60 and -30 minutes before administration of newly dispensed IP. Post-dose measurements will commence at 5 minutes after administration of IP followed by measurements at all subsequent times as listed in [Table 3](#). If a subject has taken IP or Sponsor-provided Ventolin before any on-treatment visit, either the entire visit must be rescheduled or just PFT assessment rescheduled.

**Table 3 Schedule of FEV<sub>1</sub> measurements at standard visits**

Timing of Spirometry Assessments <sup>a</sup>	Assessment Window
Pre- dose PFT -60 min	$\pm$ 15 min
Pre- dose PFT -30 min	$\pm$ 5 min
Post- dose PFT +5 min	$\pm$ 2 min
Post- dose PFT +15 min	$\pm$ 3 min
Post- dose PFT +30 min	$\pm$ 5 min
Post- dose PFT +45 min	$\pm$ 5 min
Post- dose PFT +60 min	$\pm$ 5 min
Post- dose PFT +120 min	$\pm$ 10 min
Post- dose PFT +180 min	$\pm$ 10 min
Post- dose PFT +240 min	$\pm$ 10 min
Post- dose PFT +300 min	$\pm$ 10 min
Post- dose PFT +360 min	$\pm$ 10 min

Abbreviation: min=minute; PFT=pulmonary function test

<sup>a</sup> Pre- and post- dose PFT measurements will be performed in relation to Ventolin at Visit 1, Visit 2 onward, pre- and post- dose PFT measurements will be performed in relation to IP.

### **5.1.1.1 Reversibility test**

To fulfill the reversibility inclusion criterion, the increase in FEV<sub>1</sub> relative to baseline must be  $\geq$ 15% approximately 30 minutes after inhalation of Sponsor-provided Ventolin.

Reversibility testing will be performed as follows:

1. Perform pre-dose PFTs after at least 15 minutes of rest, and before administration of Ventolin.
2. Subjects aged  $\geq 12$  years should administer 4 puffs of Ventolin. Subjects aged  $< 12$  years should administer 2 puffs of Ventolin.
3. Perform post-dose PFTs approximately 30 minutes after the administration of Ventolin.

**The reversibility is calculated as follows:**

$$\text{Reversibility} = ([\text{Post FEV}_1 - \text{Pre FEV}_1] / \text{Pre FEV}_1) \times 100$$

Pre-and post-dose FEV<sub>1</sub> measurements will be captured within the MasterScope. If the reversibility inclusion criterion is not met at Visit 1, the reversibility test may be repeated at Visit 1a prior to Visit 2 (randomization). Pre- and post-dose FEV<sub>1</sub> measurements are related to Sponsor-provided bronchodilator (Ventolin).

#### **5.1.1.2 COVID-19 and Pulmonary Function Testing**

In-clinic spirometry assessments should not be performed for subjects exhibiting signs and symptoms for COVID-19. Any suspected prior or active cases should have a diagnostic test to confirm COVID-19 status. Any subjects with confirmed COVID-19 should not perform spirometry assessments within 14 days of the cessation of symptoms and until the investigator considers the subject is no longer infectious. Device cleaning and hygiene guidance should be followed at all times.

#### **5.1.2 Asthma Control Questionnaire-5**

International guidelines for the treatment of asthma have identified that the primary clinical goal of asthma management is to optimize asthma control (minimization of symptoms, activity limitation, bronchoconstriction, and rescue  $\beta_2$  -agonist use) and thus reduce the risk of life-threatening exacerbations and long-term morbidity. The ACQ-5 ([Appendix H, Asthma Control Questionnaire](#)) was developed to meet these criteria. It measures both the adequacy of asthma control and change in asthma control, which occurs either spontaneously or as a result of treatment.

The ACQ-5 will be administered using the eDiary during site visits as indicated in [Table 1](#) (Visits 1, 2, 3, 4, 5, 6, and PDV) and [Table 2](#) for timed assessments at Visits 2, 4, 3, 5, 6, and PDV. The ACQ-5 self-administered adult version will be used for adults and adolescents aged 11 years and older. The Asthma Control Questionnaire-Interviewer-Administered [ACQ-IA] will be used for subjects aged  $< 11$  years; [Section 5.1.4](#).

Subjects will be asked to complete the ACQ-5, consisting of 5 questions on symptom control; each of the questions will be scored on a 7-point scale (0=excellent asthma control; 6=extremely

poor control). The questions take approximately 2 to 3 minutes to complete. Linguistically validated translations of the ACQ-5 into local languages will be used.

### **5.1.3      Asthma Control Questionnaire-7**

The ACQ-7 will be administered using the eDiary during site visits as indicated in [Table 1](#) and [Table 2](#) for timed assessments at Visits 2, 3, 4, 5, 6, and PDV.

The ACQ-7 will be assessed at Visits 1, 2, 3, 4, 5, 6, and PDV and consists of the top scoring 5 symptoms from the ACQ-5 with 2 additional questions regarding FEV<sub>1</sub>% predicted value and daily rescue bronchodilator use ([Appendix H, Asthma Control Questionnaire](#)). Linguistically validated translations of the ACQ-7 into local languages will be used.

### **5.1.4      Asthma Control Questionnaire-Interviewer-Administered**

The ACQ-IA version will be used for subjects aged <11 years and will be interviewer-administered ([Appendix I, Asthma Control Questionnaire-Interviewer-Administered](#)).

Linguistically validated translations of the ACQ-IA into local languages will be used, with the results of the interviewer-administered version recorded into the eCRF.

### **5.1.5      Asthma Quality of Life Questionnaire+12/Pediatric Asthma Quality of Life Questionnaire**

#### **5.1.5.1    Asthma Quality of Life Questionnaire+12**

The AQLQ+12 will be self-administered in all subjects aged  $\geq 12$  years using the eDiary during site visits as indicated in [Table 1](#) and [Table 2](#) for timed assessments at Visit 2 through Visit 6. Linguistically validated translations of the AQLQ+12 into local languages will be used.

The AQLQ was developed to measure the functional problems (physical, emotional, social, and occupational) that are most troublesome to adults with asthma [Appendix F, Asthma Quality of Life +12 Questionnaire](#).

There are 32 questions in the AQLQ+12 and they are in 4 domains (symptoms, activity limitation, emotional function, and environmental stimuli). The activity domain contains 5 subject-specific questions. This allows subjects to select 5 activities in which they are most limited and these activities will be assessed at each follow-up. Subjects are asked to think about how they have been during the previous 2 weeks and to respond to each of the 32 questions on a 7-point scale (7=not impaired at all; to 1=severely impaired). The overall AQLQ+12 score is the mean of all 32 responses and the individual domain scores are the means of the items in those domains.

#### **5.1.5.2    Pediatric Asthma Quality of Life Questionnaire**

The PAQLQ will be self-administered during site visits as indicated in [Table 1](#) and [Table 2](#) for timed assessments at Visit 2 through Visit 6 in subjects aged 7 to 11 years. Responses to PAQLQ will be provided on paper and transcribed to the eCRF by site staff.

Subjects aged 4 to 6 years will complete the questionnaire with the help of a caregiver. The subject/caregiver will complete the PAQLQ on paper and responses will also be transcribed to the eCRF by site staff. As the PAQLQ is not validated for children  $<7$  years of age, data for subjects who are aged 4 to 6 years will be excluded from the analyses of PAQLQ endpoints.

Linguistically validated translations of the PAQLQ into local languages will be used. The PAQLQ has 23 questions in 3 domains (symptoms, activity limitation, and emotional function). The activity domain contains 3 subject-specific questions.

The PAQLQ, was developed to measure the functional problems (physical, emotional, and social) that are most troublesome to children with asthma ([Appendix G, Pediatric Asthma Quality of Life Questionnaire](#)).

### **5.1.6 eDiary**

The eDiary will be utilized by all subjects enrolled in the study including children. Children, as necessary, will be assisted by a caregiver for the performance of assessments and navigation of the applicable questions.

#### **5.1.6.1 Peak expiratory flow**

Subjects will be trained at Visit 1. Throughout the study, subjects will record 3 PEF measures on rising in the morning and before going to bed in the evening prior to taking any asthma therapy.

#### **5.1.6.2 eDiary investigational product use**

Use of QID blinded IP will be collected using the eDiary. Subjects will be asked in the evenings to enter into their eDiary (device called AM3+), how many times they administered IP that day. The times of the administration and number of puffs will be recorded.

#### **5.1.6.3 eDiary Ventolin therapy use**

Monitoring of Ventolin therapy in response to asthma symptoms use will be done only through the eDiary, where the number of Ventolin puffs taken in response to symptoms will be captured twice daily (in the mornings and in the evenings). Sponsor-provided Ventolin will be dispensed from Visit 1 and inhalers will be reconciled for accountability.

Subjects will be recommended not to take more than 8 puffs of Ventolin per day and advised to contact the investigator if their symptoms necessitate more than 8 puffs in a day.

#### **5.1.6.4 eDiary recording of symptoms and alerts**

The subject will use the eDiary for daily symptom reporting, entering symptoms twice daily.

The eDiary will be programmed to alert both the subject and study center when the below prespecified alert thresholds are crossed. Alerts will include:

- Decrease in morning peak flow  $\geq 20\%$  on at least 2 consecutive days compared with baseline, and/or
- An increase in rescue medication use of  $\geq 4$  puffs on at least 2 consecutive days compared with the average use during baseline, and/or
- $>12$  puffs of Ventolin in one day, and/or
- A night-time asthma symptom score of  $>$ baseline night-time score and  $\geq 2$  for at least 2 consecutive days, and/or
- A daytime asthma symptom score of 3 for at least 2 consecutive days
- $>12$  puffs of IP per day

The purpose of the alerts is to trigger a documented contact between the site and subject for further evaluation if deemed necessary by the investigator. The Sponsor will also receive programmed alerts to monitor subject follow-up. Alerts will include:

- Triggers in the eDiary will alert the subjects to signs of change of asthma and to contact their physician
- A dedicated person from the Sponsor will review the eDiary and compliance alerts (2 consecutive days of missing data) and contact the site
- Triggers in the eDiary will alert subjects if IP is used more than 12 puffs a day as a possible sign of potential overdose
- In case of eDiary or compliance alerts, a qualified person from the site will contact the subject. For eDiary alerts, the subject's asthma status should be evaluated, and it will be determined if a clinic visit is necessary

**An eDiary alert is not an asthma exacerbation *per se*.**

Although the eDiary alert may initiate contact between the subject and the investigational site, the investigator or designee will always assess the subject's symptoms and determine whether to treat the subject for an exacerbation ([Section 5.1.8](#)).

Asthma symptoms should be captured in the eDiary by the subject every morning and evening.

### **5.1.7 Deterioration of asthma**

In this study, deterioration of asthma is defined as 1 or more of the following items for  $\geq 2$  consecutive days:

- PEF: a decline of  $\geq 20\%$  from baseline
- Ventolin therapy use:  $>4$  puffs/day and  $\geq 2 \times$ baseline
- Symptoms: night-time score that is  $>$ baseline and  $\geq 2$  OR a daytime score that is  $>$ baseline and =3

Daytime is defined as the time period between the morning PEF assessment (upon rising in the morning) and the evening PEF assessment.

Night-time is defined as the time period between the evening PEF assessment (at bedtime) and the morning PEF assessment.

