Bond Avillion 2 Development LP

Clinical Study Protocol

Drug Substance	Budesonide/Albuterol Sulfate (BDA)
Study Code	AV003
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Version	Version 4.0, Final
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A Long-term, Randomized, Double-blind, Multicenter, Parallel-group, Phase III Study Evaluating the Efficacy and Safety of PT027 Compared to PT007 Administered as Needed in Response to Symptoms in Symptomatic Adults and Children 4 Years of Age or Older with Asthma (MANDALA)

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

VERSION HISTORY

Version 4.0, 08 April 2021
Global amendment to clarify analysis of all efficacy parameters within the primary database lock and follow-up of remaining pediatric patients exposure up-to 24 weeks for safety only within the final database lock. Removal of reversibility requirement at Visit 1 for 4 to 11 year olds. Adjustment to presentation of Inhaled Corticosteroids and administrative changes.
Version 3.0, 21 July 2020
Global amendment to incorporate country-specific changes, to update a secondary endpoint to "systemic corticosteroids", to add additional exploratory endpoints, to provide clarifications for statistical analyses, to adjust inclusion criterion for pediatric subjects, and

to incorporate temporary measures taken to protect subject and site staff safety during the COVID-19 pandemic (Appendix N). Details are provided in the Summary of Changes.
Version 2.0, 29 July 2019
Global amendment to incorporate country-specific changes and provide necessary clarifications and updates to the study, including the addition of the de facto estimand as a treatment policy strategy defined in the draft International Conference on Harmonization E9 addendum, and updates to the current versions of the Asthma Quality of Life +12 Questionnaire, Pediatric Asthma Quality of Life Questionnaire, and Asthma Control Questionnaire-5 and -7. Details are provided in the Summary of Changes.
Version 1.0, 11 October 2018
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.

This protocol contains trade secrets and confidential commercial information, disclosure of which is prohibited without providing advance notice to Bond Avillion 2 Development LP and opportunity to object.

CLINICAL STUDY PROTOCOL SYNOPSIS

A Long-term, Randomized, Double-blind, Multicenter, Parallel-group, Phase III Study Evaluating the Efficacy and Safety of PT027 Compared to PT007 Administered as Needed in Response to Symptoms in Symptomatic Adults and Children 4 Years of Age or Older with Asthma (MANDALA)

International coordinating investigators

[redacted]

Study site(s) and number of subjects planned

Approximately 380 study sites are anticipated to randomize approximately 3000 adult and adolescent subjects with moderate to severe asthma to 1 of 3 treatment groups (approximately 1000 subjects per group). In addition, up to100 subjects in the 4 to 11-year age group with moderate to severe asthma will be randomized with approximately 50 subjects randomized to the albuterol sulfate (here after referred to as albuterol) metered-dose inhaler (AS MDI) and 50 subjects randomized to the low dose budesonide/albuterol metered-dose inhaler (BDA MDI) groups only. Approximately 6000 subjects will need to be screened, assuming an estimated screen failure rate of 30% to 50%.

This Phase III study is planned to be conducted globally.

Study design

This is a randomized, double-blind, multicenter, parallel-group, variable-length, event-driven study with a treatment period of at least 24 weeks for each subject. The purpose of this study is to compare 2 doses of BDA MDI with AS MDI on the time to first severe asthma exacerbation in adult, adolescent, and pediatric subjects with moderate to severe asthma as defined by Global Initiative for Asthma (GINA). Subjects will administer randomized investigational product (IP) as needed (prn) in response to asthma symptoms.

Subjects meeting all entry criteria at the screening visit (Visit 1/1a, as applicable) will enter a 14-to 28-day screening period. (Subjects may consent for the study in advance of Visit 1 and if required, request for medical records to support evidence of prior exacerbations without triggering the 28-day screening period.) If a severe exacerbation event occurs during the screening period, the screening period may be extended to a maximum of 9 weeks. Screened subjects will continue to take their regular asthma maintenance therapy throughout the study (from Visit 1 through the treatment period). At Visit 1, eligible subjects will discontinue their usual prn inhaled product used as-needed for symptom relief and begin Sponsor-provided Ventolin to be used prn in response to symptoms or prior to exercise during the screening period only. Subjects will be asked to turn in their own inhaled reliever products to the investigational sites for storage until the individual subject last study visit. Eligible subjects will be randomized at Visit 2.

Objectives

Primary Objective:	**Primary Endpoint:**
To evaluate the efficacy of budesonide/albuterol metered-dose inhaler 80/180 µg and 160/180 µg administered prn in response to symptoms compared to albuterol metered-dose inhaler 180 µg	*Time to first severe asthma exacerbation*
Secondary Objective:	**Secondary Endpoint:**
To characterize the effect of budesonide/albuterol metered-dose inhaler 80/180 µg and 160/180 µg administered prn in response to symptoms compared to albuterol metered-dose inhaler 180 µg	• *Severe exacerbation rate (annualized)* • *Total systemic corticosteroid exposure over the treatment period* • *Asthma Control Questionnaire -5 (ACQ-5) change from baseline and responder analysis at Week 24* • *Asthma Quality of Life Questionnaire for 12 years and older (AQLQ+12)/Pediatric Asthma Quality of Life Questionnaire (PAQLQ) change from baseline and responder analysis at Week 24*
Safety Objective:	**Safety Endpoints:**

To evaluate the safety and tolerability of budesonide/ albuterol metered-dose inhaler 80/180 µg and 160/180 µg administered prn in response to symptoms compared to albuterol metered-dose inhaler 180 µg	• *Adverse events/serious adverse events* • *Vital signs* • *Clinical chemistry and hematology parameters* • *Electrocardiogram*
Exploratory Objective:	**Exploratory Endpoints:**
To characterize the effect of budesonide/albuterol metered-dose inhaler 80/180 µg and 160/180 µg administered prn in response to symptoms compared to albuterol metered-dose inhaler 180 µg	• *Asthma Control Questionnaire -5 change from baseline and responder analysis at Week 24* • *Asthma Control Questionnaire-5 change from baseline and responder (3-factor) analysis at Week 12 and Week 24* • *Asthma Quality of Life Questionnaire for 12 years and older/Pediatric Asthma Quality of Life Questionnaire change from baseline and responder analysis at Week 12* • *Deteriorations of asthma (annualized rate and time to first)* • *Change from baseline in prebronchodilator forced expiratory volume in 1 second at Week 12 and Week 24* • *Morning and evening peak expiratory flow* • *Use of investigational product (reliever therapy)* • *Asthma daytime/night-time symptoms* *Time to treatment discontinuation or change in maintenance therapy* • *Asthma Control Test (ACT) or Childhood Asthma Control Test (C ACT) change from baseline and responder analysis at Week 24* • *Percentage of "as needed"-free days* • *Percentage of symptom-free days* • *Percentage of asthma control days* • *Inhaled corticosteroid exposure over the treatment period*

Target subject population

The study will enroll subjects ≥4 years of age in all countries with the exception of the following:

- In Serbia, only subjects ≥12 years of age will be enrolled.
- In Germany, Slovakia and Ukraine, only subjects ≥18 years of age will be enrolled.

Age-specific assessments will be implemented where relevant for the population enrolled.

Male and female subjects ≥4 years of age with a diagnosis of moderate to severe asthma as defined by GINA criteria and having at least 1 severe asthma exacerbation within the previous 12 months prior to screening (Visit 1/1a, as applicable) who have been taking a regular schedule of asthma maintenance therapies for 3 months with stable dosing for at least the last 4 weeks prior to Visit 1 may be eligible for this study.

Duration of study/treatment

The study will consist of 3 periods:

- Screening period (14 to 28 days), except where a severe exacerbation event occurs and the screening period may be extended to a maximum of 9 weeks. (Subjects may consent for the study in advance of Visit 1 and if required, request for medical records to support evidence of prior exacerbations without triggering the 28-day screening period.)
- Treatment period of at least 24 weeks. The study treatment period will continue (extension phase) until the required 570 first severe exacerbation events, as defined per protocol, have been reached and the last adult subject has completed 24 weeks of treatment, which will be defined as the primary completion date (PCD). Paediatric subjects will continue until 24 weeks of treatment have been reached for each paediatric patient, defined as the final completion date.
    - In the event 570 events are captured **before** the last adult patient has had 24 weeks of treatment, all subjects on treatment for ≥24 weeks will have their end-of-study (EOS) visit at their next scheduled clinic visit. All subjects on treatment for < 24 weeks will continue until 24 weeks at which point they will complete their EOS visit
    - In the event 570 events will be captured **after** the last subject has had 24 weeks of treatment, each subject will return to complete the EOS visit at their next scheduled clinic visit
- Safety follow-up period: where a safety follow-up telephone contact will occur 2 weeks (±4 days) after EOS or premature discontinuation visit (PDV), whichever occurs first.

The study will be completed when the last subject has completed his or her post-study follow-up telephone contact. Subjects who discontinue IP will complete a PDV, and adverse events (AEs)/serious adverse events (SAEs) will be followed up if medically indicated.

Estimated date of first subject enrolled: Q4 2018.

Estimated date of last subject completed: Q1 2022.

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 (HFA) propellant. The co-suspension formulation ensures that subjects receive a consistent delivery of the drug from each actuation of the MDI.

Investigational product will be used in response to asthma symptoms as they would normally take their reliever medication. If subjects take IP in advance of exercise for the prevention of exercise induced symptoms, IP usage in relation to exercise will be captured within the eDiary. No other reliever products will be used during the treatment period.

At randomization (Visit 2), adolescents and adults (aged ≥12 years) who meet the eligibility criteria will be randomly assigned to 1 of the following 3 treatment groups in a 1:1:1 ratio as reliever therapy on top of usual care. Children aged 4 to 11 years will be randomized in a 1:1 ratio only to the lower BDA MDI dosage or AS MDI:

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

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

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

In order to ensure safety and monitor daily treatment status, all subjects will be provided with an electronic diary (eDiary: AM3 device). The eDiary transfers data every 24 hours across a range of asthma symptom scores and drug usage (ie, number of puffs inhaled) to assess a subject's asthma status. Subjects will use the eDiary for reporting daily use of IP and any symptoms. If symptoms and/or daily dosage exceed a protocol-specified threshold, the eDiary will generate an alert to the subject and the investigational site. In this way, daily IP usage will be monitored closely by the investigators and medical monitors to assess any worsening of subject status. Action will be taken where clinically indicated.

Statistical methods

Sample size calculation

A sample size of 1000 adult and adolescent subjects per treatment group and observation of the 570 first severe exacerbation events provides this study with 87% power to observe a 25% reduction in the risk of severe exacerbation with at least 1 dose of BDA MDI versus AS MDI assuming the Hochberg procedure (Hochberg 1988) for multiple testing and a 2-sided significance level of 5%.

In addition, up to 100 subjects in the 4 to 11-year age group with moderate to severe asthma will be randomized with approximately 50 subjects randomized to the AS MDI group and 50 subjects randomized to the low dose BDA MDI group only.

Primary efficacy analysis

The primary variable, time to first severe asthma exacerbation, will be analyzed using a Cox proportional hazards regression model to compare treatment arms. The model will be adjusted for the randomization stratification factors (age group [≥ 4 to 11, ≥12 to 17, ≥18]); region (North America, Western Europe and South Africa [Region 1] and rest of world [Region 2]); and number of prior severe exacerbations (1, >1) in the 12 months prior to screening (Visit 1) plus any severe exacerbation event experienced during the screening period and key covariates of interest with more detail to be provided in the statistical analysis plan (SAP). The 2 primary treatment comparisons will be 2-sided with the 5% overall alpha level controlled using the Hochberg procedure. The primary efficacy analysis will include all data up to the primary outcome database lock (pDBL), scheduled to occur following the PCD and once all randomized adults have attended their EOS visit.

Secondary efficacy analyses

Annualized severe asthma exacerbation rate will be analyzed using negative binomial regression to compare treatment groups. The response variable in the model will be the number of severe asthma exacerbations. The model will adjust for (age group [≥ 4 to 11, ≥12 to 17, ≥18]); region (North America, Western Europe and South Africa [Region 1] and rest of world [Region 2]); and number of prior severe exacerbations (1, >1) in the 12 months prior to screening (Visit 1) plus any severe exacerbation event experienced during the screening period and key covariates of interest with more detail to be provided in the SAP.

Responder variables for Asthma Control Questionnaire-5 (ACQ-5) and Asthma Quality of Life Questionnaire for 12 years and older (AQLQ+12)/ Pediatric Asthma Quality of Life Questionnaire (PAQLQ) at Week 24 will each be analyzed using a logistic regression model to compare treatment groups. The model will be adjusted for the randomization stratification factors and key covariates as described above.

The total systemic corticosteroid (SCS) exposure as total annualized dose of SCS (mg/year) will be presented descriptively by treatment. A comparison in total annualized SCS dose between BDA MDI 80/180 vs AS MDI 180 and BDA MDI 160/180 vs AS MDI 180 will be analyzed using a Wilcoxon rank sum test and associated p-values will be presented along with the descriptive summary.

Additionally, total SCS exposure will be summarized descriptively as the total number of days with SCS treatment due to asthma for all subjects. A similar descriptive summary will be completed for all subjects who administered at least 1 dose of SCS during the study.

If both doses of BDA MDI are statistically superior to AS MDI for the primary endpoint, the full alpha will be available to pass to the family of secondary endpoints.

The type-I error will be controlled for secondary endpoint treatment comparisons via a hierarchical testing procedure. The secondary objectives will be tested under the efficacy estimand in the following sequential order, grouped by secondary endpoint:

Annualized severe exacerbation rate

1. BDA MDI 160/180 µg versus AS MDI 180 µg
2. BDA MDI 80/180 µg versus AS MDI 180 µg

Total annualized dose of systemic corticosteroid

3. BDA MDI 160/180 µg versus AS MDI 180 µg
4. BDA MDI 80/180 µg versus AS MDI 180 µg

Asthma Control Questionnaire-5 (ACQ-5) change from baseline responder analysis at Week 24

5. BDA MDI 160/180 µg versus AS MDI 180 µg
6. BDA MDI 80/180 µg versus AS MDI 180 µg

Asthma Quality of Life Questionnaire for 12 years and older (AQLQ+12) change from baseline responder analysis at Week 24

7. BDA MDI 160/180 µg versus AS MDI 180 µg
8. BDA MDI 80/180 µg versus AS MDI 180 µg

Statistical tests for the secondary analyses will be conducted at the 5% level of significance (2-sided). Inference for a test in the defined order is dependent on statistical significance having been achieved in the preceding tests, if this is not achieved then nominal p-values will be provided. As per the primary analysis, comparisons of BDA MDI 160/180 versus AS MDI will exclude the pediatric population, whilst comparisons of BDA 80/180 versus AS MDI will include all ages.

Statistical significance can only be claimed on the key secondary endpoints if a statistically significant treatment effect is observed on both BDA MDI 160/180 µg and BDA MDI 80/180 µg versus AS MDI for the primary endpoint of time to first severe exacerbation.The secondary efficacy analyses will include all data up to the pDBL.

Estimands

Three 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 usage and assuming that maintenance therapy is not changed. 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 assuming that maintenance therapy is not changed. For this estimand, discontinuation of randomized treatment for tolerability or change in maintenance therapy for lack of asthma control is considered a negative outcome. This estimand is a mixture of composite and hypothetical strategies as defined in the draft ICH E9 addendum.

The third estimand of interest is the effectiveness estimand which is a combination of the hypothetical and treatment policy strategies as defined in the draft ICH E9 addendum. The strategy is hypothetical in that the treatment effect will be estimated without collecting data post the intercurrent event of discontinuation from randomized treatment. However, the strategy is consistent with the treatment policy strategy in that the treatment effect is estimated irrespective of the occurrence of the intercurrent event of a change in the maintenance therapy.

The fourth estimand of interest is the de facto estimand, defined as the effect of a treatment policy regardless of occurrence of intercurrent event; changes in maintenance therapy or premature discontinuation of randomized treatment. This estimand is considered a treatment policy strategy 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
ACT	Asthma Control Test
AE	adverse event
AIT	allergy immunotherapy
ALT	alanine aminotransferase (or alanine transaminase)
AQLQ+12	Asthma Quality of Life Questionnaire for 12 years and older
AS MDI (PT007)	albuterol sulfate metered-dose inhaler
AST	aspartate aminotransferase
BDA	budesonide/albuterol
BDA MDI (PT027)	budesonide/albuterol metered-dose inhaler
β-hCG	β-human chorionic gonadotropin
BMI	body mass index
C ACT	Childhood Asthma Control Test
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
ECG	electrocardiogram
eCRF	electronic case report form
EOS	end-of-study
ePRO	electronic patient reported outcome
FAS	full analysis set
FEV_1	forced expiratory volume in 1 second
FVC	forced vital capacity
GCP	Good Clinical Practice
GINA	Global Initiative for Asthma
GMP	Good Manufacturing Practice
HFA	hydrofluoroalkane
HL	Hy's Law
ICF	informed consent form
ICH	International Conference on Harmonization
ICS	inhaled corticosteroid
IDMC	Independent Data Monitoring Committee

Abbreviation or special term	Explanation
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 β2-agonist
LAMA	long-acting muscarinic antagonist
LTRA	leukotriene receptor antagonist
MDI	metered-dose inhaler
med	medium
MID	minimal important difference
MMRM	mixed model repeated measures
OCS	oral corticosteroids
PAQLQ	Pediatric Asthma Quality of Life Questionnaire
PCD	primary completion date
PDV	premature discontinuation visit
PEF	peak expiratory flow
PFT	pulmonary function test
PHL	Potential Hy's Law
Prn	as needed
SABA	short/rapid-acting β2-adrenoreceptor agonist
SAMA	short-acting muscarinic antagonist
SAE	serious adverse events
SAP	Statistical Analysis Plan
SCS	systemic corticosteroids
SMART	Symbicort is approved for maintenance and reliever therapy
TBL	total bilirubin
TC	telephone call
ULN	upper limit of normal
WBDC	Web Based Data Capture

1 INTRODUCTION

1.1 Background and rationale for conducting this study

Bond Avillion 2 Development LP (Sponsor) is developing budesonide/albuterol sulfate (PT027; hereafter referred to as budesonide and albuterol metered-dose inhaler [BDA MDI] and albuterol sulfate (hereafter referred to as albuterol [AS MDI]) pressurized inhalation suspension products in adults and children 4 years of age or older with asthma. Please refer to the current Investigator Brochure (2019) for additional information.

Albuterol is a short/rapid-acting β2-adrenoreceptor agonist (SABA), inducing airway smooth muscle relaxation and reducing or preventing bronchoconstriction. Albuterol is approved in many countries in multiple formulations for treatment or prevention of bronchoconstriction, and is also known under the generic name of salbutamol. In clinical practice, albuterol is used as an as needed (prn) reliever therapy (Global Initiative for Asthma [GINA] 2018).

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 β2-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 FACET study (Tattersfield 1999) revealed that asthma symptoms and increased reliever therapy use were noted over several days before the start of an asthma exacerbation. Combining the use of a SABA (albuterol) with budesonide in the proposed budesonide and albuterol metered-dose inhaler (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 moderate or severe asthma. Studies of budesonide and a rapid-acting LABA (formoterol) as reliever 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 significantly reduced severe exacerbation risk in pediatric patients (O'Byrne 2007).

In some markets, Symbicort Turbuhaler (hereafter referred to as Symbicort) is approved for maintenance and reliever therapy (SMART). 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. It is important to note that the prn administration of ICS in this treatment regimen is not expected to significantly increase overall steroid load (mostly because of a reduction in the number of severe exacerbation episodes, resulting in fewer patients requiring systemic corticosteroid (SCS) doses as acute treatment). BDA MDI is proposed to be available prn for symptom control to all patients with asthma, regardless of maintenance therapy.

When patients use the BDA MDI products as needed in response to asthma symptoms, it is expected that their risk of experiencing an asthma exacerbation will be lower than in subjects using albuterol alone.

1.2 Rationale for study design, doses, and control groups

The study will compare BDA MDI at 2 different doses with AS MDI in adults and children 4 years of age or older with moderate to severe asthma.

The clinical standard of care for subjects with moderate to severe asthma is a medium-to-high-dose ICS or low-to-high-dose ICS in combination with LABA, with a SABA such as albuterol to use prn in response to symptoms (ie, reliever therapy). When subjects require frequent reliever therapy, additional anti-inflammatory medication may provide benefit by early reaction to increased asthma symptoms that are reflective of an incipient severe exacerbation. BDA MDI would prevent or reduce bronchoconstriction and provide additional anti-inflammatory medication when needed at the time of symptoms. Safety and efficacy of BDA MDI will be compared with AS MDI because albuterol is the standard of care reliever therapy in response to symptoms.