### **5.1.8     Asthma exacerbation definition**

An asthma exacerbation is defined as deterioration of asthma which includes:

- Worsening of asthma signs/symptoms ([Section 5.1.8.1](#))
- Increased use of 'as needed' reliever therapy
- Deterioration of lung function
- A medical intervention as described below ([Section 5.1.8.3](#))

These descriptions above are provided for definition, however, only severe asthma exacerbations will be assessed during this study ([Section 5.1.8.3](#))

#### **5.1.8.1     Definition of asthma symptom worsening**

The worsening/onset of symptoms must include at least one of the following:

- shortness of breath
- wheezing
- chest tightness
- cough
- sputum
- night-time awakening due to asthma
- activity limitation due to asthma
- decreased PEF
- decreased FEV<sub>1</sub>

#### **5.1.8.2     Investigator justified asthma exacerbations**

A vast majority of asthma exacerbations are associated with worsening of the symptoms described in [Section 5.1.8.1](#). However, clinical presentations may vary among subjects. If a subject's symptoms and the overall clinical findings support the diagnosis of a severe asthma exacerbation (defined by required medical intervention as described in [Section 5.1.8.3](#)), but the symptomatic worsening does not meet the definition in [Section 5.1.8.1](#) the investigator must justify the decision for defining the event as an exacerbation and document the reasoning in the eCRF.

### 5.1.8.3 Severe asthma exacerbations

All protocol-defined severe asthma exacerbations need to fulfill the symptom criteria as defined in [Section 5.1.8.1](#) and be supported by an eDiary alert or an investigator justification.

An asthma exacerbation will be considered **severe** if it results in at least 1 of the following:

- A temporary bolus/burst of SCS for at least 3 consecutive days to treat symptoms of asthma worsening; a single depo-injectable dose of corticosteroids will be considered equivalent to a 3-day bolus/burst of SCS
- An emergency room or urgent care visit (defined as evaluation and treatment for  $\geq 4$  hours in an emergency department or urgent care center) due to asthma that required SCS (as per the above)
- An in-patient hospitalization (defined as admission to an in-patient facility and/or evaluation and treatment in a healthcare facility for  $\geq 24$  hours) due to asthma

### 5.1.8.4 Treatment for severe asthma exacerbations

The treatment for a **severe** asthma exacerbation is at least 3 consecutive days of SCS.

- The recommended treatment ([GINA 2018](#)) for a severe exacerbation is prednisolone (1 mg/kg/day up to 50 mg for adults and adolescents) once per day (preferably in the morning) for 5 to 7 days
- Tapering the prednisolone dose is not needed if the treatment has been given for  $<2$  weeks ([GINA 2018](#))

Treatment for  $<3$  days does not constitute a severe asthma exacerbation, except if the subject is hospitalized due to asthma.

### 5.1.8.5 Onset and duration of asthma exacerbations

For **severe** exacerbations, the duration is defined by the **prescribed treatment**.

For **severe** exacerbations:

- The start date will be defined as the start date of prescribed treatment with a SCS
- The stop date will be defined as the last day of prescribed treatment with a SCS
- A single depot injectable dose of corticosteroids will be considered equivalent to a 3-day course of SCS. The corresponding stop date for this treatment will consequently be determined as the date of administration plus 2 days
- If multiple treatments are prescribed for the same exacerbation, the earliest start date and the latest stop date will be used
- For a severe asthma exacerbation requiring hospitalization with no documented corticosteroid treatment, hospitalization admission/discharge dates, or emergency visit date will be used as start/stop dates

### **5.1.8.6 Approach for capturing asthma exacerbations**

#### **5.1.8.6.1 Asthma exacerbation eCRF**

All post-screening severe asthma exacerbations (including investigator justified asthma exacerbations) must be captured using the Severe Asthma Exacerbation eCRF.

If a severe asthma exacerbation requires hospitalization, the exacerbation should be reported as an SAE ([Section 3.9](#)) as well as on the Severe Asthma Exacerbation eCRF.

Severe asthma exacerbations will be considered study efficacy endpoints and will not be reported as AEs unless considered an SAE.

## **5.2 Safety assessments**

Safety assessments include clinical laboratory (hematology, chemistry, and pregnancy tests for females of childbearing potential) parameters, 12-lead ECG readings, vital sign measurements, and collection of AEs.

### **5.2.1 Laboratory safety assessments**

Blood samples for determination of clinical chemistry and hematology will be taken at the times indicated in [Table 1](#) and [Table 2](#) for timed assessments at Visit 2 through Visit 6.

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

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

The following laboratory variables described in [Table 4](#) will be measured:

**Table 4      Laboratory Safety Variables**

<b>Hematology/Hemostasis (whole blood)</b>	<b>Clinical Chemistry (serum or plasma)</b>
Red blood cells (erythrocytes)	Albumin
Hemoglobin	ALT
Hematocrit	ALP
Mean Corpuscular Hemoglobin	AST
Mean Corpuscular Hemoglobin Concentration	Bilirubin, total
Mean Corpuscular Volume	Calcium, total
White blood cells (leukocytes)	Chloride
Basophils (%)	Cholesterol, total
Basophils Abs	Creatinine
Eosinophils (%)	Creatine kinase
Eosinophils Abs	Gamma-glutamyl transpeptidase
Lymphocytes (%)	Glucose (random)
Lymphocytes Abs	Magnesium
Monocytes (%)	Phosphate
Monocytes Abs	Potassium
Neutrophils (%)	Protein, total
Neutrophils Abs	Sodium
Platelet count	Triglycerides
<b>Urine</b>	Urea
Urine $\beta$ -hCG pregnancy (at all other clinic visits, except Visit 1 and EOT or PDV)	Serum $\beta$ -hCG pregnancy (Visit 1 and treatment discontinuation [EOT or PDV])

Abbreviations: Abs=absolute; ALP=alkaline phosphatase; ALT=alanine transaminase; AST=aspartate transaminase  $\beta$ -hCG= $\beta$ -human chorionic gonadotropin; EOT=end-of-treatment; PDV premature discontinuation visit

If a subject shows  $\geq 2 \times$  AST or ALT  $\geq 3 \times$  the upper limit of normal (ULN) **and** TBL  $\geq 2 \times$ ULN please refer to [Section 3.9](#) and [Appendix E, Hy's Law](#) for further instructions.

### **5.2.2 Resting 12-lead electrocardiogram**

A 12-lead ECG will be performed at the visits detailed in [Table 1](#) and [Table 2](#) for timed assessments at Visits 2, 6, and PDV. The timing and number of ECGs may be adjusted in response to the emerging safety profile.

Twelve-lead ECGs will be obtained using a centralized laboratory after the subject has been resting semi supine for at least 10 minutes. All ECGs should be recorded with the subject in the same physical position. A standardized ECG machine should be used and the subject should be examined using the same machine throughout the study, where feasible.

After paper 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, an overall evaluation will be recorded.

### **5.2.3 Vital sign measurements**

Vital signs including resting pulse, and blood pressure, should be assessed at the visits detailed in [Table 1](#) and [Table 2](#) for timed assessments at Visit 2 and Visit 6. Measurements should be taken in the sitting position after at least 10 minutes of rest.

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

### **5.2.4 Adverse event assessments**

AEs will be collected from time of signature of informed consent/assent through to the follow-up period as described in [Section 6](#).

## **5.3 Other assessments**

### **5.3.1 Physical examination**

A complete physical examination will be performed at screening (Visit 1), Visit 6, and PDV (if applicable) as detailed in [Table 1](#). 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.

### **5.3.2 Concomitant medications**

The collection and recording of all concomitant medications, including all pre-enrollment asthma therapies, will be performed at the visits detailed in [Table 1](#). Permitted and restricted concomitant medications are described in [Section 7.8](#).

All prescription drugs, herbal products, vitamins, minerals, and over-the-counter medications taken within 3 months before screening (Visit 1) will be recorded as previous medications. All medications taken after screening and through the safety follow-up visit will be recorded as concomitant therapy.

Subjects will be maintained, after Visit 1, on IP and Ventolin to be used in response to asthma symptoms throughout the treatment period.

For restrictions relating to concomitant medications see [Sections 3.1](#) and [3.2](#).

## **5.4 Pharmacokinetics**

Not applicable.

## **5.5 Pharmacodynamics**

Not applicable.

## **5.6 Genetics**

Not applicable.

## **5.7 Biomarker analysis**

Not applicable.

# **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.

SAEs 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 event**

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 visit), 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 D, Additional safety information](#) to the Clinical Study Protocol.

### **6.3 Recording of adverse events**

#### **6.3.1 Period for collection of adverse events**

Adverse events and SAEs will be collected from time of signature of informed consent/assent, through the safety follow-up period.

#### **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 final study visit) 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)
- The date when the AE started and stopped
- Maximum severity
- Seriousness
- Investigator causality rating against the IP (yes or no)
- Action taken with regard to IP
- Outcome

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

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

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- Date of discharge
- Probable cause of death
- Date of death
- Whether 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 IP?’

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 D, Additional safety information](#) of this Clinical Study Protocol.

#### **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/the child had any health problems since the previous visit/you were last asked?’ or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnosis is preferred (when possible) over recording 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 IP due to 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, and other safety assessments will be summarized in the Clinical Study Report. Deterioration from baseline in these parameters should therefore only be reported as an AE if it fulfills any of the AE criteria or is the reason for discontinuation of treatment with the IP or is considered 'clinically significant'.

The criteria for determining whether the mandated laboratory tests, ECGs, vital signs, and other safety 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 safety assessment is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign 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 findings at the baseline assessment will be reported as an AE.

### **6.3.7 Hy's Law**

Cases where a subject shows elevations in liver biochemistry may require further evaluation and occurrences of AST and/or ALT  $\geq 3 \times \text{ULN}$  combined with TBL  $\geq 2 \times \text{ULN}$  may require IP suspension/discontinuation and study withdrawal, and may need to be reported as SAEs. Please refer to [Section 3.9](#) and [Appendix E, Hy's Law](#) for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law.

### **6.3.8 COVID-19 adverse events**

For subjects experiencing signs and symptoms indicating respiratory infection, confirmatory testing for COVID-19 is expected in line with national guidelines.

Non-serious confirmed COVID-19 AEs will be recorded within the clinical database but additional information may be collected within the safety database and/or narratives as required.

If serious COVID-19 infection is confirmed via testing, it should be reported with the diagnosis “COVID-19 confirmed” in the SAE report form. If COVID-19 infection is suspected, symptoms (eg, cough, fever, etc.) should be recorded in the SAE report form until diagnosis is confirmed. If test is not available and signs and symptoms, as judged by the investigator, are highly suspicious of COVID-19 infection, “COVID-19 suspected” should be reported.

All SAEs in relation to COVID-19 shall be reported in line with the instructions for SAE reporting described in [Section 6.4](#).

#### **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 in the course of the study, then investigators or other site personnel should inform [REDACTED] Safety and Pharmacovigilance Department within 1 day ie, immediately but **no later than 24 hours** of when he or 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] Safety and Pharmacovigilance Department works 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.

#### **6.5 Overdose**

For the purpose of this study, an accidental or deliberate intake of blinded treatment of more than 12 puffs during one day is defined as an overdose and must be reported as such as described below.

All overdoses must be recorded on 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 an overdose 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 overdose.

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 the 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, 'Pregnancy' recorded as the reason for discontinuation on the eCRF, and 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 or she becomes aware of it. Any conception occurring from the date of dosing through the safety follow-up visit 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 visit 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.

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
- Dispensing 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)

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)
- Subject failed to return unused medication or empty packaging
- Errors related to background medication, or standard of care medication in open-label studies, even if it is a Sponsor's product

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, [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 5) as both micronized budesonide and micronized albuterol co-suspended with spray-dried porous particles in a hydrofluoroalkane propellant. The co-suspension formulation ensures that subjects receive a consistent delivery of the drug from each actuation of the MDI.