The objective of this randomized, double-blind, multicenter, parallel-group study is to evaluate, within a typical design for the development of new asthma therapies, the benefit of BDA MDI administered prn in response to symptoms in adults and children 4 years of age or older with moderate to severe asthma receiving medium-to-high-dose ICS or low-to-high-dose ICS in combination with LABA, with or without an additional controller therapy (leukotriene receptor antagonist [LTRA], long-acting muscarinic antagonist [LAMA] or theophylline).

The primary endpoint is the time to first severe asthma exacerbation, and secondary endpoints include the annualized severe exacerbation rate and asthma symptom control as measured by Asthma Control Questionnaire-5 (ACQ-5).

The treatment duration for the study will be at least 24 weeks for each subject to support the subject exposure data. The study treatment period will continue (extension phase) until the required 570 first severe exacerbation events, as defined per protocol, have been reached and the last adult subject has completed 24 weeks of treatment, which will be defined as the primary

completion date (PCD). Not all pediatric subjects will have 24 weeks of treatment at time of PCD.

Two dosage levels of BDA MDI, 80/180 µg and 160/180 µg (given as 40/90 µg and 80/90 µg, respectively, per actuation), 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 µg, or AS MDI (90 µg per actuation).

BDA MDI and AS MDI are IPs. The dose chosen for AS MDI (albuterol) is in line with the approved label for Proventil® with which AS MDI has been demonstrated to be equivalent in the D6930C00002 cumulative dose study and D6930C00001 dose finding study. Budesonide doses were assessed in the dose-ranging Study PT008001. The budesonide doses chosen for BDA MDI will allow assessment of the potential to provide therapeutic benefit in practise while avoiding excessive steroid dosing within the applicable age ranges.

1.3 Benefit/risk and ethical assessment

BDA MDI may provide benefit in subjects in terms of potential reduction in the risk of asthma exacerbation and improvement in the control of asthma symptoms and lung function beyond what is typically seen with albuterol alone (Rabe 2006; O'Byrne 2005; O'Byrne 2007). In addition, the Sponsor believes that the administration of BDA MDI to subjects with asthma will achieve the rapid improvement in lung function from albuterol, the anti-inflammatory effect attributable to budesonide, and potentially additional benefits attributable to the combination of albuterol and budesonide.

The risk of adrenal suppression, particularly during a period of stress (infection, surgery, etc) has been noted in the Canadian product monograph for Pulmicort Turbuhaler®. The Sponsor considers it is relevant to monitor steroid effects in subjects. As such, routine tests of adrenal cortisol function have been built into this study to monitor for adrenal suppression risk: morning serum cortisol will be assessed.

Further, height (cm) measurements will be assessed more frequently in subjects ≤18 years of age, to monitor for any possible effects on growth.

COVID-19

Recent information from the American Academy of Allery Asthma and Immunology (AAAAI) published on their website (https://www.aaaai.org/conditions-and-treatments/library/asthma-library/covid-asthma) in [redacted] indicates that currently there is no evidence of increased infection rates in patients with asthma and that best practice is to ensure that a patient's asthma is controlled. In the MANDALA study, subjects are maintained on a stable asthma treatment regimen and closely monitored while staying in the study. The sponsor believes that the benefit risk assessment for trial participants to enroll and continue in the study is positive.

1.4 Study design

This is a randomized, double-blind, multicenter, parallel-group, variable-length, event-driven study with a treatment period of at least 24 weeks for each subject. The purpose of this study is to compare 2 doses of BDA MDI with AS MDI on the time to first severe asthma exacerbation (Section 5.1.1) in adult, adolescent, and pediatric subjects with moderate to severe asthma as defined by GINA. Subjects will administer randomized investigational product (IP) prn in response to asthma symptoms. See Figure 1 for a graphical presentation of the study schema and Table 1 for a list of study assessments.

Subjects attending screening (Visit 1) will enter a 14- to 28-day screening and run-in period. The screening period may be extended to a maximum of 9 weeks for subjects who have a severe asthma exacerbation after Visit 1. Subjects may consent for the study in advance of Visit 1 and if required, request for medical records to support evidence of prior exacerbations without triggering the 28-day screening period. Screened subjects will continue to take their regular asthma maintenance therapy throughout the study (from screening [Visit 1/1a, as applicable]) through the treatment period). At Visit 1, eligible subjects will discontinue their usual prn inhaled product used for symptom relief and begin Sponsor-provided Ventolin to be used prn in response to symptoms or prior to exercise during the screening period only. Subjects will be asked to turn in their own inhaled reliever products to the investigational sites for storage until the individual subject last study visit. Eligible subjects will be randomized at Visit 2.

At randomization (Visit 2), adult and adolescent subjects (aged ≥12 years) who meet the eligibility criteria will be randomly assigned to 1 of the following 3 treatment groups in a 1:1:1 ratio as reliever therapy on top of usual care. Children aged 4 to 11 years will be randomized in a 1:1 ratio only to the lower BDA MDI dosage or AS MDI:

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

The maximum daily dosage of IP should not exceed 12 puffs per day. Subjects will be recommended not to take more than 8 puffs per day and advised to contact the investigator if their symptoms necessitate more than 8 puffs in a day.

The maximum daily dosage is 12 puffs (BDA MDI 480/1080 µg or 960/1080 µg, or AS MDI 1080 µg). In order to ensure safety and monitor daily treatment status, all subjects will be provided with an electronic diary (eDiary: AM3 device). The eDiary transfers data every 24 hours across a range of asthma symptom scores and drug usage (ie, number of puffs inhaled) to assess a subject's asthma status. Subjects will use the eDiary for reporting daily use of IP and daily symptoms. If symptoms and/or daily dosage exceed a protocol-specified threshold, the eDiary will generate an alert to the subject and the investigational site. In this way, daily IP

usage will be monitored closely by the investigators and medical monitors to assess any worsening of subject status. Action will be taken where clinically indicated.

The study will consist of 3 periods:

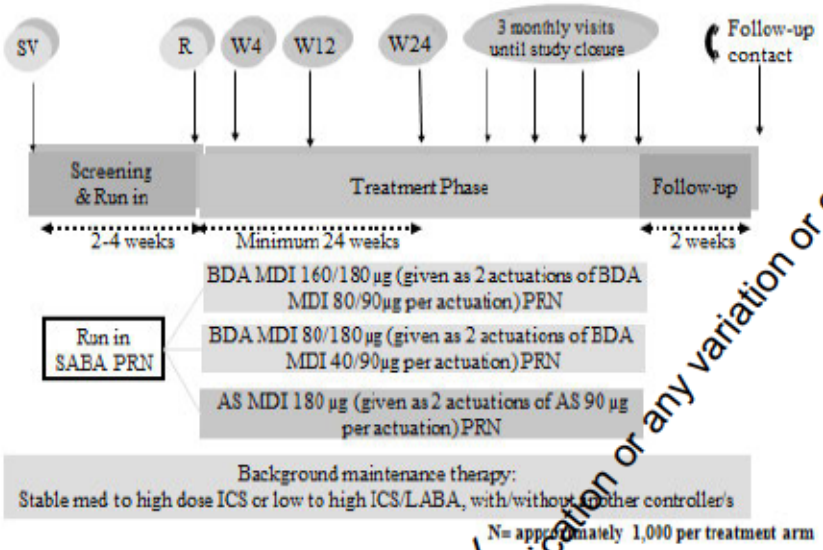
- Screening period (14 to 28 days) except where a severe exacerbation event occurs during the screening period, and this may be extended to a maximum of 9 weeks. (Subjects may consent for the study in advance of Visit 1 and if required, request for medical records to support evidence of prior exacerbations without triggering the 28-day screening period.)
- Treatment period of at least 24 weeks. The study treatment period will continue (extension phase) until the required 570 first severe exacerbation events, as defined per protocol, have been reached and the last adult subject has completed 24 weeks of treatment, which will be defined as the PCD. Not all pediatric subjects will have 24 weeks of treatment at time of PCD.

  In the event 570 events will be captured **before** the last subject has had 24 weeks of treatment, all subjects on treatment for ≥24 weeks will have their end-of-study (EOS) visit at their next scheduled clinic visit. All subjects on treatment for <24 weeks will continue until 24 weeks at which point they will complete their EOS visit

  In the event 570 events will be captured **after** the last subject has had 24 weeks of treatment, each subject will return to complete the EOS visit at their next scheduled clinic visit
- Safety follow-up period: where a safety follow-up telephone contact will occur 2 weeks (±4 days) after the subject's EOS visit or premature discontinuation visit (PDV), whichever occurs first

The study will be completed when the last subject has completed his/her post-study follow-up telephone contact. Subjects who discontinue IP will complete a PDV, and adverse events (AEs)/serious adverse events (SAEs) will be followed up if medically indicated.

Figure 1 Study design



Abbreviations: AS MDI=albuterol metered-dose inhaler; BDA MDI=budesonide/albuterol metered-dose inhaler; ICS=inhaled corticosteroid; LABA=long-acting β2-agonist; N=number; PRN=as needed; R=randomization; SABA=short-acting β2-adrenoreceptor agonist; SV=screening visit; W=week.

1.5 Study governance and oversight

1.5.1 Independent data monitoring committee

An independent data monitoring committee (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.

1.5.2 Adjudication committee

An independent adjudication committee will adjudicate centrally and in a blinded fashion after medical monitoring review, cases where a reported death, emergency room visit, urgent care visit and/or hospitalization, change in medication and/or other sign/symptom is indicative of a worsening of asthma but has not been recorded as such in the electronic case report form (eCRF). For any event that qualifies for adjudication, study sites will be asked to provide de-identified (anonymized) clinical documentation such as discharge summaries, to support the external event adjudication. The tasks and responsibilities of the adjudication committee will be filed in a charter before initiation of the study and will contain written operating procedures. The adjudication committee will maintain the adjudication results in writing and will enter details of events not recorded within the eCRF into an adjudication platform. This data will be reported alongside the eCRF data in the Clinical Study Report.

2 STUDY OBJECTIVES

2.1 Primary objective

Primary Objective:	Primary endpoint:
To evaluate the efficacy of budesonide/albuterol metered-dose inhaler 80/180 µg and 160/180 µg administered prn in response to symptoms compared to albuterol metered-dose inhaler 180 µg	*Time to first severe asthma exacerbation*

2.2 Secondary objective

Secondary Objective:	Secondary endpoint:
To characterize the effect of budesonide/albuterol metered-dose inhaler 80/180 µg and 160/180 µg administered prn in response to symptoms compared to albuterol metered-dose inhaler 180 µg	• *Severe exacerbation rate (annualized)* • *Total systemic corticosteroid exposure over the treatment period* • *Asthma Control Questionnaire-5 (ACQ-5) change from baseline and responder analysis at Week 24* • *Asthma Quality of Life Questionnaire for 12 years and older (AQLQ+12)/Pediatric Asthma Quality of Life Questionnaire (PAQLQ) change from baseline and responder analysis at Week 24*

2.3 Safety objective

Safety Objective:	Safety Endpoints:
To evaluate the safety and tolerability of budesonide/ albuterol metered-dose inhaler 80/180 µg and 160/180 µg administered prn in response to symptoms compared to albuterol metered-dose inhaler 180 µg	• *Adverse events/serious adverse events* • *Vital signs* • *Clinical chemistry and hematology parameters* • *Electrocardiogram*

2.4 Exploratory objective

Other Objective:	Exploratory Endpoints:
To characterize the effect of budesonide/albuterol metered-dose inhaler 80/180 µg and 160/180 µg administered prn in response to symptoms compared to albuterol metered-dose inhaler 180 µg	• *Asthma Control Questionnaire-5 change from baseline and responder analysis at Week 12* • *Asthma Control Questionnaire-5 change from baseline and responder (3-factor) analysis at Week 12 and Week 24* • *Asthma Quality of Life Questionnaire for 12 years and older/Pediatric Asthma Quality of Life Questionnaire change from baseline and responder analysis at Week 12* • *Deteriorations of asthma (annualized rate and time to first)* • *Change from baseline in prebronchodilator forced expiratory volume in 1 second at Week 12 and Week 24* • *Morning and evening peak expiratory flow* • *Use of investigational product (reliever therapy)* • *Asthma daytime/night-time symptoms* • *Time to treatment discontinuation or change in maintenance therapy* • *Asthma Control Test (ACT) or Childhood Asthma Control Test (C ACT) change from baseline and responder analysis at Week 24* • *Percentage of "as needed"-free days* • *Percentage of symptom-free days* • *Percentage of asthma control days* • *Inhaled corticosteroid exposure over the treatment period*

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 waivers will be granted from the Sponsor for any subject not meeting inclusion or exclusion criteria.

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 ≥4 years at the time of informed consent in all countries with the exception of the following: in Serbia, only subjects ≥12 years old will be enrolled; in Germany, Slovakia, and Ukraine, only subjects ≥18 years old will be enrolled.

3 Diagnosis of asthma as defined by GINA criteria at least 1 year before Visit 1

4 Receiving 1 of the following scheduled asthma maintenance therapies for 3 months with stable dosing for at least the last 4 weeks before Visit 1:

(a) Medium-to--high-dose ICS (Appendix C; GINA 2018)

(b) Medium-to--high-dose ICS and 1 additional maintenance therapy from the following: LTRA, LAMA, or theophylline

(c) Low-to-high-dose ICS in combination with LABA with or without 1 additional maintenance therapy from the following: LTRA, LAMA, or theophylline

i. Up to 20% of all randomized subjects (on ICS alone or ICS in combination with LABA) will be permitted to have an additional maintenance medication (theophylline, leukotriene receptor antagonist, or LAMA).

The below 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 ICS or ICS/LABA inhaler (or names and doses, if used as separate inhalers) and LTRA, LAMA, or theophylline, if applicable, and/or

- Evidence of prescriptions for an ICS, ICS/LABA, and LTRA, LAMA, or theophylline if applicable, medications that demonstrate coverage for the duration specified in inclusion criteria

5 Prebronchodilator forced expiratory volume in 1 second (FEV_1) of ≥40 to <90% predicted normal value for adults, and ≥60% predicted normal value for subjects aged 4 to 17 years after withholding the medications specified in Table 4. If FEV_1 values are not within the permitted range at Visit 1, 1 re-test must be performed at Visit 1a before advancing to Visit 2 or confirming screen failure. Note: Subjects 4 to 17 years of age who previously failed inclusion criterion 5 due to the previous upper FEV_1 limit will be permitted to re-screen once and will be required to meet all other eligibility criteria upon re-screening.

6 Subjects aged ≥12 years of age must demonstrate reversibility at Visit 1, with an increase in FEV_1 ≥12% (and ≥200 mL for subjects aged ≥18 years) relative to baseline after administration of Sponsor-provided Ventolin via central spirometry. If reversibility is not demonstrated at Visit 1, 1 re-test for reversibility testing must be done at Visit 1a before advancing to Visit 2 or confirming screen failure. Subjects aged 4 to 11 years of age will perform the reversibility test, but do not require demonstration of reversibility during Visit 1 and may enroll provided documented historical reversibility within 1 year is available. Subjects aged 4 to 11 years who previously failed inclusion criterion 6 will be permitted to rescreen. Each subject may re-screen only once.

7 Demonstrate acceptable spirometry performance (ie, meet American Thoracic Society/European Respiratory Society acceptability/repeatability criteria) (Appendix M, Spirometry Assessment Criteria). Subjects 4 to 11 years will be eligible if they provide 2 acceptable/repeatable measurements.

8 A documented history of at least 1 severe asthma exacerbation within 12 months before Visit 1

For inclusion, a severe exacerbation is considered to be any deterioration of asthma that led to at least 1 of the following conditions:

- A temporary bolus/burst of SCS for at least 3 consecutive days; a single depo-injectable dose of corticosteroids will be considered equivalent to a 3-day course of SCS
- An emergency room or urgent care visit (defined as evaluation and treatment for <24 hours in an emergency department or urgent care center) because of asthma that require 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 ≥24 hours) because of asthma

The below defines what is acceptable to document exacerbations for inclusion in this study:

- Discharge summaries from a hospital, emergency room, or an urgent care facility indicating that a subject was hospitalized or treated with SCS for an asthma exacerbation
- Signed and dated notes from a referring physician, including information regarding diagnosis and treatment of an exacerbation with SCS
- Subjects can provide evidence of prescriptions for SCS used during an exacerbation

9 Asthma Control Questionnaire-7 (ACQ-7) score ≥1.5 assessed at Visit 1

10 ACQ-5 score ≥1.5 assessed at Visit 2

11 Use of Sponsor-provided Ventolin prn medication because of asthma symptoms on at least 3 days during the last week of the run-in period before Visit 2

12 Demonstrate acceptable MDI administration technique as assessed by the investigator; use of spacers prohibited

13 Able to perform acceptable and reproducible peak expiratory flow (PEF) measurements as assessed by the investigator

14 Body mass index <40 kg/m^2

15 Willing to remain at the study site as required per protocol and complete all visit assessments

16 Negative pregnancy test (serum at Visit 1) for female subjects of childbearing potential

17 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 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 (ie, a combination of male condom with either cap, diaphragm, or sponge with spermicide, a condom with spermicide, intrauterine device [IUD] and intrauterine hormone-releasing system [IUS])

iii. Maintenance of a monogamous sexual relationship with a male partner who has been surgically sterilized by vasectomy provided that the male partner is the

sole sexual partner of the female (of childbearing potential) participant and that the vasectomized partner has received medical assessment of the surgical success (ie, documented history of medical confirmation of success of vasectomy).

Note: Women are considered to be of nonchildbearing potential if they are physiologically incapable of becoming pregnant, including any female who is 2 years postmenopausal (a postmenopausal state is defined as no menses for 12 months without an alternative medical cause), or surgically sterile, defined as having a bilateral salpingectomy, bilateral oophorectomy, or hysterectomy. Tubal ligation will be considered an acceptable permanent birth control measure for this protocol. For purposes of this protocol, menopausal women are defined as women who 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 development (even if not having reached menarche), the subject will be considered a female of child bearing potential.

Contraceptive methods may be recommended for adolescent females only if they are already sexually active. Use of hormonal contraceptives in adolescent females must always be in consultation with a gynecologist.

18 Male subjects who are sexually active in heterosexual relationships must be surgically sterile or agree to use a double-barrier method of contraception (ie, a combination of male condom with either cap, diaphragm or sponge with spermicide) from the first dose of randomized 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), including regular or occasional use of oxygen

2 Oral/SCS use (any dose and any indication) within 6 weeks before Visit 1

Subjects who have experienced an asthma exacerbation requiring oral/systemic glucocorticosteroid in the 6 weeks before Visit 1 cannot be enrolled in the study because of the 6 weeks wash out of the oral/SCS, but can enter Visit 1 once the wash out period has been met

3 Chronic use of oral corticosteroids (OCS, ≥3 weeks use in 3 months prior to Visit 1)

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

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 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 or asthma exacerbation within 6 weeks of Visit 1

8 Upper respiratory infection involving antibiotic treatment not resolved within 7 days before Visit 1

9 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 >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

Note: Laboratory tests may be repeated once: if laboratory tests have to be repeated, the results must be available for review before Visit 2 (randomization).

10 Having 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 ≥12 years)/ ≥460 ms (subjects aged 4 to 11 years, based on the Fridericia correction where QTCF=QT/RR0.33)

11 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

12 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.

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

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

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

16 Having a known or suspected hypersensitivity to albuterol/salbutamol, or budesonide and/or their excipients

17 Having a scheduled/planned hospitalization during the study

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

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

20 Having received a live attenuated vaccination within 7 days of Visit 1.

21 Currently pregnant or breastfeeding

22 Study investigators, subinvestigators, coordinators, and their employees or immediate family members, or employees of the Sponsor

23 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

24 Currently participating in any interventional study

25 Having previously been randomized in this study or any other PT007 or PT027 clinical study

26 Subjects who experience ≥ 1 asthma exacerbation during the screening period

Procedures for withdrawal of incorrectly enrolled subjects are described in Section 3.4.

3.3 Subject Enrollment and randomization

Approximately 3000 adult and adolescent subjects with moderate to severe asthma will be randomized to 1 of 3 treatment groups (approximately 1000 subjects per group). In addition, up to 100 subjects in the 4 to 11-year age group with moderate to severe asthma will be randomized with approximately 50 subjects randomized to the AS MDI and 50 subjects randomized to the low dose BDA MDI groups only. Approximately 6000 subjects will need to be screened, assuming an estimated screen failure rate of 30% to 50%. 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) eCRF to enable the allocation of subject identification (Ecode)

3 Determine subject eligibility (see Sections 3.1 and 3.2)

4 Enter the information required to enable the Interactive Web Response System (IWRS) to initiate randomization and generate the randomization code

Randomization codes will be assigned through IWRS strictly sequentially to subjects eligible for randomization. If a subject withdraws from participation in the study, then his/her 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. Subjects who are enrolled, but subsequently found not to meet all the eligibility criteria must not be randomized or initiated on treatment, and must be screen-failed and withdrawn from the study.