**Table 5** **Investigational Product Strength and Dosage Form**

Investigational product name and dose	Product strength	Dosage Form/ Fill Count	Administration	Manufacturer
BDA MDI 80/180 µg	BDA MDI 40 µg budesonide and 90 µg albuterol <sup>a</sup> per puff	MDI/120 actuations	Taken as 2 actuations	[REDACTED]
BDA MDI 160/180 µg	BDA MDI 80 µg budesonide and 90 µg albuterol <sup>a</sup> per puff	MDI/120 actuations	Taken as 2 actuations	[REDACTED]
BD MDI 160 µg	80 µg budesonide per puff	MDI/120 actuations	Taken as 2 actuations	[REDACTED]
AS MDI 180 µg	AS MDI 90 µg albuterol per puff <sup>a</sup>	MDI/120 actuations	Taken as 2 actuations	[REDACTED]
Placebo MDI	0 µg of active product <sup>b</sup>	MDI/120 actuations	Taken as 2 actuations	[REDACTED]
<b>Additional study medication (Ventolin<sup>®</sup> therapy)</b>				
Ventolin HFA <sup>c</sup>	108 µg albuterol sulfate (90 µg albuterol base) as an aerosol formulation	Albuterol (salbutamol) sulfate inhalation aerosol 200 puffs per canister	Use for reversibility testing during screening and (Section 5.1.1.1) as needed (generally 2 actuations per dose) during screening and treatment periods	[REDACTED]

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

Ventolin is a non-investigational medicinal product since it is taken as directed for reversibility testing (Visit 1 and repeat Visit 1a, if necessary) and as needed for symptoms during the screening period.

<sup>a</sup> Each puff contains 108 µg albuterol sulfate corresponding to 90 µg albuterol base per actuation.

<sup>b</sup> Each puff contains 183 µg of porous particles and 63 µg of HFA-134a propellant made to be identical in appearance to BDA MDI, BD MDI, and AS MDI.

<sup>c</sup> This table represents commercially available Ventolin formulation for the United States, each country participating in the study will utilize commercially available Ventolin in that country, product strength may vary.

## 7.2 Dose and treatment regimens

Treatment groups include:

- BDA MDI 80/180 µg QID (given as 2 actuations of BDA MDI 40/90 µg per puff)
- BDA MDI 160/180 µg QID (given as 2 actuations of BDA MDI 80/90 µg per puff)
- BD MDI 160 µg QID (given as 2 actuations of BD MDI 80 µg per puff)
- AS MDI 180 µg QID (given as 2 actuations of AS MDI 90 µg per puff)
- Placebo MDI QID (given as 2 actuations)

Randomization for adults and adolescents will be centralized and stratified by pre-study background therapy consisting of either ICS or non-ICS (subjects not previously treated with ICS), by ACQ-7 ( $\leq 1.5$ ,  $> 1.5$ ), and by age ( $\geq 12$  to  $17$ ,  $\geq 18$ ). Randomization for children aged 4 to 11 years will not be stratified.

The maximum daily dosage of IP is 12 puffs per day. Subjects should not take more than 8 puffs of Ventolin per day ([Section 6.5](#) for overdose). The evening before clinic visits, subjects should be advised to take the last dose at 22:00 (10 PM)  $\pm 2$  hours.

Handling and cleaning instructions for the MDI device will be available for the site to train subjects and also for the subjects to retain throughout the study ([Appendix J, Metered Dose Inhaler Handling and Cleaning](#)).

### 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.

The subject will receive a kit containing 2 MDI devices, individually wrapped in foil bags 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. A kit will be dispensed for every 15 days of treatment. Subjects will receive 2 kits at some visits.

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)
- Investigational product 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 dispensed)
- The period of use eg, expiry date

The label will include the following standard statements:

- 'For clinical study use only' (or the required local statement)
- 'Keep out of reach of children'

#### **7.4 Storage**

Blinded supplies: BDA MDI 40/90 µg per puff, BDA MDI 80/90 µg per puff, BD MDI 80 µg per puff, AS MDI 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).

Ventolin supplies: Store between 15°C and 25°C (59°F and 77°F). Store the inhaler with the mouthpiece down. For best results, the inhaler should be at room temperature before use. Do not use or store near heat or open flame. Exposure to temperatures above 120°F (49°C) may cause bursting. Never throw into a fire or incinerator. Temperature readings of the storage area (minimum/maximum) should be recorded on every working day at a minimum.

#### **7.5 Compliance**

The administration of all IPs will be captured in the subject's eDiary and not recorded in the eCRF, 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 including the dose indicator readings for the returned kits. Data from the dose indicator will be compared with the subject's eDiary entries and any discrepancies will be used to help in training the subject to accurately capture all IP administration in the eDiary.

During the screening period, Ventolin usage will be reviewed to ensure the Study inclusion/exclusion criteria are adhered to. Ventolin will be dosed prn; therefore, compliance will not be applicable, other than the number of devices dispensed/returned and the usage being monitored.

#### **7.6 Accountability**

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

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

## 7.7 Metered-dose inhaler: handling and cleaning

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. An ‘Instructions For Use’ document can be found in [Appendix J, Metered-dose Inhaler Handling and Cleaning](#), focusing on the IP MDI device.

The importance of the device cleaning and priming requirements should be emphasised to subjects. 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 medications and other treatments

### 7.8.1 Investigational product and Ventolin therapies

Only Sponsor-provided IP dosed QID and Sponsor-provided Ventolin therapy to be used in response to asthma symptoms are allowed during the study. No other asthma medications are allowed during the study.

Subjects on maintenance allergy immunotherapy (AIT) are allowed to continue their AIT; the new initiation of AIT during the study is not allowed.

### 7.8.2 Medications that may affect reversibility and FEV<sub>1</sub> testing

Subjects are only eligible for enrollment in the DENALI study if they are taking SABA alone prn or with low-dose ICS; subjects presenting at Visit 1 being treated with any other asthma medication are ineligible. Therefore, the only restriction for eligible subjects’ reversibility testing at Visit 1 (or 1A, if applicable) is the requirement not to take SABA (Visit 1) or Sponsor-provided Ventolin (Visit 1A) within 6 hours of lung function testing. At Visit 2 onwards, both IP and Sponsor-provided Ventolin should not be administered within 6 hours prior to lung function testing.

### 7.8.3 Prohibited medications

Prohibited concomitant medications during the study include:

- Oral, parenteral, or rectal corticosteroids (except if required to treat asthma exacerbation)
- Any other asthma medication except Sponsor-provided IP and Ventolin
- Montelukast, for **any** indication
- Inhaled disodium cromoglycate or inhaled nedocromil sodium
- 5-lipoxygenase inhibitors (ie, zileuton)
- Inhaled anticholinergics
- Phosphodiesterase inhibitors (ie, roflumilast)

- Omalizumab, benralizumab, mepolizumab, reslizumab, dupilumab or any other monoclonal or polyclonal antibody therapy for any reason (intra-ocular administration of monoclonal or polyclonal antibody therapy is allowed)
- Beta2-adrenergic blockers including eye-drops (specific cardio-selective beta-blockers in low daily doses, eg, metoprolol in doses up to 100 mg/d, are allowed)
- Systemic treatment with potent cytochrome P450 3A4 inhibitors (eg, ketoconazole, itraconazole, and ritonavir)

## 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.

The IDMC will have access to unblinded data in closed sessions with an unblinded statistician upon their request (see IDMC charter).

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

#### 8.1.1 Estimands

Two estimands are of interest in this study:

The primary estimand of interest is the efficacy estimand, defined as the effect of the randomized treatment in all subjects assuming continuation of randomized treatment for the duration of the study, regardless of actual compliance. This estimand could be considered as a while-on-treatment strategy or a hypothetical strategy as defined in the draft International Conference on Harmonization (ICH) E9 Addendum.

The second estimand of interest is the attributable estimand, defined as the effect of treatment in subjects attributable to the randomized treatment. For this estimand, discontinuation of randomized treatment for reasons such as tolerability or lack of efficacy is considered a negative outcome. This estimand is a mixture of composite and hypothetical strategies as defined in the draft ICH E9 addendum.

### 8.2 Sample size estimate

#### 8.2.1 Initial assumptions and estimates

A blinded sample size re-estimation was performed once 44% of subjects had completed Week 12. Based on the blinded estimate of variability, approximately 1000 subjects are required in order to demonstrate at least 90% power. Consequently, the total randomized adult and

adolescent subjects has been increased to 1000. This section details the initial assumptions of variability prior to calculating the blinded sample size re-estimation. Please refer to [Section 8.2.2](#) for details on the sample size and power calculations following the blinded sample size re-estimation.

Prior to the blinded sample size re-estimation, randomization of approximately 120 subjects to each treatment group expected provide at least 93% probability to detect a 100 mL difference in the change from baseline in trough FEV<sub>1</sub> at Week 12 for comparison of BD MDI versus placebo MDI, BDA MDI versus placebo MDI, or BDA MDI versus AS MDI. This calculation was based on a standard deviation of 210 mL obtained from the placebo MDI group of Study PT008001 and an assumed dropout rate of 10% and 15% for active and placebo treatment group, respectively, prior to Week 12.

Prior to the blinded sample size re-estimation, it was assumed that the sample size of 120 subjects per treatment group would also provide >99% probability to detect a 130 mL difference in FEV<sub>1</sub> AUC<sub>0-6 hours</sub> over 12 weeks for comparison of BDA MDI versus BD MDI (effect sizes for AS MDI or BDA MDI versus placebo MDI should be considerably larger). This calculation assumed a 2% dropout prior to Week 1 and an effective standard deviation of 140 mL which was derived from the following: a per visit standard deviation of 200 mL (ProAir Respiclick Studies 301 and 304 and the AS MDI Dose-Ranging Study DC6930C00001), a correlation between visits of 65%, and projected subject completion of 4 out of 5 visits.

### **8.2.2 Blinded sample size re-estimation**

Following the blinded sample size re-estimation, randomization of approximately 200 subjects ( $\geq 18$  years of age) to each treatment group will provide 90% probability to detect a 100 mL difference in the change from baseline in trough FEV<sub>1</sub> at Week 12 for comparison of BD MDI versus placebo MDI, BDA MDI versus placebo MDI, or BDA MDI versus AS MDI. This calculation is based on a standard deviation of 290 mL obtained from the blinded sample size re-estimation performed after 44% of subjects completed Week 12 and an estimated overall dropout rate of 11% prior to Week 12.

Following the blinded sample size re-estimation, the sample size of 200 subjects ( $\geq 18$  years of age) per treatment group will also provide >99% probability to detect a 130 mL difference in FEV<sub>1</sub> AUC<sub>0-6 hours</sub> over 12 weeks for comparison of BDA MDI versus BD MDI (effect sizes for AS MDI or BDA MDI versus placebo MDI should be considerably larger). This calculation assumes 2% dropout prior to Week 1 and an effective standard deviation of 290 mL obtained from the blinded sample size re-estimation performed after 44% of subjects completed Week 12.