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. Adult and adolescent subjects (aged ≥12 years) will be randomized in a 1:1:1 ratio into 1 of the 3 treatment groups as reliever therapy on top of usual care (BDA MDI 80/180 µg, or BDA MDI 160/180 µg, or AS MDI 180 µg) according to a SAS-generated randomization schedule. Children aged 4 to 11 years will be randomized in a 1:1 ratio only to the lower BDA MDI dosage (80/180 µg) or AS MDI 180 µg. Randomization for adolescents and adults will be stratified by age group (≥12 to 17, ≥18); region (North

America, Western Europe and South Africa [Region 1] and rest of world [Region 2]); and number of prior severe exacerbations (1, >1) in the 12 months prior to screening (Visit 1) plus any severe exacerbation event experienced during the screening period. Randomization for children 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 3 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 judgment when the appropriate management and welfare of the subject requires knowledge of the treatment allocation. Individual treatment details, for each subject, will be available to the investigator(s) or pharmacists from the IWRS, if needed. If unblinding occurs, the investigator must notify the Sponsor as soon as possible, but without revealing the treatment assignment of the unblinded subject. Routines for this will be described in the IWRS user manual that will be provided to each center. The IWRS provides unblinding procedures, if needed.

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

With the exception of emergency unblinding as described above, all members of the study team, investigators, and site staff will be blinded. 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, dupilumab) or investigational biologic treatments or other investigational treatments other than the IPs are not allowed during the treatment period/extension phase. Subjects requiring chronic OCS are excluded. All asthma maintenance therapies, as documented at baseline, should remain stable throughout the study. In the investigator's opinion, if a subject requires a change in their asthma maintenance therapy, this should be discussed with the medical monitor.

Changes to maintenance therapy doses would be permissible in specific circumstances and when clinically indicated. In the event that the investigator considers the introduction of additional maintenance therapy or intensification of the existing maintenance therapy (change) is required, the medical monitors should be contacted.

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:

- Adverse event
- Subjects who suffer ≥3 severe exacerbations within a 3-month period or ≥5 total severe exacerbation events, or a single severe exacerbation event longer than 20 days in duration 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 (an exacerbation alone does not require subject discontinuation)
- In the opinion of the investigator, the subject is noncompliant with the Clinical Study Protocol (eg, post-enrollment eligibility violation) 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 ≥3 times the upper limit of normal (×ULN) and total bilirubin (TBL) ≥2×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 TBL reach these elevated levels again, after recommencement of IP, the subject will be discontinued from IP and withdrawn from the study.

The study will be completed when the last subject has completed his/ or her post- study follow-up telephone contact. Subjects who discontinue IP will 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). Adverse events and SAEs will be followed up (See Section 6); eDiary and all IPs should be returned by the subject.

Subjects who discontinue study treatment prior to EOS will be encouraged to remain in the study to complete all remaining study visits during the treatment/extension phase period. Treatment discontinuation subjects will return to appropriate maintenance asthma medications, per the investigator's discretion. For subjects recorded as Treatment Discontinuations who do not complete at least 1 post-treatment data collection, a telephone follow-up call is required at least 14 days after last IP dose.

If a subject chooses not to continue with study assessments, at a minimum the subject will complete the PDV (as indicated in Table 1). These subjects will return to appropriate maintenance medications, per the investigator's discretion. A follow-up telephone call (TC) will be performed at least 14 days after the last IP dose. In the event the PDV is performed >14 days post last IP dosing, a follow-up TC will not be required. These subjects who do not withdraw consent for follow-up will be followed for survival/death, severe exacerbations, AEs/SAEs, and concomitant medications including asthma treatment (maintenance and rescue therapies) at quarterly intervals until EOS.

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 judgment of the Sponsor, study subjects are placed at undue risk because of clinically significant 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 should have the reason for study withdrawal recorded as "Screen Failure". Subjects who screen fail will not be rescreened except for children and adolescents who screen failed because they did not meet the now obsolete upper FEV_1 % predicted limit. Children and adolescents who previously failed to meet the upper FEV_1 % 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. Repeat assessments, if needed, will be captured in unscheduled visits.

Table 1 Study Assessments and Procedures

Visit [a]	*Screening and run-in* 1/1a [b]	*Double-blind Treatment Period* 2	3	4	5	6 [c]	7	*Extension Phase* (every 12 weeks ±4 days until the PCD)	*EOS* [d] *(last clinic visit)*	*PDV* [e] *(if applicable)*	*Safety Follow-up TC (2 weeks [±4 days]after EOS or PDV)*
Week	*-4 to -2*	*0*	*4*	*8*	*12*	*24*	*36*				
Day	*-28 to -14*	*1*	*28 ±2*	*56 ±2*	*84 ±4*	*168 ±4*	*252 ±4*				
Informed consent/assent	X										
Eligibility criteria	X	X									
Clinical procedures											
Medical/surgical history	X [b]										
Demography	X										
Physical examination	X							X	X	X	
Height (cm) [f]	X					X [f]			X [f]	X [f]	
Concomitant medications	X [b]	X	X		X	X	X	X	X	X	X
Albuterol/salbutamol reversibility test [g]	X										
Safety measurements											
Vital signs	X [b]	X	X	X	X	X	X	X	X	X	
12-lead ECG	X [b]	X				X			X	X	
Adverse events	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test [h]	serum	urine	urine [h]	urine [h]	urine [h]	serum	urine [h]	urine [h]	serum	serum	
Safety laboratory assessments (clinical chemistry and hematology)	X [b]					X			X	X	
Morning serum cortisol assessment	X					X			X	X	

Visit [a]	*Screening and run-in* 1/1a [b]	*Double-blind Treatment Period* 2	3	4	5	6 [c]	7	*Extension Phase* (every 12-weeks ±4 days until the PCD)	*EOS* [d] (last clinic visit)	*PDV* [e] (if applicable)	*Safety Follow-up TC* (2 weeks [±4 days]after EOS or PDV)
Week	-4 to -2	0	4	8	12	24	36				
Day	-28 to -14	1	28 ±2	56 ±2	84 ±4	168 ±4	252 ±4				
Efficacy measurements											
Collection/review of exacerbations [i]	X	X	X	X	X	X	X	X	X	X	
ACQ-5 [j]		X	X	X	X	X	X	X	X	X	
ACQ-7 [k]	X										
ACT/C ACT		X	X	X	X	X	X	X	X	X	
AQLQ+12/PAQLQ		X	X	X	X		X	X	X	X	
Review of PEF, use of IP (reliever therapy), asthma daytime/night-time symptoms, night-time awakenings due to asthma symptoms [l]	X	X	X	X	X	X	X	X	X	X	
Spirometry (FEV_1) [m]	X	X		X	X						
eDiary	d								c	c	
Review compliance with eDiary		X	X	X	X	X	X	X	X	X	
Investigational product administration											
Randomization		X									
IP (dispense/collect)		d	c/d	c/d	c/d	c/d	c/d	c/d	c	c	
Ventolin (dispense)	d										

Abbreviations: ACQ-5/7=Asthma Control Questionnaire-5/7; ACT=Asthma Control Test; AQLQ+12=Asthma Quality of Life Questionnaire for 12 years and older; β-hCG=β-human chorionic gonadotropin; BMI=body mass index; c=collect; C ACT=Childhood Asthma Control Test; d=dispense; ECG=electrocardiogram; EOS=end-of-study; FEV_1=forced expiratory volume in 1 second; IP=investigational product; LABA=long-acting β2-agonist; PAQLQ=Pediatric Asthma Quality of Life Questionnaire; PCD=primary completion date; PDV=premature discontinuation visit; PEF=peak expiratory flow; TC=telephone call; V=visit

[a] Repeat assessments/visits, if needed, will be captured in unscheduled visits.

[b] Visit 1 will be split and used for repeated assessments, if needed (ie, Visit 1a will be needed for the repeat assessment of albuterol/salbutamol reversibility test and FEV_1, if applicable). Subjects may consent for the study in advance of Visit 1 and if required, request for medical records to support evidence of prior asthma exacerbations without triggering the 28-day screening period. Where a severe exacerbation event occurs during the screening period, this may be extended to a maximum of 9 weeks (to account for a course of systemic corticosteroids of up to 1 week duration followed by a 4-week washout period). In the event of an extension to the screening period due to a severe exacerbation event, the following will be repeated: safety laboratory assessments, ECG, vital signs, concomitant medications, and medical/surgical history.

[c] The treatment duration for the study will be at least 24 weeks for each subject to support the subject exposure data. The study treatment period will continue (extension phase) until the required 570 first severe exacerbation events, as defined per protocol, have been reached; and the last adult subject has completed 24 weeks of treatment, which will be defined as the PCD. After Visit 6, visits will be scheduled every 12 weeks with the assessments from Visit 7 to be performed in all of them.

[d] The EOS visit will be planned once the first 570 severe exacerbation events occur. If a subject's treatment lasts ≥24 weeks then the subject's EOS visit will occur at their next scheduled clinic visit. Once the PCD has been reached, any ongoing subject will return to complete an EOS visit at their next scheduled clinic visit.

[e] Subjects who prematurely withdraw from the study will undergo a PDV. In the event the PDV is performed >14 days post last IP dosing, a follow-up TC will not be required. These subjects who do not withdraw consent for follow-up will be followed for survival/death, severe exacerbations, AEs/SAEs, and concomitant medications including asthma treatment (maintenance and rescue therapies) at quarterly intervals until EOS.

[f] Additional height (cm) assessments to be collected for subjects ≤18 years of age ONLY. Assessments of height will continue in accordance with a subject's age at the time of signed informed consent/assent (where a subject changes age during the study).

[g] Demonstrate reversibility at Visit 1, with an increase in FEV_1 ≥12% (and ≥200 mL for subjects ≥18 years) relative to baseline after administration of Sponsor-provided Ventolin via central spirometry at either Visit 1 or Visit 1a (reversibility must be demonstrated at either Visit 1 or Visit 1a); Visit 1a must be used for re-testing, if needed; with only 1 reversibility re-test permitted in advance of randomization (Visit 2).

[h] A serum pregnancy test (β-hCG) will be performed at Visit 1, 2 and EOS/PDV; urine β-hCG test will be performed at all other clinic visits (for women of childbearing potential only). (In Argentina, women of childbearing potential will have additional pregnancy testing at monthly time points.)

[i] Asthma exacerbations data will be reviewed, and severe exacerbations identified as per Section 5.1.1. Subjects are to be reminded not to take any albuterol product except for the IP.

[j] Asthma Control Questionnaire-5 self-administered adult version to be used for adults and adolescents 11 years and older; the interviewer-administered version should be used for children 4 to 10 years. Subject will need to satisfy ACQ-5 (≥1.5) entry requirements at Visit 2.