Approximately 1000 adults ( $\geq 18$  years of age) and adolescent subjects (12 - 17 years of age, where approved) with asthma will be randomized 1:1:1:1:1 to 1 of 5 treatment groups (approximately 200 subjects per group: BDA MDI 80/180  $\mu$ g QID, BDA MDI 160/180  $\mu$ g QID, BD MDI 160  $\mu$ g QID, AS MDI 180  $\mu$ g QID, or placebo MDI). In addition, where approved, up

to 30 child subjects (aged 4 to 11 years) with asthma will be enrolled but will not receive high dose ICS and will be randomized 1:1:1 to receive low-dose BDA MDI 80/180 µg QID, AS MDI 180 µg QID, or placebo MDI. Approximately 2000 subjects will need to be screened, assuming an estimated screen failure rate of approximately 50% prior to randomization. This Phase III study is planned to be conducted globally.

A second blinded sample size re-estimation will be performed once approximately 65% of the revised sample size has completed 12 weeks and prior to the last subject being randomized. This will allow the re-assessment of variability in a larger sample and at a point where any impact from COVID-19 with respect to lung function variability and dropout rates can be quantified more accurately. Final total enrollment in the study will be confirmed following the second blinded sample size re-calculation in order to ensure 90% power.

Any further potential increase in sample size will be capped at 1300, a 30% increase above the revised 1000 subjects.

### **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 take any amount of IP. Subjects will be analyzed according to the treatment they were assigned at randomization.

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

The efficacy and attributable estimand will include all data obtained before subjects discontinue randomized treatment.

#### **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. If a subject receives >1 IP, he or she will be summarized according to the treatment the subject received the most. All safety summaries will be based on the safety analysis set.

### **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 discontinue randomized treatment and will use the full analysis set, in accordance with the primary estimand ([Section 8.1.1](#)).

#### 8.5.1.1 Dual-primary efficacy endpoints

The primary efficacy analysis comprises of 2 dual-primary endpoints of change from baseline in  $FEV_1 AUC_{0-6 \text{ hours}}$  over 12 weeks and change from baseline in trough  $FEV_1$  at Week 12. Baseline  $FEV_1$  will be taken as the average of the 60- and 30-minute pre-dose spirometry measures at randomization (Visit 2).

##### 8.5.1.1.1 Derivation for $FEV_1 AUC_{0-6 \text{ hours}}$

$FEV_1 AUC_{0-6 \text{ hours}}$  will be calculated for the changes from the baseline (randomization visit) using the trapezoidal rule and will be normalized by dividing by the time (in hours) from dosing to the last measurement included (typically 6 hours).

##### 8.5.1.1.2 Derivation for trough $FEV_1$

Trough  $FEV_1$  will be taken as the average of the 60- and 30-minute pre-dose spirometry measures prior to dosing of IP.

In subjects with only 1 pre-dose assessment for trough, the value will be calculated from the single measurement.

### 8.5.2 Secondary efficacy analyses

The secondary analyses will include all data obtained before subjects discontinue randomized treatment and will use the full analysis set, in accordance with the primary estimand ([Section 8.1.1](#)).

#### 8.5.2.1 Derivation for time to onset (15% increase in $FEV_1$ ) on Day 1 and duration of effect on Day 1

Time to onset (minutes) on Day 1 will be calculated as the time from dosing on Day 1 (randomization day; Visit 2) to the first instance within 30 minutes in which a percentage change from baseline in  $FEV_1$  greater or equal to 15% is observed:

*Time of first 15% increase in percentage change from baseline in  $FEV_1$  – Time of dosing on Day 1 (randomization, Visit 2)*

The duration of effect for each subject will be defined as the time from onset of at least a 15% increase in  $FEV_1$  to the offset of the 15% increase in  $FEV_1$  relative to baseline. If the offset of response was not achieved during the assessment period, the last available time of assessment will be used as the offset. If a subject had a second onset of response subsequent to achievement

of offset, their data for that subsequent period will be excluded from the duration of response calculation.

### 8.5.2.2 Derivation of Asthma Control Questionnaire-7 variables

All 7 items are assessed on a 7-point scale (0=good control; 6=poor control). The overall score is the mean of the 7 items. At least 6 out of the 7 items are needed to provide an ACQ-7 score.

The minimal important difference (MID) in ACQ-7 score is estimated to be 0.5 ([Juniper 2005](#)). On the basis of the MID, responders at Week 12 are defined as subjects achieving a decline from baseline of at least 0.5:

- Responder: (Week 12 – baseline)  $\leq -0.5$
- Non-responder: (Week 12 – baseline)  $> -0.5$

Subjects who discontinue treatment for any reason before Week 12 will be classified as non-responders. Baseline is defined as the most recent non-missing score before the first dose of randomized IP.

Additionally, an exploratory endpoint will be considered to assess the changes from baseline ACQ-7 overall score at Week 12 as the following 3-level factor:

- Improvement: (Week 12 – baseline)  $\leq -0.5$
- No Change:  $-0.5 < (\text{Week 12} - \text{baseline}) < 0.5$
- Worsening: (Week 12 – baseline)  $\geq 0.5$

Subjects who discontinue treatment for any reason before Week 12 will be classified as non-responders.

The interviewer-administered version will be implemented for children aged 4 to 10 years. As the ACQ-7 is not validated for children  $< 6$  years old, data for subjects who are 4 or 5 years of age will be excluded from the analyses of ACQ-7 endpoints.

### 8.5.3 Exploratory efficacy analyses

The exploratory analyses will include all data obtained before subjects discontinue randomized treatment and will use the full analysis set, in accordance with the primary estimand ([Section 8.1.1](#)).

#### 8.5.3.1 Derivation of severe exacerbation endpoints

For the production of summary statistics, the raw annualized severe asthma exacerbation rate will be calculated according to the following formula:

*Annualized severe exacerbation rate =  $\sum \text{number of severe exacerbations} * 365.25 / \sum \text{follow-up}$ ,*  
where the summations are over all subjects within a treatment group.

For subjects who do not prematurely discontinue, the *follow-up* is calculated as:

*Date of latest follow-up-date of randomization (Visit 2) + 1.*

Otherwise, follow-up is calculated as the discontinuation date of randomized treatment:

*Date of randomized treatment discontinuation-date of randomization (Visit 2) + 1.*

#### **8.5.3.2 Derivation of deterioration of asthma variables**

The deterioration of asthma rate will be calculated in a similar way as the raw annualized severe asthma exacerbation rate ([Section 8.5.3.1](#)).

#### **8.5.3.3 Derivation of peak FEV<sub>1</sub>**

Peak change from baseline in FEV<sub>1</sub> will be calculated using the largest FEV<sub>1</sub> value measured following dosing of IP.

#### **8.5.3.4 Derivation of peak expiratory flow**

The best of at least 3 PEF measurements will be recorded by the subject in the morning and before going to bed in the evening prior to taking any asthma therapy. PEF will be analyzed separately for the morning and evening.

#### **8.5.3.5 Derivation of Asthma Control Questionnaire-5 variables**

Derivations for responder status for ACQ-5 will be performed as described in [Section 8.5.3.2](#). At least 4 out of the 5 symptom items are needed to provide an overall ACQ-5 score.

#### **8.5.3.6 Derivation of Asthma Quality of Life Questionnaire +12 and Pediatric Asthma Quality of Life Questionnaire variables**

AQLQ consists of 32 questions in 4 domains and PAQLQ consists of 23 questions in 3 domains. Both are assessed on separate 7-point Likert scales from 1 to 7, with higher values indicating better health-related quality of life.

For overall health-related quality of life and for each of the domains, the MID has been determined to be a change in score of 0.5 ([Juniper 1994](#)). On the basis of the MID, responders at Week 12 are defined as subjects achieving an increase from baseline of at least 0.5:

- Responder: (Week 12 – baseline)  $\geq 0.5$
- Non-responder: (Week 12 – baseline)  $< 0.5$

Subjects who discontinue treatment before Week 12 for any reason will be classified as non-responders. Baseline is defined as the most recent non-missing score before the first dose of randomized IP.

### 8.5.3.7 Derivation of Ventolin therapy variables

Ventolin therapy will be analyzed through the average number of administrations (puffs) per day.

Total daily number of puffs will be calculated for each subject as the sum of the cumulative puffs of Ventolin therapy divided by the number of days the subject was in the study prior to treatment discontinuation.

Total daily number of puffs will be further characterized within 4-weekly time intervals throughout the randomized treatment period. Further details will be provided in the SAP.

Baseline number of puffs per day will be based on the last 10 days of the run-in period prior to before the first dose of randomized IP.

### 8.5.3.8 Derivation of other eDiary variables

#### Symptom-free days

A symptom-free day is defined as the fulfillment of both of the following criteria:

- A day and night with no asthma symptoms (ie, asthma symptom score=0)
- A night with no awakenings due to asthma symptoms

#### Asthma control days

An asthma control day is defined as the fulfillment of all of the following criteria:

- A day and night with no asthma symptoms (ie, asthma symptom score=0)
- A night with no awakenings due to asthma symptoms
- A day and night with no use of prn Ventolin therapy

## 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.

### 8.6.1 Analysis of the dual-primary variable

The first and second dual-primary variables, change from baseline in  $FEV_1 AUC_{0-6\text{ hours}}$ , and change from baseline in trough  $FEV_1$  will each be analyzed using a repeated measures (RM) linear model to compare treatment groups. The model will include baseline  $FEV_1$ , percentage reversibility to Ventolin, and age as continuous covariates, and visit, treatment, the treatment-

by-visit interaction, and prior ICS use (Yes/No) as categorical covariates. Baseline will be defined as the average of the pre-dose assessments collected on randomization (Visit 2).

An unstructured variance-covariance matrix will be implemented. If this model fails to converge, a heterogeneous Toeplitz (TOEPH) will be fit.

FEV<sub>1</sub> AUC<sub>0-6 hours</sub> over 12 weeks will be calculated using an appropriate contrast. Two-sided p-values and point estimates with two-sided 95% confidence intervals will be calculated for each pairwise treatment contrast. More details will be provided in the SAP.

The planned treatment comparisons for the primary analysis will be sequentially tested in the 8 step sequence as specified below. Comparisons will stop if a non-statistically significant result occurs. All comparisons are of superiority. Formally, the null and alternative hypotheses for each comparison are:

$$H_0: \text{Difference between treatment} = 0,$$

$$H_A: \text{Difference between treatment} \neq 0.$$

Change from baseline in FEV<sub>1</sub> AUC<sub>0-6 hours</sub> over 12 weeks:

1. AS MDI 180 µg QID versus placebo MDI QID
2. BDA MDI 160/180 µg QID versus placebo MDI QID
3. BDA MDI 160/180 µg QID versus BD MDI 160 µg

Change from baseline in trough FEV<sub>1</sub> at Week 12:

4. BD MDI 160 µg QID versus placebo MDI QID
5. BDA MDI 160/180 µg QID versus placebo MDI QID
6. BDA MDI 160/180 µg QID versus AS MDI 180 µg QID

Statistical testing for BDA 80/180 µg will proceed in a similar manner as for BDA 160/180 µg, as shown below:

Change from baseline in trough FEV<sub>1</sub> at Week 12:

7. BDA MDI 80/180 µg QID versus placebo MDI QID
8. BDA MDI 80/180 µg QID versus AS MDI 180 µg QID

The Type I error will be controlled sequentially by testing in the above order. If a comparison is significant (alpha=0.05, two-sided), testing will proceed to the next comparison.

The above tests in steps 1 to 8 will exclude children (age 4 to 11 years). The analysis will be repeated to include children, but will be considered a supportive analysis of the dual-primary endpoint. In the supportive analysis including all ages, the comparison of BDA MDI 160/180 µg versus AS MDI 180 µg will exclude the child subjects aged 4 to 11 years as they will not be randomized to BDA MDI 160/180 µg. However, the comparison of BDA MDI 80/180 µg versus AS MDI 180 µg and BDA MDI 80/180 µg versus placebo MDI will include subjects from all age groups.