[k] Subject will need to satisfy ACQ-7 (≥1.5) entry requirements at Visit 1.

[l] The AM3 device will be dispensed at screening and PEF measurements will be taken through the screening period in advance of Visit 2.

[m] Prebronchodilator FEV_1 will be measured in the morning between 06:00 and 11:00 AM at Visits 1, 2, 5, and 6. Prebronchodilator FEV_1 of ≥40 to <90% predicted normal value for adults and ≥60% predicted normal value for subjects aged 4 to 17 years after withholding SABA ≥6 hours (and at Visit 1 and Visit 1a [used for repeated assessments, if needed], if applicable, as confirmed by centralized spirometry). Sponsor-provided Ventolin should be withheld ≥6 hours at Visit 2. At subsequent treatment visits, IP should be withheld ≥6 hours before Visit 5 and Visit 6. At all visits where FEV_1 is measured (Visits, 1, 2, 5, and 6), subjects whose maintenance therapy includes LABA should be instructed not to use their maintenance therapy within the timeframe specified in Table 4 in advance of the visit as these are considered bronchodilators. If these medications were taken within the restricted time periods, visits should be re-scheduled.

4.1 Screening and run-in period

Procedures will be performed according to study assessments and procedures presented in Table 1. Subjects may consent for the study in advance of Visit 1 and if required, request for medical records to support evidence of prior exacerbations without triggering the 28-day screening period. The screening period will be 14 to 28 days except where a severe asthma exacerbation event occurs during this period. Where a severe asthma exacerbation occurs during the screening period, the period may be extended to a maximum of 9 weeks (to account for a course of SCS of up to 1 week in duration followed by a 4-week washout period). In the event of an extension to the screening period due to a severe exacerbation event, the following assessments and procedures will be repeated following washout of SCS before Visit 2: safety laboratory assessments, ECG, vital signs, concomitant medications, and medical/surgical history.

At screening, consenting subjects are assessed to ensure that they meet eligibility criteria at Visit 1 or Visit 1a, as applicable. Subjects who do not meet these criteria must not be enrolled in the study.

The study procedures carried out during this period will include medical and surgical history, demographics, physical examination (including body mass index [BMI], weight and height), 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 in advance of randomization [Visit 2]), vital signs, 12-lead ECG, AEs, pregnancy test, blood samples for hematology and clinical chemistry (1 re-test is permitted in advance of Visit 2); and morning serum cortisol assessment, collection/review of exacerbations, spirometry (if needed, FEV_1 must be re-tested once at Visit 1a; only 1 re-test is permitted), ACQ-7, PEF, and dispensing eDiary.

Subjects aged 4 to 11 years of age who previously failed inclusion criterion 6 will be permitted to rescreen.

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, medication, and surgical history will be obtained with review of the selection criteria for the subject. Previous asthma related treatments and duration of asthma related treatments will be recorded.

4.2 Randomization/treatment period/extension phase

Procedures will be performed according to study assessments and procedures presented in Table 1.

Subjects should not administer Sponsor-provided Ventolin on the morning of their randomization visit (Visit 2). Subjects taking ICS, LABA, or other maintenance medications that can impact the performance of spirometry should refer to Table 4 for medications that can interfere with pulmonary function tests (PFTs).

At randomization (Visit 2), eligible subjects will enter a 24-week double-blind treatment period.

The study treatment period will continue (extension phase) until the required 570 first severe exacerbation events, as defined per protocol, have been reached and the last adult subject has completed 24 weeks of treatment, which will be defined as the PCD.

- In the event 570 events will be captured before the last adult subject has had 24 weeks of treatment, all subjects on treatment for ≥24 weeks will have their EOS visit at their next scheduled clinic visit. All subjects on treatment for < 24 weeks will continue until 24 weeks at which point they will complete their EOS visit.
- In the event 570 events will be captured after the adult last subject has had 24 weeks of treatment, each subject will return to complete the EOS visit at their next scheduled clinic visit.
- Children and adolescents ongoing in treatment after the PCD will continue in follow-up until they have completed 24 weeks of treatment.

The study procedures carried out during this period will include: randomization, concomitant medications review, height (for subjects ≤18 years of age at time of informed consent), vital signs, 12-lead ECG, AEs, pregnancy test, blood samples for hematology, and clinical chemistry; and morning serum cortisol assessment, collection/review of exacerbations, spirometry, ACQ-5, asthma control test (ACT)/childhood asthma control test(C ACT), Asthma Quality of Life Questionnaire for 12 years and older (AQLQ+12)/Pediatric Asthma Quality of Life Questionnaire (PAQLQ) (where populations are approved), PEF, use of IP (reliever therapy), asthma daytime/night-time symptoms, night-time awakenings due to asthma symptoms, eDiary/IP compliance, and dispensing and/or collection of IP.

4.3 End-of-study visit

Procedures will be performed according to study assessments and procedures presented in Table 1. The EOS visit will be planned once the 570 first severe exacerbation events occur. If a subject's treatment is ≥24 weeks then the subject's EOS visit will occur at their next scheduled clinic visit. Once the PCD has been reached, any ongoing subject will return to complete their EOS visit at their next scheduled clinic visit.

The study procedures carried out during this visit will include: physical examination (including weight), concomitant medications review, height (for subjects ≤18 years of age at time of informed consent), vital signs, 12-lead ECG, AEs, pregnancy test, blood samples for

hematology, and clinical chemistry; and morning serum cortisol assessment, review of asthma exacerbations, ACQ-5, ACT/C ACT, AQLQ+12/PAQLQ, review of PEF, use of IP (reliever therapy), asthma daytime/night-time symptoms, night-time awakenings due to asthma symptoms, eDiary/IP compliance, and collection and final reconciliation of the IP.

4.4 Unscheduled visit and premature discontinuation 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.

Procedures will be performed according to study assessments and procedures presented in Table 1.

The study procedures carried out during the PDV visit will include: physical examination (including weight), height (for subjects ≤18 years of age), concomitant medications review, vital signs, 12-lead ECG, AEs, pregnancy test, blood samples for hematology, and clinical chemistry; and morning serum cortisol assessment, review of asthma exacerbations, ACQ-5, ACT/C ACT, AQLQ+12/PAQLQ, review of PEF, use of IP (reliever therapy), asthma daytime/night-time symptoms, night-time awakenings due to asthma symptoms, eDiary compliance, randomization, and collection and reconciliation of the IP.

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 (±4 days) after EOS or PDV, whichever occurs first.

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

4.6 Follow-up

If a subject chooses not to continue with study assessments, at a minimum the subject will complete the PDV (as indicated in Table 1). These subjects will return to appropriate maintenance medications, per the investigators discretion. A follow-up TC will be performed at least 14 days after the last IP dose.

In the event the PDV is performed >14 days post last IP dosing, a follow-up TC will not be required. These subjects who do not withdraw consent for follow-up will be followed for survival/death, severe exacerbations, AEs/SAEs, concomitant medications including asthma treatment (maintenance and rescue therapies) at quarterly intervals until EOS.

5 STUDY ASSESSMENTS

The Rave WBDC system and the electronic patient reported outcome (ePRO) device 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 including an AM3 device which will also be used to collect ACQ-5, ACQ-7, PEF, and eDiary data. In addition to this, a tablet will be used to collect the AQLQ+12 and ACT/C ACT questionnaire 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 asthma exacerbations, AQLQ+12/PAQLQ, ACQ-5, ACT/C ACT, PEF, use of IP (reliever therapy), asthma daytime/night-time symptoms, night-time awakenings due to asthma symptoms, and review of eDiary compliance.

5.1.1 Asthma exacerbation definition

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

- Worsening of asthma signs/symptoms (see Section 5.1.1.1)
- Increased use of "as needed" reliever therapy
- Deterioration of lung function (ie, decreased PEF and/or decreased FEV_1)
- A medical intervention as described below (see Section 5.1.1.3)

These descriptions above are provided for definition, however, only severe asthma exacerbations will be assessed during this study (Section 5.1.1.3).

5.1.1.1 Definition of asthma signs/symptoms worsening

The worsening/onset of symptoms must include at least 1 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_1

5.1.1.2 Investigator-justified asthma exacerbations

A vast majority of asthma exacerbations are associated with worsening of the signs/symptoms described in Section 5.1.1.1. Clinical presentations may, however, vary among subjects. If a subject's symptoms and the overall clinical findings support the diagnosis of an asthma exacerbation, but the symptomatic worsening does not meet the definition in Section 5.1.1.1, the investigator must justify the decision for defining the event as an exacerbation and document the reasoning in the eCRF.

5.1.1.3 Severe asthma exacerbations

All protocol-defined severe asthma exacerbations need to fulfill the symptom criteria as defined in Section 5.1.1.1 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 <24 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 ≥24 hours) due to asthma

Note: all deaths will be adjudicated to determine if they meet the criteria for severe exacerbation events.

5.1.1.4 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 less than 2 weeks (GINA 2018)

Treatment for less than 3 days does not constitute a severe asthma exacerbation.

5.1.1.5 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.
- If the timeframe between successive SCS use is ≥7 days, the event of severe asthma exacerbation will be considered as 2 separate events of severe asthma exacerbation. An event of severe asthma exacerbation is considered "singular" if SCS use is <7 days.
- 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.

5.1.1.6 Approach for capturing asthma exacerbations

5.1.1.6.1 Severe Asthma Exacerbation eCRF

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

Severe asthma exacerbations will be considered expected study endpoints and will not be reported as AEs unless they also meet the criteria for an SAE (Section 6.3.5).

5.1.1.6.2 Symptom Reporting

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

If symptoms meet the below threshold, the eDiary generates an alert to the subject and the investigational site:

- Decrease in morning peak flow ≥20% on at least 2 consecutive days compared with baseline, and/or

- An increase in rescue medication use of ≥4 puffs on at least 2 consecutive days compared with the average use during baseline and/or
- >12 puffs of rescue medication in 1 day, and/or
- A night-time asthma symptom score of >baseline night-time score *and* ≥2 for at least 2 consecutive days, and/or
- A daytime asthma symptom score of 3 for at least 2 consecutive days

This alert should generate contact between the subject and the investigational site. The investigator then makes the decision whether or not to initiate (or escalate, as appropriate) treatment (ie, with inhaled or SCS and/or hospitalization).

NB: 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. Subjects will also be recommended not to take more than 8 puffs per day and advised to contact the study site/investigator if their symptoms necessitate more than 8 puffs in a day.