The comparisons of BDA MDI 80/180 µg QID versus placebo MDI QID and BDA MDI 80/180 µg QID versus BD MDI 160 µg QID for  $FEV_1 AUC_{0-6 \text{ hours}}$  over 12 weeks are not included in the Type I error control procedure as they redundantly evaluate the contribution of albuterol to the combination, which is already captured in Steps 2 and 3. However, these comparisons will be reported for completeness.

All subjects who are randomized and are part of the full analysis set will be analyzed according to the strata they were allocated to in IVRS/IWRS in this primary analysis. A sensitivity analysis will be conducted based on subjects' actual strata to assess the impact of miss-stratification on the model results.

## **8.6.2 Analysis of the secondary efficacy variables**

For all secondary analyses the same treatment comparisons as for the primary analysis will be conducted ([Section 8.6.1](#)).

### **8.6.2.1 Median time to onset (15% increase in $FEV_1$ ) and duration of effect**

The median time to onset (defined as 15% increase in  $FEV_1$ ) over the pre-treatment value at randomization (Visit 2) will be compared among treatment groups using a Wilcoxon rank sum test. Confidence intervals for the median treatment difference will be calculated using the Hodges-Lehmann method.

Descriptive statistics for duration of response will be reported by treatment group.

Only the subjects who achieve the 15% increase in  $FEV_1$  within 30 minutes post-dose will be included in these calculations.

### **8.6.2.2 Asthma Control Questionnaire-7**

The primary analyses of ACQ-7 will be conducted in subjects that are uncontrolled at baseline ( $ACQ-7 \geq 1.5$ ) as these are the subjects capable of demonstrating a clinically meaningful response with treatment.

The responder variable described in [Section 8.5.2.2](#) at Week 12 will be analyzed using a logistic regression model with treatment and previous ICS use (Yes/No) as categorical covariates, and baseline ACQ-7 score, baseline post-dose percent predicted  $FEV_1$  and age as continuous

covariates. From the logistic regression model treatment effects will be estimated by odds ratios and its corresponding 95% confidence interval along with p-values.

Baseline is defined as the most recent non-missing score before the first dose of randomized IP. Subjects who discontinue treatment for any reason will be classified as non-responders. The frequency and percentage of responders will be summarized descriptively for all study visits.

The treatment effect for change from baseline in ACQ-7 will be estimated using a mixed model RM (MMRM) analysis. All data up to Week 12 will be included in the model, with terms for age, treatment, visit, treatment\*visit, prior ICS use (Yes/No), baseline ACQ-7 score and baseline post-dose percent predicted FEV<sub>1</sub>. Visit will be fitted as a categorical variable, and the variance-covariance matrix will be assumed to be unstructured. If the procedure does not converge, then a heterogeneous TOEPH will be used instead. This model will be used to give an overall assessment of the treatment effect as well as 95% confidence intervals.

Change from baseline will also be described descriptively for all study visits.

### **8.6.3 Analysis of safety variables**

The safety analyses will include all data obtained before subjects discontinue randomized treatment and will use the safety analysis set.

#### **8.6.3.1 Adverse events**

Adverse events will be summarized by treatment group, system organ class and preferred term assigned to the event by the Medical Dictionary for Regulatory Activities. AEs will also be listed for each subject.

#### **8.6.3.2 Vital signs**

Change from baseline throughout the study will be assessed for vital signs variables collected on the eCRF.

Baseline is defined as the most recent non-missing measurement before the first dose of randomized IP.

#### **8.6.3.3 Clinical chemistry and hematology**

Clinical chemistry and hematology parameters will be summarized by treatment group and Visit and will also be listed by subject.

Baseline is defined as the most recent non-missing measurement before the first dose of randomized IP.

#### **8.6.3.4 ECG**

ECG parameters will be summarized by treatment group and Visit and will also be listed by subject.

Baseline is defined as the most recent non-missing measurement before the first dose of randomized IP.

#### **8.6.3.5 Concomitant medication**

The number and percentage of subjects who take allowed concomitant medications, and those who take disallowed concomitant medications during the study, will be presented by treatment group.

#### **8.6.4 Analysis of exploratory variables**

The treatment comparisons in the secondary analyses given below are compared in the same way as the primary analysis.

##### **8.6.4.1 Severe exacerbations**

The raw annualized exacerbation rate will be summarized descriptively by treatment, using the derivation described in [Section 8.5.3.1](#).

##### **8.6.4.2 Deterioration of asthma**

Annualized deterioration of asthma will be summarized in the same way as the annualized severe asthma exacerbation rate ([Section 8.6.4.1](#)).

##### **8.6.4.3 Peak FEV<sub>1</sub>**

Peak FEV<sub>1</sub> at Day 1 (Visit 2) and Day 14 (Visit 3) will be analyzed using the same method as for trough FEV<sub>1</sub> and FEV<sub>1</sub> AUC<sub>0-6 hours</sub>. Baseline will be defined as the average of the pre-dose assessments collected on Day 1.

##### **8.6.4.4 Peak expiratory flow**

The mean value of change from baseline in PEF data during the randomized treatment period will be analyzed by analysis of covariance with treatment, ACQ-7 at randomization ( $\leq 1.5$ / $> 1.5$ ), and prior ICS use (Yes/No) as factors, and age and baseline PEF score as continuous covariates. The summary measure for the comparison of treatments will be the estimated mean difference, presented with the corresponding 95% confidence interval.

Additionally, an RM analysis will be conducted and will be partitioned into 4-weekly time intervals across the randomized treatment period. The analysis model will additionally include time point and treatment\*time point as factors.

##### **8.6.4.5 Asthma Control Questionnaire-5 variables**

The responder variable for ACQ-5 at Week 12 will be analyzed using a logistic regression model in the same way as ACQ-7 ([Section 8.6.2.2](#)).

The treatment effect for change from baseline in ACQ-5 will be estimated using an MMRM analysis in the same way as ACQ-7 ([Section 8.6.2.2](#)).

The 3-factor categorization of ACQ-7 (Improvement; No change; Worsening) will be considered in an exploratory analysis using a logistic regression model adjusted for the same covariates as for the binary response of ACQ-7 ([Section 8.6.2.2](#)).

#### **8.6.4.6    Asthma Quality of Life Questionnaire +12 and Pediatric Asthma Quality of Life Questionnaire**

The responder analysis will be conducted in the same way as ACQ-7 ([Section 8.6.2.2](#)).

The domain scores as well as the overall scores are calculated from the unweighted arithmetic means of the individual question scores. The treatment effect for change from baseline in AQLQ+12 and PAQLQ overall scores up to Week 12 will be estimated in the same way as ACQ-5, using an MMRM analysis.

Change from baseline will also be described descriptively for all study visits for each of the domains and the overall scores.

In all the scenarios above, baseline is defined as the most recent non-missing measurement before the first dose of randomized IP.

As the PAQLQ is not validated for children <7 years of age, data for subjects who are aged 4 to 6 years will be excluded from the analyses of PAQLQ endpoints.

#### **8.6.4.7    Ventolin therapy**

Change from baseline in Ventolin therapy use compared with the mean value of available data during the study. The data will be analyzed using analysis of covariance with treatment, ACQ-7 at randomization ( $\leq 1.5 / > 1.5$ ), and prior ICS use (Yes/No) as factors, and age and baseline daily number of puffs as continuous covariates. The summary measure for the comparison of treatments will be the estimated mean difference, presented with the corresponding 95% confidence interval.

Additionally, an RM analysis will be conducted on the change from baseline Ventolin therapy partitioned into 4 weekly time intervals across the randomized treatment period. The analysis model will additionally include time point and treatment\*time point as factors.

#### **8.6.4.8    Other eDiary variables**

Asthma daytime/night-time symptoms and night-time awakenings due to asthma will be compared with the mean value of available data during the study. The data will be analyzed using analysis of covariance with treatment, ACQ-7 at randomization ( $\leq 1.5 / > 1.5$ ), and prior ICS use (Yes/No) as factors, and age and baseline as continuous covariates. The summary measure for the comparison of treatments will be the estimated mean difference, presented with the corresponding 95% confidence interval.

Additionally, an RM analysis will be conducted on the aforementioned eDiary endpoints, partitioned into 4-weekly time intervals across the randomized treatment period. The analysis model will additionally include time point and treatment\*time point as factors.

Change from baseline will also be summarized for each subject by treatment group using summary statistics. In all the scenarios above, baseline is defined as the most recent score before the first dose of randomized IP.

### **8.6.5 Subgroup analysis**

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

### **8.6.6 Interim analysis**

No interim analyses will be conducted in this study and the study blind is to be maintained until all subjects have completed the treatment period and until after the database has been locked.

### **8.6.7 Sensitivity analysis**

#### **8.6.7.1 Tipping point analysis**

Multiple imputations tipping point analysis under the missing not at random assumption (MNAR) will be conducted. For subjects in the BDA MDI groups, and subjects in AS MDI and BD MDI when comparing to placebo MDI, this method will impute missing values post-study discontinuation for lack of asthma control assuming they were more likely to have a worse outcome than as implied under the missing at random assumption (MAR). The tipping point analysis will incrementally penalize the missing data under the missing not at random assumption until a non-statistically significant comparison is observed.

The tipping point approach described above will be repeated and all missing data over the randomized treatment period will be imputed under the MNAR assumption. Further details will be provided in the SAP.

#### **8.6.7.2 Attributable estimand**

Analysis of the attributable estimand will be conducted in the full analysis set, but data that are missing due to treatment discontinuation will be imputed based on the 95th or the 5th percentile of the reference group's distribution if the reason is reasonably attributable to tolerability or lack of efficacy. The 95th percentile would apply to an endpoint for which a higher value is a worse outcome, while the 5th percentile would apply to an endpoint for which a higher value is a better outcome. More detail about the computation of the attributable estimand will be provided in the SAP.

### **8.6.7.3 COVID-19 pandemic impacts**

As the trial is ongoing during the coronavirus disease (COVID-19) pandemic, it will be necessary to evaluate any potential intercurrent events due to COVID-19 and quantify their impact on the efficacy and safety profile of the study.

At a minimum, the number of missed visits, premature withdrawals, and efficacy assessments not done will be summarized descriptively by treatment group and overall across treatment groups. Where appropriate, the subject level data for missed visits and assessments will be listed along with the corresponding link to COVID-19, as recorded in the eCRF. It is not anticipated that missing data and premature withdrawals due to COVID-19 will be related to randomized treatment. Therefore, missing data due to COVID-19 will be assumed missing at random in accordance with the efficacy estimand. If further sensitivity analyses are deemed necessary following a blinded review of missing efficacy due to COVID-19, further details will be provided in the statistical analysis plan, prior database lock and unblinding.

Similarly, at a minimum, the number of missed scheduled safety assessments due to COVID-19 will be summarized descriptively by treatment group and across treatment groups. Subjects with suspected or confirmed diagnosis of COVID-19, and/or COVID-19 related AEs and SAEs will be summarized descriptively. Subject level listings of missed safety assessments and COVID-19 related (S)AEs will be listed.

## **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 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 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, dispensation, and return of all IP
- Ensure withdrawal of informed consent/assent to the use of the subject's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the subject

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

### **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/participating center 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/participating center 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-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 BDA MDI.

### **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.

AEs 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 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’ 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 informed consent/assent form 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. 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 informed consent/assent form 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 informed consent/assent form 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 informed consent/assent form, 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 handles the distribution of any of these documents to the national regulatory authorities.

The Sponsor or designated representative will provide regulatory authorities, ECs, and investigators 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 risks and benefit of the study
- Ensure each subject and/or parent/legal representative is notified that they are free to discontinue from the study at any time
- Ensure that each subject and/or parent/legal representative is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each subject and/or parent/legal representative provides signed and dated informed consent/assent before conducting any procedure specifically for the study
- Ensure the original, signed informed consent/assent form(s) is/are stored in the investigator's study file
- Ensure a copy of the signed informed consent/assent form is given to the subject
- 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 informed consent/assent form that is approved by an EC

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

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(s) for distribution to EC see [Section 10.3](#).

If a change to a Clinical Study Protocol requires a change to a center's informed consent/assent form, the Sponsor and the center's EC are to approve (or a notification to the national regulatory authority is submitted where applicable for) the revised informed consent/assent form 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 and 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 SUMMARY OF CHANGES

The following table provides a brief summary of major changes. It does not include all non-substantial changes (eg, formatting, minor clerical, and typographical corrections).

### 11.1 Changes to protocol amendment 2 (Version 3.0)

Section	Changes to Protocol Amendment 2 (Version 3.0)
Clinical Protocol Synopsis	<p>Updated the number of adult and adolescent subjects randomized from <b>600</b> to <b>1000</b>, the number of subjects within each treatment arm from <b>120</b> to <b>200</b>, and the number of subjects screened from <b>1000</b> to <b>2000</b>. Updated the estimated screen failure rate from <b>40%</b> to <b>50%</b>.</p> <p>Exploratory endpoint: Specified that the change from baseline in the Asthma Control Questionnaire-5 (ACQ-5) and responder analysis is <b>at Week 12</b>.</p> <p>Target subject population: Clarified to include subjects <math>\geq 4</math> years of age, <b>where approved, <math>\geq 18</math> years of age for all other countries</b>.</p> <p>Clarified ages for adult (<b><math>\geq 18</math> years of age</b>) and adolescent subjects (<b>aged 12-17 years, where approved</b>).</p> <p>Added <b>Subjects will be recommended not to take more than 8 puffs of Ventolin per day and advised to contact the investigator if their symptoms necessitate more than 8 puffs of Ventolin in a day</b>.</p> <p>Addition of initial assumptions for calculations of sample size and information about the blinded sample size-re-</p>

<u>Section</u>	<u>Changes to Protocol Amendment 2 (Version 3.0)</u>
	<p>estimation. Re-estimation was performed once 44% of subjects had completed Week 12.</p> <p>Updated to describe and justify a second blinded same size re-estimation once approximately 65% of the revised sample size completes 12 weeks of the study and before the last subject is randomized.</p> <p>Modified the cap in sample size to <b>1300</b>, and specified this is a <b>30% increase above the revised number of 1000 subjects</b> as opposed to the previously calculated cap of 800, a <b>33% increase above the planned number of 600 subjects</b>.</p>
1 Introduction	<p><b>1.1 Background</b></p> <p>Added <i>Albuterol is approved in many countries as salbutamol in multiple formulations for the treatment or prevention of bronchoconstriction.</i></p> <p><b>1.3 Benefit/risk and ethical assessment</b></p> <p>Added justification to continue study enrollment and treatment during the COVID-19 pandemic.</p> <p><b>1.4 Study design</b></p> <p>Added recommendation to not exceed 8 puffs of Ventolin per day.</p> <p><b>Figure 1:</b> Updated to reflect new sample size estimates.</p>
2 Study Objectives	<p><b>2.4 Exploratory objectives</b></p> <p>Specified that the change from baseline in the Asthma Control Questionnaire-5 (ACQ-5) and responder analysis is <b>at Week 12</b></p>
3 Subject selection, enrollment, randomization, restrictions, treatment, discontinuation and study termination	<p><b>3.1 Inclusion criteria</b></p> <p>Inclusion criteria 2 updated to add <b><i>In the Czech Republic, Germany, Serbia, Slovakia, and Ukraine only subjects ≥18 years will be included.</i></b></p> <p>Inclusion criteria 5 updated the predicted normal value of pre-bronchodilator FEV<sub>1</sub> for subjects age 4-7 to <b>≥50%</b> (from <b>≥50 to &lt; 90%</b>) and to add <b><i>Subjects 4 to 17 years of age who previously failed inclusion criteria 5 due to the</i></b></p>

<u>Section</u>	<u>Changes to Protocol Amendment 2 (Version 3.0)</u>
	<p><i>upper FEV<sub>1</sub> limit will be permitted to re-screen once and will be required to meet all eligibility criteria upon re-screening.</i></p> <p>Inclusion criteria 7 updated: <i>Subjects 4 to 11 years will be eligible if they provide 2 acceptable / repeatable measurements.</i></p> <p>Inclusion criteria 15 revised to define the practice of complete abstinence, to remove <i>highly</i> when describing methods of effective birth control methods, and modified to clarify appropriate methods of double-barrier birth control. The definition of menopausal women was updated to remove the reference to <math>\geq 50</math> years of age.</p> <p>Inclusion criteria 16 modified to remove the word <i>highly</i> when referring to effective methods of double-barrier contraception.</p> <p><b>3.2 Exclusion criteria</b></p> <p>Exclusion criteria 4 updated to include <i>dupilumab</i></p> <p>Exclusion criteria 24 updated to include <i>Currently pregnant or breastfeeding.</i></p> <p>Exclusion criteria 28 updated to <i>previously been randomized</i> from <i>enrolled</i> and to add <i>For pediatrics, see inclusion criterion 4.</i></p> <p><b>3.3 Subject enrollment and randomization</b></p> <p>Updated the number of adult and adolescent subjects randomized from <i>600</i> to <i>1000</i>, the number of subjects within each treatment arm from <i>120</i> to <i>200</i>, and the number of subjects screened from <i>1000</i> to <i>2000</i>. Updated the estimated screen failure rate from <i>40%</i> to <i>50%</i>.</p> <p><b>3.7 Methods for unblinding</b></p> <p>Clarified methods for unblinding and specified that decisions will be based on the investigator's clinical judgement. The requirement that the investigator should discuss with the Sponsor medical monitor or other appropriate personnel, when possible, was removed.</p>

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<u>Section</u>	<u>Changes to Protocol Amendment 2 (Version 3.0)</u>
	<p><b>3.9 Treatment discontinuation by subject and/or Sponsor</b></p> <p>The following reason for IP discontinuation was added: <i>In subjects who have elevated liver enzymes AST and/or ALT <math>\geq 3</math> times the upper limit of normal (<math>\times</math>ULN) and total bilirubin <math>\geq 2 \times</math>ULN (ie, meeting the criteria of at least potential Hy's Law), IP will be suspended until the liver test values return to the normal range. If the AST, ALT, or total bilirubin reach these elevated levels again, after recommencement of IP, the subject will be discontinued from IP and withdrawn from the study.</i></p> <p><b>3.11 Screen failures</b></p> <p>The following exception for screen failures was added: <i>Subjects who are screen failures will not be re-screened with the exception of children and adolescents who screen-failed because they did not meet the now obsolete upper FEV1 % predicted limit. Children and adolescents who previously failed to meet the upper FEV1 % predicted threshold, but who met all other eligibility requirements, may re-screen once. Upon re-screening, these subjects must meet all eligibility requirements in order to be randomized.</i></p>
Section 4 Study plan and timing of procedures	<p><b>Table 1:</b> Added <i>pregnancy testing</i> to Visits 3 and 5, added <i>Ventolin administration (recorded in MasterScope)</i> to Screening, and removed <i>IP administration (recorded in MasterScope)</i> at Screening.</p> <p><b>Footnote h:</b> Updated from <i>Visits 2 and 4</i> to <b><i>all other visits</i></b> for pregnancy testing.</p> <p><b>Footnote i:</b> updated upper threshold values for FEV<sub>1</sub> to <math>\geq 50\%</math> from <math>\geq 50- &lt; 90\%</math> in subjects aged 4-17 years.</p> <p><b>4.2 Randomization/treatment period</b></p> <p>Added urine pregnancy testing at Visits 3 and 5 in the Czech Republic and at the safety follow up visit in Argentina. Clarified that serum pregnancy tests are required at Visit 6 <b><i>or the premature discontinuation visit (PDV).</i></b></p>
5 Study Assessments	<p>Administrative changes</p> <p><b>5.1.1.1 Reversibility test</b></p> <p>Clarified that pre-dose PFTs are to be done after <b><i>at least 15 minutes of rest and before administration of Ventolin.</i></b></p>

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<u>Section</u>	<u>Changes to Protocol Amendment 2 (Version 3.0)</u>
	<p><b>5.1.1.2 COVID-19 and Pulmonary Function Testing</b></p> <p>New section added to specify that spirometry should not be done if subjects are showing signs and symptoms of COVID-19 and to indicate that participants with suspected COVID-19 should receive a test to confirm diagnosis.</p> <p><b>5.1.2 Asthma Control Questionnaire-5</b></p> <p>Sentence revised to <i>Linguistically validated translations of the ACQ-5 into local languages will be used (removed with results transcribed into the eCRF)</i>.</p> <p><b>5.1.3 Asthma Control Questionnaire-7</b></p> <p>Sentence revised to <i>Linguistically validated translations of the ACQ-7 into local languages will be used (removed with results transcribed into the eCRF)</i>.</p> <p><b>5.1.6.1 Peak expiratory flow</b></p> <p>Modified to record <b>3 PEF measures</b> from <i>the best of at least 3</i>.</p> <p><b>5.1.6.3 eDiary Ventolin therapy use</b></p> <p>Added recommendation that subjects should not take more than 8 puffs of Ventolin per day and to contact the investigator if more than 8 puffs are needed.</p> <p><b>5.1.8.5 Treatment for severe asthma exacerbations</b></p> <p>Clarified that <i>treatment for less than 3 days doesn't constitute a severe asthma exacerbation except if the subject is hospitalized due to asthma</i>.</p> <p><b>Table 4 Laboratory safety variables</b></p> <p>Updated urine pregnancy test timing, added PDV to list of abbreviations, and added a reference to section 3.9.</p>
6 Safety reporting and medical management	<p><b>6.3.7 Hy's Law</b></p> <p>Updated that <i>occurrences of AST and/or ALT <math>\geq 3 \times ULN</math> combined with TBL <math>\geq 2 \times ULN</math> may require IP suspension/discontinuation and study withdrawal and</i></p>

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<u>Section</u>	<u>Changes to Protocol Amendment 2 (Version 3.0)</u>
	<p><i>may need to be reported as SAEs.</i> A reference to section 3.9 was also added.</p> <p><b>6.3.8 COVID-19 adverse events</b></p> <p>Added to provide instructions on how to handle AEs related to the COVID-19 pandemic.</p>
7 Investigational product and other treatments	<p><b>7.2 Dose treatment regimens</b></p> <p>Updated that subjects <i>should not take more than 8 puffs of Ventolin per day.</i></p> <p><b>7.5 Compliance</b></p> <p>Updated that Ventolin usage will be monitored during the study.</p> <p><b>7.8.1 Investigational product and Ventolin therapies</b></p> <p>Added <i>Subjects on maintenance allergy immunotherapy (AIT) are allowed to continue their AIT; the new initiation of AIT during the study is not allowed.</i></p> <p><b>7.8.3 Prohibited medications</b></p> <p>Clarified the <i>use of oral, parenteral, or rectal corticosteroids to include (except if required to treat asthma exacerbation).</i></p> <p>Added <i>Montelukast, for any indication</i></p> <p><b>Dupilumab</b> was added to the list of prohibited monoclonal or polyclonal antibodies and the use of <i>intra-ocular</i> monoclonal or polyclonal antibody therapy was clarified to be allowed.</p> <p>Clarified the use of beta2-adrenergic blockers including eye-drops <i>specific cardio-selective beta-blockers in low daily doses, eg, metoprolol in doses up to 100 mg/d, are allowed.</i></p>
8 Statistical analysis	<p><b>8.2 Sample size estimate</b></p>