Asthma signs or symptoms will be recorded as AEs only when: the sign or symptom is serious, causes the subject to discontinue IP, or is new to the subject or inconsistent with the subject's pre-existing asthma history (Section 6.3.6).

5.1.2 Asthma Quality of Life Questionnaire+12/Pediatric Asthma Quality of Life Questionnaire

5.1.2.1 Asthma Quality of Life Questionnaire+12

The AQLQ+12 will be used in subjects 12 years and older. The AQLQ+12 will be self-administered using an ePRO device during site visits as indicated in Table 1. Linguistically validated translations of the AQLQ+12 into local languages will be used.

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

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.

5.1.2.2 Pediatric Asthma Quality of Life Questionnaire

The PAQLQ will be self-administered during site visits as indicated in Table 1 in subjects aged 7 to 11 years. Subjects aged 4 to 6 years will complete the questionnaire with the help of a caregiver. As the PAQLQ is not validated for children less than 7 years of age, data for subjects who are aged 4 to 6 years will be excluded from the analyses of PAQLQ endpoints.

The subject/caregiver will complete the PAQLQ on paper and responses will be transcribed to the eCRF by site staff. Linguistically validated translations of the PAQLQ into local languages will be used.

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

The PAQLQ has 23 questions in 3 domains (symptoms, activity limitation, and emotional function). The activity domain contains 3 subject-specific questions. Children (subjects aged 7 to 11 years) are asked to think about how they have been during the previous week and to provide responses to each of the 23 questions on a 7-point scale (7=not bothered at all; 1=extremely bothered). The overall PAQLQ score is the mean of all 23 responses and the individual domain scores are the means of the items in those domains.

5.1.3 Asthma Control Questionnaire-5 and -7

The ACQ-5 will be administered using an ePRO device during site visits as indicated in Table 1. The ACQ-5 self-administered adult version will be used for adults and adolescents 11 years and older. As the ACQ-5 is not validated for children less than 6 years old, the interviewer-administered version will be implemented for children aged 4 to 10 years. The questions take approximately 2 to 3 minutes to complete. Linguistically validated translations of the ACQ-5 into local languages will be used.

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 β2-agonist use) and thus reduce the risk of life-threatening exacerbations and long-term morbidity. The Asthma Control Questionnaire (5-item version; Appendix H, Asthma Control Questionnaire-5 and -7) 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 questionnaire will be self-administered for adults and adolescents 11 years and older. The interviewer-administered version will be used for children aged 4 to 10 years.

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).

Note: The ACQ-7 will be completed once at screening only and consists of the top scoring 5 symptoms from the ACQ-5, with the addition of FEV_1% predicted value and daily rescue bronchodilator use. Subjects are required to score ≥1.5 for eligibility to the study.

5.1.4 Asthma Control Test

The ACT will be self-administered using an ePRO device during site visits as indicated in Table 1. Linguistically validated translations of the ACT into local languages will be used.

The ACT (Appendix I, Asthma Control Test) is a 5-question health survey used to measure asthma control in subjects aged 12 and older. The survey measures the elements of asthma control as defined by the National Heart, Lung, and Blood Institute. The ACT is an efficient, reliable, and valid method of measuring asthma control, with or without lung functioning measures such as spirometry.

The development of the ACT follows a paradigm shift in the treatment of asthma, from a focus on asthma severity to asthma control. Specifically, ACT helps identify and detect asthma subjects who are not well controlled. It was designed with input from asthma experts who helped establish cut-point scores to improve the clinical utility of the survey.

5.1.5 Childhood Asthma Control Test

The C ACT will be self-administered using an ePRO device during site visits as indicated in Table 1. Linguistically validated translations of the C ACT into local languages will be used.

The C ACT report (Appendix J, Childhood Asthma Control Test) is a validated tool for subjects aged 4 to 11 years to assess asthma control and identify children with inadequately controlled asthma.

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 the best of 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 Use of investigational product (reliever therapy)

Use of IP as reliever therapy will be collected using an ePRO device. Subjects will be asked twice daily (in the evenings and in the mornings) to enter into their eDiary (device called AM3+), how many puffs of rescue/reliever medication (ie, study IP) they took since the previous measure.

5.1.6.3 eDiary maintenance therapy compliance

Monitoring of compliance for medium-to-high-dose ICS or low-to-high-dose ICS in combination with LABA will be done only through the eDiary question "have you taken your regular maintenance therapy today?" (Appendix K, List of e-Diary questions). There will be no collection of the actual devices for measurement/assessment of compliance; rather, compliance will be assessed by subject reported response. Responses will be "Yes" or "No", where "Yes" is taken as compliant to dose and regimen and a "No" equating to noncompliance (missed dose).

5.1.6.4 eDiary recording of asthma symptoms

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

The device will be programmed to alert both the subject and study center when the below prespecified alert thresholds are crossed. 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. Sponsor will also receive programmed alerts to monitor subject follow-up.

- Triggers in the ePRO device will alert the subjects to signs of change of asthma and to contact their physician.
- A dedicated person from the Sponsor will review the ePRO and compliance alerts (2 consecutive days of missing data) and contact the site.
- In case of ePRO or compliance alerts, a qualified person from the site will contact the subject. For ePRO 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.

Asthma symptoms should be captured in the eDiary by the subject every morning and evening (Appendix K, List of e-Diary questions).

5.1.7 Deterioration of asthma

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

- PEF: a decline of ≥20% from baseline
- Reliever therapy use: >4 puffs/day and ≥2×baseline
- Symptoms: night-time score that is >baseline *and* ≥2 OR a daytime score that is >baseline *and* =3

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

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

Severe asthma exacerbations will also be considered to be deterioration of asthma and included in the analyses of this endpoint.

5.1.8 Lung function measurement by spirometry

Prebronchodilator spirometry will be performed on a MasterScope provided for the study by the central reader at screening (Visit 1 and/or Visit 1a, as applicable), Visit 2 (baseline), Visit 5 and Visit 6 (endpoint measurements). It is important that all spirometry assessments are performed after 06:00 and no later than 11:00 AM and that the spirometry at Visits 5 and 6 are performed ±1 hour in relation to the time of spirometry 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 3, a short pause (1 minute) between measurements is recommended.

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.

Subjects should have previously discontinued bronchodilator medications as specified in Section 7.8.2 for reversibility tests as these can affect bronchodilation. If these medications were taken within the restricted time periods, visits should be re-scheduled.

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

5.1.8.1 Reversibility Test

To fulfill the reversibility inclusion criterion, the increase in FEV_1 relative to baseline must be ≥12% (and ≥200 mL for subjects ≥18 years) approximately 30 minutes after inhalation of Sponsor-provided Ventolin.

Reversibility testing will be performed as follows:

1. Determine if morning doses of all maintenance asthma medications (Table 4) were withheld and that short-acting bronchodilators were not administered within 6 hours of testing (if applicable).
2. Perform prebronchodilator PFTs after at least 15 minutes of rest, and before administration of Ventolin.
3. Subjects aged ≥12 years should administer 4 puffs of Ventolin. Subjects aged <12 years should administer 2 puffs of Ventolin.
4. Perform post-bronchodilator 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 postbronchodilator FEV_1 measurements will be captured within the MasterScope. If the reversibility inclusion criterion is not met at Visit 1, the reversibility test must be repeated at Visit 1a in advance of Visit 2 (randomization).

5.1.8.2 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 PI considers the subject is no longer infectious. Device cleaning and hygiene guidance should be followed at all times.

5.2 Safety assessments

Safety assessments include clinical laboratory (hematology, chemistry, morning serum cortisol, 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,hematology, and morning serum cortisol will be taken at the times indicated in Table 1.

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

The clinical chemistry,hematology, serum cortisol 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 2 will be measured:

Table 2 Laboratory Safety Variables

Hematology/Hemostasis (whole blood)	**Clinical Chemistry (serum or plasma)**
Basophils (%)	Albumin
Basophils Abs	Alanine transaminase
Eosinophils (%)	Alkaline phosphatase
Eosinophils Abs	Aspartate transaminase
Hemoglobin	Bilirubin, total
Hematocrit	Calcium, total
Mean Corpuscular Hemoglobin	Chloride
Mean Corpuscular Hemoglobin Concentration	Cholesterol, total
Mean Corpuscular Volume	Creatinine
Monocytes (%)	Creatine kinase
Monocytes Abs	Gamma-glutamyl transpeptidase
Neutrophils (%)	Glucose (random)
Neutrophils Abs	Magnesium
Red blood cells (erythrocytes)	Phosphate
White blood cells (leukocytes)	Potassium
Platelet count	Protein, total
Lymphocytes (%)	Sodium
Lymphocytes Abs	Triglycerides
	Morning (serum) cortisol
Urine	Urea
Urine β-hCG pregnancy (Visit 2) [a]	Serum β-hCG pregnancy (Visit 1, 6 and EOS/PDV)

Abbreviations: Abs=absolute; β-hCG=β-human chorionic gonadotropin; EOS=end-of-study; PDV=premature discontinuation visit

Notes:

[a] In Argentina only, additional pregnancy testing to be conducted at monthly time points in women of childbearing potential.

If a subject shows an AST **or** ALT ≥3× ULN **and** total bilirubin (TBL) ≥2×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. 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. 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

Adverse events 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 and EOS/PDV as detailed in Table 1. This will include an assessment of the following items: BMI (height in centimeters [for all subjects at Visit 1 and for subjects ≤18 years of age only at Week 24 (Visit 6) and EOS/PDV, as detailed in Table 1] and 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 asthma therapies, will be performed at the visits detailed in Table 1. Permitted and restricted concomitant medications are descried in Section 7.8.

All prescription drugs, herbal products, vitamins, minerals, and over-the-counter medications taken within 3 months before screening will be recorded as previous medications. Asthma medication history will be recorded for 12 months before screening. All medications taken after screening and through the EOS/PDV visit will be recorded as concomitant therapy.

All asthma therapies taken during the study (Visit 1 through EOS/PDV) including SCS for exacerbations as well as concomitant ICSs will be recorded in the concomitant medication form in the subject's eCRF. Asthma maintenance therapy (ie, an ICS, or ICS/LABA ± 1 of LTRA, LAMA, or theophylline) must be recorded at baseline. Any changes to the maintenance therapy presented at screening (Visit 1/1a, as applicable), including changes in dosing, will also be collected on the concomitant medication page in the eCRF.

Subjects will be maintained, after Visit 1, on their current maintenance regimen. Changes to maintenance therapy are discouraged unless clinically indicated. Investigators should contact the medical monitor assigned to the project in advance of any proposed change to maintenance therapy for study subjects; considerations should be made to subject drug compliance and other factors in advance of making changes to maintenance therapy.