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<u>Section</u>	<u>Changes to Protocol Amendment 2 (Version 3.0)</u>
	<p>Added <b>Section 8.2.1</b> to describe the initial assumptions for sample size estimates and <b>Section 8.2.2</b> to describe the process for blinded sample size re-estimation. This re-estimation resulted in updates to the number of adult and adolescent subjects randomized from <b>600</b> to <b>1000</b>, the number of subjects within each treatment arm from <b>120</b> to <b>200</b>, and the number of subjects screened from <b>1000</b> to <b>2000</b>. The screen failure rate was updated from <b>40%</b> to <b>50%</b>. The potential increase in sample size cap was increased from <b>800</b> to <b>1300</b>.</p> <p>Described processes for a second blinded sample size re-estimation.</p> <p><b>8.5.1.1 Dual-primary efficacy endpoints</b></p> <p>Specified that baseline FEV<sub>1</sub> <i>will be taken as the average of the 60- and 30-minute pre-dose spirometry measures at randomization and not on or before randomization.</i></p> <p><b>8.5.2.2 Derivation of Asthma Control Questionnaire-7 variables</b></p> <p>Added an exploratory endpoint for the 3 factor endpoint categorization (Improved, No change, Worsening) from baseline to Week 12.</p> <p><b>8.5.3.4 Derivation of peak expiratory flow</b></p> <p><i>The best of at least 5 PEF measurements was updated to at least 3 PEF measurements.</i></p> <p><b>8.6.1 Analysis of the dual-primary variable</b></p> <p>Clarified that primary comparisons <i>will exclude the children (ages 4-11 years)</i> and specified that the analysis <i>will be repeated to include children, but will be considered a supportive analysis of the dual-primary endpoint.</i></p> <p>Added supportive analysis of participants randomized according to actual strata they were allocated to.</p> <p><b>8.6.4.5 Asthma Control Questionnaire-5 variables</b></p> <p>Added exploratory analysis of the 3-factor categorization endpoint for ACQ-7.</p>

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<u>Section</u>	<u>Changes to Protocol Amendment 2 (Version 3.0)</u>
	<b>8.6.7.3 COVID-19 pandemic impacts</b>  Added to describe statistical methods that will be used to evaluate the impact of the COVID-19 pandemic on efficacy and safety variables.
12 List of References	Added reference to the American Academy of Allergy Asthma and Immunology for information regarding COVID-19 and Asthma.
Appendix E, Hy's Law	Indicated when subjects with elevated liver enzymes will be suspended from or discontinued from IP.  Updated definitions of potential Hy's Law and Hy's Law.
Appendix L, COVID-19 emergency measures permitted to ensure subject safety	Added processes to ensure subject safety during the COVID-19 pandemic. Instructions for management of subjects with or suspected COVID-19 infection, delayed visits, remote visits, subject discontinuation, shipment of study drug to subjects, laboratory testing, and spirometry testing are provided.

## 11.2 Changes to protocol amendment 1 (Version 2.0)

<u>Section</u>	<u>Changes to Protocol Amendment 1 (Version 2.0)</u>
Clinical Study Protocol Synopsis	Administrative change.  Clarification provided on the target subject population.  Clarification on Sponsor-provided IP dose frequency ( <b>QID</b> ).
4.0 Study plan and timing of procedures	Administrative changes.  <b>Table 1:</b> Addition of and adjustments to table/footnote(s) to confirm that new IP will be dispensed and used for FEV <sub>1</sub> measurements and that at Visit 6 and PDV, IP will be dispensed for the purposes of completing FEV <sub>1</sub> measurements but will not be taken home by the subjects.  <b>Table 2:</b> Table title updated to <i>Timed assessments at Visit 2 through Visit 6 and Premature Discontinuation Visit</i> .

	<p>Adjustments to the table to clarify drug dispensing and dose timing.</p> <p><b>4.2 Randomization/treatment period</b></p> <p>Clarification and instructions regarding proper IP preparation, dispensing, and dosing for post-dose assessments (ie, new IP in relation to FEV<sub>1</sub>) at each in-clinic dosing visit.</p> <p>Addition of new recommendation for opening the seal around the study day treatment box.</p> <p><b>4.3 Treatment discontinuation</b></p> <p>Addition of <i>dispensation of IP (for spirometry only) and dosing</i> to procedures carried out during PDV visit.</p>
5.0 Study assessments	<p><b>5.1.1 Lung function measurement by spirometry</b></p> <p>Administrative changes including clarification that IP should be dosed before 10:00 AM in all in-clinic dosing visits.</p> <p><b>5.1.1 Reversibility test</b></p> <p>Clarification that pre- and post-dose FEV<sub>1</sub> measurements are in relation to Sponsor-provided bronchodilator (Ventolin).</p> <p><b>5.1.6 eDiary</b></p> <p>Administrative changes.</p> <p><b>5.2.3 Vital signs measurements</b></p> <p>Removal of <i>supine</i> as position for measuring blood pressure.</p>
7.8 Concomitant medications and other treatments	<p><b>7.8 Concomitant medications and other treatments</b></p> <p>Addition of <b>medications</b> to the title.</p> <p><b>7.8.1 Investigational product and Ventolin therapies</b></p>

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	<p>Clarification on Sponsor-provided IP dose frequency (<i>dosed QID</i>).</p> <p><b>7.8.3 Prohibited medications</b></p> <p>Correction of naming for cytochrome P450 3A4 inhibitors.</p>
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**APPENDIX A, AVILLION PROTOCOL SIGNATURE PAGE**

Avillion Signature Form for the Clinical Study Protocol

We, the undersigned, to the best of our knowledge and ability attest to the accuracy and validity of the contents of the Clinical Study Protocol.



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## APPENDIX B, PRIMARY INVESTIGATOR SIGNATURE PAGE

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

---

Principal Investigator's Name (print)

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Principal Investigator's Signature

---

Date

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

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**APPENDIX C, GLOBAL INITIATIVE FOR ASTHMA (GINA, 2018)**

The table below is not a table of equivalence, but of estimated clinical comparability. Categories of low, medium, and high doses are based on published information and available studies, including direct comparisons where applicable. Doses may be country-specific depending on labelling requirements, drug formulation, or inhalation device. Most of the clinical benefit from ICS is seen at low-doses, and clear evidence of dose-response relationships is seldom available within dose ranges evaluated for regulatory purposes. High doses are arbitrary, but for most ICSs are those that, with prolonged use, are associated with increased risk of systemic side effects.

Subjects enrolling in this study may be taking low-dose ICS, the below table shows GINA guidance in relation to low-dose ICS in relation to inclusion criterion 4.

**Low, Medium, and High Doses of Inhaled Corticosteroids**

Adults and adolescents (12 years and older)			
DRUG	Daily dose (µg)		
	LOW	MEDIUM	HIGH
Beclometasone dipropionate (CFC) <sup>a</sup>	200-500	>500-1000	>1000
Beclometasone dipropionate (HFA)	100-200	>200-400	>400
Budesonide (DPI)	200-400	>400-800	>800
Ciclesonide (HFA)	80-160	>160-320	>320
Fluticasone furoate (DPI)	100	NA	200
Fluticasone propionate (DPI)	100-250	>250-500	>500
Fluticasone propionate (HFA)	100-250	>250-500	>500
Mometasone furoate	110-220	>220-440	>440
Triamcinolone acetonide	400-1000	>1000-2000	>2000
Children 6-11 years			
Beclometasone dipropionate (CFC) <sup>a</sup>	100-200	>200-400	>400
Beclometasone dipropionate (HFA)	50-100	>100-200	>200
Budesonide (DPI)	100-200	>200-400	>400
Budesonide (nebulizer)	250-500	>500-1000	>1000
Ciclesonide	80	>80-160	>160
Fluticasone furoate (DPI)	NA	NA	NA
Fluticasone propionate (DPI)	100-200	>200-400	>400
Fluticasone propionate (HFA)	100-200	>200-500	>500
Mometasone furoate	110	>220-440	>440

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Triamcinolone acetonide	400-800	>800-1200	>1200
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Abbreviations: CFC=chlorofluorocarbon propellant; DPI=dry powder inhaler; HFA=hydrofluoroalkane propellant; NA=not applicable

<sup>a</sup> Beclometasone dipropionate CFC is included for comparison with other literature.

### Low Daily Doses of Inhaled Corticosteroids for Children 5 Years and Younger

DRUG	Low daily dosage (µg) (age group with adequate safety and effective data)
Beclometasone dipropionate (HFA)	100 (ages $\geq$ 5 years)
Budesonide nebulized	500 (ages $\geq$ 1 year)
Fluticasone propionate (HFA)	100 (ages $\geq$ 4 years)
Mometasone furoate	110 (ages $\geq$ 4 years)
Budesonide pMDI + spacer	Not sufficiently studied in this age group
Ciclesonide	Not sufficiently studied in this age group
Triamcinolone acetonide	Not sufficiently studied in this age group

Abbreviations: HFA=hydrofluoroalkane propellant; pMDI=pressurized metered-dose inhaler

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## APPENDIX D, ADDITIONAL SAFETY INFORMATION

### Further guidance on the definition of a serious adverse event

#### 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 an AE occurred in a more severe form, it might have caused death (eg, hepatitis that resolved without hepatic failure).

#### Hospitalization

Outpatient 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 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 after 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 judgement. With limited or insufficient information in the case, it is likely that the event(s) will be assessed as 'not 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 E, HY'S LAW

### Introduction

This Appendix describes the process to be followed to identify and appropriately report cases of Hy's Law. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

During the course of the study, the investigator will remain vigilant for increases in liver biochemistry. In subjects who have elevated liver enzymes AST and/or ALT  $\geq 3 \times \text{ULN}$  and total bilirubin  $\geq 2 \times \text{ULN}$ , IP will be suspended until the liver test values return to the normal range. If the AST, ALT, or total bilirubin reach these elevated levels again, after recommencement of IP, the subject will be discontinued from IP and withdrawn from the study. The investigator is responsible for determining whether a subject meets potential Hy's Law criteria at any point during the study.

The investigator participates, with the Sponsor's clinical project representatives, in review and assessment of cases meeting potential Hy's Law (PHL) criteria to agree whether Hy's Law (HL) criteria are met. Hy's Law criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than drug induced liver injury caused by the IP.

The investigator is responsible for recording data pertaining to potential HL/HL cases and for reporting AEs and SAEs according to the outcome of the review and assessment in line with standard safety reporting processes.

### Definitions

#### Potential Hy's Law

Aspartate aminotransferase and/or alanine transaminase  $\geq 3 \times \text{ULN}$  **combined with** TBL  $\geq 2 \times \text{ULN}$  at any point during the study after the start of IP irrespective of an increase in alkaline phosphatase.

#### Hy's Law

AST and/or ALT  $\geq 3 \times \text{ULN}$  **combined with** TBL  $\geq 2 \times \text{ULN}$ , where no other reason, other than the IP, can be found to explain the combination of increases, eg, elevated alkaline phosphatase indicating cholestasis, viral hepatitis, or another drug.

For potential HL and HL, the elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

#### Identification of potential Hy's Law cases

To identify cases of PHL it is important to perform a comprehensive review of laboratory data for any subject who meets any of the following identification criteria in isolation or in combination:

- ALT  $\geq 3 \times \text{ULN}$
- AST  $\geq 3 \times \text{ULN}$
- TBL  $\geq 2 \times \text{ULN}$

When a subject meets any of the identification criteria, in isolation or in combination, the central laboratory will immediately send an alert to the investigator and the medical monitor assigned to the project.

The investigator will also remain vigilant for any local laboratory reports where the identification criteria are met; where this is the case, the investigator will:

- Notify the medical monitor assigned to the project.
- Request a repeat of the test (new blood draw) by the central laboratory.
- Contact the medical monitor to discuss the elevated local laboratory values and whether these constitute an AE. Where an AE is entered due to elevations of local laboratory values, the AE will be queried in the eCRF and elevated local laboratory values, units and ranges will be entered to the query response.
- When the identification criteria are met from central or local laboratory results, the investigator will without delay:
  - Determine whether the subject meets PHL criteria by reviewing laboratory reports from all previous visits (including both central and local laboratory results).
- The investigator will, without delay, review each new laboratory report and if the identification criteria are met, will:
  - Notify the medical monitor assigned to the project.
  - Determine whether the subject meets PHL criteria by reviewing laboratory reports from all previous visits.
  - Promptly enter the laboratory data into the laboratory eCRF.

## **Follow-up**

### **Potential Hy's Law criteria not met**

If the subject does not meet PHL criteria the investigator will:

Inform the medical monitor assigned to the project that the subject has not met PHL criteria.

Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol.

### **Potential Hy's Law criteria met**

If the subject does meet PHL criteria, the investigator will:

Determine whether PHL criteria were met at any study visit before starting IP ([Actions required when potential Hy's Law criteria are met before and after starting IP](#))

Notify the medical monitor assigned to the project who will then inform the central study team

The medical monitor assigned to the project will discuss the issue with the investigator to provide guidance and agree an approach for the study subjects' follow-up and the continuous review of data. Subsequent to this contact the investigator will:

Monitor the subject until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated

Investigate the cause of the event and perform diagnostic investigations as discussed with the medical monitor assigned to the project. For studies using a central laboratory add: This includes deciding which the tests available in the HL laboratory kit should be used.

Complete the 3 Liver eCRF modules as information becomes available

If at any time (in consultation with the medical monitor assigned to the project) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures.

### **Review and assessment of potential Hy's Law cases**

No later than 3 weeks after the biochemistry abnormality was initially detected, the medical monitor assigned to the project contacts the investigator to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than drug induced liver injury caused by the IP. The medical monitor assigned to the project and global safety physician will also be involved in this review with other subject matter experts, as appropriate.

According to the outcome of the review and assessment, the investigator will follow the instructions below.

If there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for an SAE:

If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate eCRF

If the alternative explanation is an AE/SAE, record the AE/SAE in the eCRF accordingly and follow the Sponsor's standard processes

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the IP:

Report an SAE (report term ‘Hy’s Law’) according to the Sponsor’s standard processes.

- The ‘Medically Important’ serious criterion should be used if no other serious criteria apply.
- As there is no alternative explanation for the HL case, a causality assessment of ‘related’ should be assigned.

If, there is an unavoidable delay, of over 3 weeks, in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

Report an SAE (report term ‘potential Hy’s Law’) applying serious criteria and causality assessment as per above

Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the SAE report according to the outcome of the review amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

#### **Actions required when potential Hy’s Law criteria are met before and after starting IP**

This section is applicable to subjects who meet PHL criteria on study treatment having previously met PHL criteria at a study visit before starting IP.

At the first on study treatment occurrence of PHL criteria being met the investigator will:

Determine if there has been a significant change in the subjects’ condition compared with the last visit where PHL criteria were met

- If there is no significant change no action is required.
- If there is a significant change, notify the Sponsor representative, who will inform the central study team, then follow the subsequent process described in [Potential Hy’s Law criteria met](#) of this Appendix.

A ‘significant’ change in the subject’s condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST, or TBL) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the investigator; this may be in consultation with the medical monitor assigned to the project if there is any uncertainty.

### **Actions required for repeat episodes of potential Hy's Law**

This section is applicable when a subject meets PHL criteria on study treatment and has already met PHL criteria at a previous on study treatment visit.

The requirement to conduct follow-up, review, and assessment of a repeat occurrence(s) of PHL is based on the nature of the alternative cause identified for the previous occurrence.

The investigator should determine the cause for the previous occurrence of PHL criteria being met and answer the following question:

Was the alternative cause for the previous occurrence of PHL criteria being met found to be the disease under study or did the subject meet PHL criteria before starting study treatment and at their first on study treatment visit as described in [Actions required when potential Hy's Law criteria are met before and after starting IP](#).

If No: follow the process described in [Potential Hy's Law criteria met](#) of this Appendix.

If Yes:

Determine if there has been a significant change in the subject's condition compared with when PHL criteria were previously met

If there is no significant change, no action is required

If there is a significant change:

A 'significant' change in the subject's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST, or TBL) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the investigator; this may be in consultation with the medical monitor assigned to the project if there is any uncertainty.





























































## APPENDIX K, SPIROMETRY ASSESSMENT CRITERIA

### Acceptable Versus Usable Tests

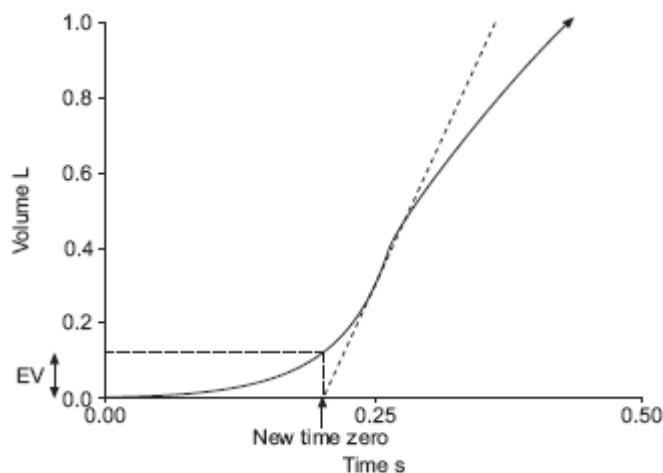
*Acceptable* Tests must meet the following Criteria:

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  $\geq 1$  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 PEF rate, to determine the new "time zero". Forced vital capacity -4.291 L; EV – 0.123 L (2.9% FVC): back extrapolation line through peak expiratory flow.

### **Between-Maneuver 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<sub>1</sub> 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<sub>1</sub> 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<sub>1</sub> 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<sub>1</sub> 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).

## APPENDIX L, COVID-19 EMERGENCY MEASURES PERMITTED TO ENSURE SUBJECT SAFETY

The following activities were implemented in order to ensure subject safety during the global lockdown due to the COVID-19 pandemic. While global lockdown restrictions are currently being released, the pandemic continues and in certain territories cases remain on the rise.

Therefore, necessary emergency measures accepted during the initial global lockdown will be permitted to protect subject safety in the event that infection rates return to levels requiring the return of government or local restrictions on movement of people and goods.

Any procedure performed outside the protocol specified requirements will be documented as a protocol deviation.

### **Visit Management:**

<b>Delayed Visits</b>	<ul style="list-style-type: none"><li>Out of window visits should be considered if it is necessary to safeguard the health of the subject and site staff or enables an on-site subject visit.</li><li>If a return to lockdown is announced or the site is on lockdown and cannot process a visit, if possible, visits should be rescheduled to earlier/later as required to safeguard subjects and site staff.</li><li>Randomization: If a subject is in screening and cannot complete the randomisation visit within 28 days due to local COVID-19 lockdown restrictions, the screening period may be extended to a maximum of 9 weeks. In the event of an extension to the screening period &gt;28 days due to COVID, the following safety measurements should be repeated in advance of randomisation: safety laboratory assessments, ECG, vital signs, concomitant medications, and medical/surgical history.</li><li><b>Visit 6/Week 24:</b> All efforts should be made to complete the associated assessments in the clinic, even if this is visit is delayed. If necessary, while waiting for the time to complete this visit, an unscheduled call and drug dispensing should be done to ensure the subject has sufficient IP during this time.</li></ul>
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<b>Remote Visits</b>	<ul style="list-style-type: none"><li>Where subjects have COVID-19 infection or infectious, the site is on lock down, local restrictions prohibit attendance, or similar, a telephone visit should be completed. All assessments performed should be documented in the same way they would if the visit would have happened on-site.</li><li>Before performance of a remote visit, verbal consent must be obtained and documented in the subject's medical notes to ensure that the subject understands the implications of continuing in the study when face to face visits are temporarily not possible due to COVID 19 restrictions. Where possible, the Principal Investigator should ask the subject to confirm their agreement in writing either by email or via a letter. Where multiple in-clinic visits will be missed, written consent of the subject will be required.</li><li>If a remote visit is completed and it is considered appropriate and safe to continue study drug, this could be dispatched direct to the subject by courier.</li><li>Randomization visits cannot be conducted remotely and therefore subjects in screening who do not wish to attend an on-site visit should be screen-failed as 'withdrawal of consent'.</li></ul>
<b>Subject Discontinuation</b>	<ul style="list-style-type: none"><li>Where repeated visits are likely to be missed, the site should discuss with the subject and consider ongoing treatment options. Where a subject does not wish to attend further clinic visits, a PDV visit should be scheduled.</li></ul>
<b>Shipment of Drug from Site to Subjects</b>	<ul style="list-style-type: none"><li>Subjects should provide verbal consent via a telephone call to use their personal details to complete the site to subject shipment request. Consent must be documented in the subject medical records and preferably confirmed in writing via an email or other written means (eg, via post) via a phone call initially and followed up by written consent at the earliest possibility.</li></ul>
<b>Safety Labs</b>	<ul style="list-style-type: none"><li>Where central analysis is not possible, local testing is permitted. Lab normal ranges would need to be made available.</li></ul>

	<ul style="list-style-type: none"><li>• In the event that routine safety lab tests are missed due to temporary inability of subject to get to site due to COVID-19, an unscheduled lab should be done at their next clinic visit if possible.</li></ul>
<b>Spirometry</b>	<ul style="list-style-type: none"><li>• The investigator should request confirmation from the subjects to confirm that they are not aware of having been exposed to COVID-19 that they are not currently infected or infectious, and should exercise their medical judgement with respect to this information prior to conducting spirometry assessments. Sites should continue to follow hygiene and cleaning guidance within the manuals to minimize possible cross-contamination.</li></ul>
<b>Subjects with Confirmed COVID-19 Infection</b>	<ul style="list-style-type: none"><li>• If a subject has confirmed COVID-19 this is to be reported as an AE/SAE, but is not per se a reason to withdraw the subject.</li><li>• The investigator should determine whether the subject's IP should continue, be interrupted, or stopped in accordance with the Clinical Study Protocol.</li><li>• The investigator should continue to reassess the benefit-risk of continued study involvement for a study subject infected with COVID-19. In-clinic visits for this subject should only re-commence once the infection has resolved and the subject is no longer considered to be infectious.</li><li>• For new subjects previously identified as COVID-19 positive, a re-test must be performed after resolution of symptoms (if present). The subject can only be considered for enrollment 4 weeks after having a negative result.</li></ul>