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 is familiar with the content of this section.

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

6.1 Definition of adverse events

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

The term AE is used to include both serious and nonserious 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 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 serious AE
- Date investigator became aware of serious AE
- Reason why the AE is considered serious
- Treatment given for the SAE
- Date of hospitalization
- Date of discharge
- Probable cause of death.
- Date of death.
- Whether 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 of this Clinical Study Protocol.

6.3.5 Deteriorations of asthma and severe asthma exacerbations

All severe asthma exacerbations (Section 5.1.1.3) must be captured on the eCRF. Deterioration of asthma (Section 5.1.7) will be captured on the basis of symptoms as recorded by the subject in the eDiary. Severe asthma exacerbations will be considered expected study endpoints and will not be reported as AEs unless they also meet the criteria for an SAE (Section 6.2).

6.3.6 Adverse events based on signs and symptoms

All AEs spontaneously reported by the subject or care provider or reported in response to the open question from the study site staff: "Have you/ your child had any health problems since the previous visit you (or your child) were last asked?" or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, 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.

6.3.7 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.

6.3.8 Hy's Law

Cases where a subject shows elevations in liver biochemistry may require further evaluation and occurrences of AST and/or ALT ≥3×ULN combined and with TBL ≥2×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.

6.3.9 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 an SAE of 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, the 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 nonoperational, SAEs shall be sent in paper form to:

[redacted]

[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.

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

6.5 Overdose

For the purpose of this study, an accidental or deliberate intake of blinded treatment of more than 12 puffs during 1 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/symptom on the relevant AE/SAE modules in the eCRF.

Investigators and the medical monitors will receive a safety notification alert from the subject's eDiary on a daily basis from any subject whose dosage exceeds 12 puffs in a single day. Upon receipt of alerts, the investigator will contact the subject to remind them that they should not take more than 12 puffs per day. If indicated, the investigator will arrange an unscheduled clinic visit with the subject.

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 and "Pregnancy" recorded as the reason for discontinuation on the eCRF.

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 EOS/PDV 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 EOS/PDV 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 fridge 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 AE should also be recorded as the AE diagnosis/symptom 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 the [redacted] Safety and Pharmacovigilance Department representative. For medication errors associated with an SAE, the standard SAE reporting timelines apply (see Section 6.4).

6.8 Management of investigational product-related toxicities

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

7 INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

7.1 Identity of investigational product(s)

BDA MDI is formulated (Table 3) as both micronized budesonide and micronized albuterol co-suspended with spray-dried porous particles in a hydrofluoroalkane (HFA) propellant. The co-suspension formulation ensures that subjects receive a consistent delivery of the drug from each actuation of the MDI.

Table 3 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 per puff	MDI/120 actuations	Taken as 2 actuations	[redacted]
BDA MDI 160/180 µg	BDA MDI 80 µg budesonide and 90 µg albuterol per puff.	MDI/120 actuations	Taken as 2 actuations	[redacted]
AS MDI 180 µg	AS MDI 90 µg albuterol per puff[a]	MDI/120 actuations	Taken as 2 actuations	[redacted]
Additional study medication				
Ventolin HFA[b]	108 µg albuterol sulfate (90 µg albuterol base) as an aerosol formulation	Albuterol (salbutamol) sulfate inhalation aerosol. 200 puffs per canister	Use as needed during screening period	[redacted]

Albuterol sulfate (salbutamol sulfate) 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.

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

[b] Table represents commercially available Ventolin formulation for the United States, each country will utilize commercially available Ventolin in that country, product strength may differ

7.2 Dose and treatment regimens

Investigational product will be used in response to asthma symptoms as subjects would normally take their reliever medication. If subjects take IP in advance of exercise for the prevention of exercise induced symptoms, IP usage in relation to exercise will be captured within the eDiary. No other reliever products will be used during the treatment period.

At randomization (Visit 2), adolescents and adults (aged ≥12 years) who meet the eligibility criteria will be randomly assigned to 1 of the following 3 treatment groups in a 1:1:1 ratio as reliever therapy on top of usual care. Children aged 4 to 11 years will be randomized in a 1:1 ratio only to the lower BDA MDI dosage or AS MDI:

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

Randomization for adolescents and adults will be stratified by age group (≥12 to 17, ≥18), region (North America, Western Europe and South Africa [Region 1] and rest of world [Region 2]); and number of prior severe exacerbations (1, >1) in the 12 months prior to screening (Visit 1plus any severe exacerbation event experienced during the screening period. Randomization for children will not be stratified.

The maximum daily dosage of IP should not exceed 12 puffs per day and subjects will be advised to contact the investigator if their symptoms necessitate more than 8 puffs per day (see Section 6.5 for overdose).

Handling instructions for the MDI device will be available for the site to train subjects and also for the subjects to retain throughout the study.

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 4 weeks of treatment. Each kit will contain the following blinded labels:

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

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

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 dose indicator readings and will be captured within the appropriate sections of the eCRF. Data from the dose counter 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.

The subject will be asked to record in their eDiary whether or not they have taken their maintenance therapy today via a yes/no question, which will be captured in the appropriate sections of the eCRF.

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 trial with regards to IP. An "Instructions For Use" document can be found in Appendix L, Metered-dose Inhaler Handling and Cleaning, focusing on the IP MDI device.

The importance of the device cleaning and priming requirements should be emphasized to subjects. Device priming should not be conducted in the same room as spirometry assessments are being conducted.

7.8 Concomitant and other treatments

7.8.1 Maintenance therapies

Inhaled corticosteroids (ICS)/LABA, LTRA, theophylline, and LAMAs are permitted to be used as maintenance therapy on study as specified in the inclusion criteria. No subject can be on >3 maintenance therapies.

During the study, subjects should maintain stable dosing of their maintenance therapies as presented at screening (Visit 1/1a, as applicable). Dose changes to maintenance therapy are discouraged unless clinically indicated in accordance with GINA guidelines. Investigators should notify the study medical monitors of any change to maintenance therapy for study subjects; considerations should be made to subject drug compliance and other factors in advance of making changes to maintenance therapy.

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

7.8.2 Medications that may affect reversibility and FEV_1 testing

The medications presented in Table 4 may affect reversibility assessments. Investigators should notify the study medical monitors of any change to maintenance therapy for study subjects. If subjects have taken any of the medications below within the timeframe indicated of the planned reversibility test, the test should not be carried out and the subject should return to perform the reversibility testing.

Table 4 Medications Restricted Time Limit Prior to any Lung Function Testing (reversibility and FEV_1)

Medication	Restricted time limit before lung function testing
SABA/Sponsor-provided Ventolin/Study IP	6 hours
Inhaled LABA	
Formoterol	12 hours
Salmeterol	12 hours
Olodaterol	24 hours
Indacaterol	24 hours
Vilanterol	24 hours
LTRA	24 hours
Theophylline twice daily	12 hours
Theophylline once daily	24 hours
LAMA	24 hours

Abbreviations: IP=investigational product; LABA=long-acting β2-agonist; LAMA= long-acting muscarinic antagonist; LTRA=leukotriene receptor antagonist.

7.8.3 Prohibited medications

Prohibited concomitant medications during the study include:

- Oral, parenteral, or rectal corticosteroids (except if required to treat severe asthma exacerbation)
- Any other asthma medication except stable doses of maintenance therapy taken at entry into the study and provided by the Sponsor
- Inhaled disodium cromoglycate or inhaled nedocromil sodium
- 5-lipoxygenase inhibitors (ie, zileuton)
- Inhaled short-acting anticholinergics (or short-acting muscarinic antagonists [SAMA], ie, ipratropium)
- Inhaled long-acting anticholinergics (LAMA), except those that were started before screening and continued as part of maintenance treatment (see inclusion criterion 4).
- 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 P3A4 inhibitors (eg, ketoconazole, itraconazole, and ritonavir)

7.8.4 Other concomitant treatment

Medication other than that described in Section 7.8.1, which is considered necessary for the subject's safety and wellbeing, including short-term concomitant treatment with prohibited asthma treatments to treat severe exacerbations, may be given at the discretion of the investigator and recorded in the appropriate sections of the eCRF.

8 STATISTICAL ANALYSES

8.1 Statistical considerations

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

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 before the first unblinded analysis for IDMC and any subsequent amendments will be documented with final amendments completed before the unblinding of the data.

8.1.1 Estimands

Three 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 usage and assuming that maintenance therapy is not changed. 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 assuming that maintenance therapy is not changed. For this estimand, discontinuation of randomized treatment for tolerability or change in maintenance therapy for lack of asthma control is considered a negative outcome. This estimand is a mixture of composite and hypothetical strategies as defined in the draft ICH E9 addendum.

The third estimand of interest is the effectiveness estimand which is a combination of the hypothetical and treatment policy strategies as defined in the draft ICH E9 addendum. The strategy is hypothetical in that the treatment effect will be estimated without including data post the intercurrent event of discontinuation from randomized treatment. However, the strategy is consistent with the treatment policy strategy in that the treatment effect is estimated irrespective of the occurrence of the intercurrent event of a change in the maintenance therapy.

The fourth estimand of interest is the de facto estimand, defined as the effect of a treatment policy regardless of changes in maintenance therapy or premature discontinuation of randomized treatment. This estimand is considered a treatment policy strategy as defined in the draft ICH E9 addendum.

8.1.2 Primary outcome analysis

Primary outcome database lock (pDBL) will commence once all randomized adults (≥18 years) have attended their EOS visit at the PCD. The analyses of primary, secondary, exploratory and safety objectives will include all data up to the pDBL, which may include data for children (4 to 11 years) who are still on-going in the trial and have not yet completed the 24-week treatment period.

A final data base lock will occur after the pDBL, once all children have completed the EOS visit and safety follow-up.

Patient level listings of data for children who were on-going at the pDBL will be reported at the final database lock. No efficacy analyses will be conducted on data collected following the pDBL.

8.1.3 Type 1 error control

Comparisons of BDA MDI 80/180 µg versus AS MDI and BDA MDI 160/180 µg versus AS MDI for the primary endpoint, time to first severe exacerbation using the efficacy estimand, will be conducted using Hochberg's step-up method (Hochberg 1988).

The type-I error will be controlled for secondary endpoint treatment comparisons via a hierarchical testing procedure. The following secondary endpoints will be tested under the efficacy estimand in the following sequential order, grouped by secondary endpoint:

Annualized severe exacerbation rate

1. BDA MDI 160/180 µg versus AS MDI 180 µg
2. BDA MDI 80/180 µg versus AS MDI 180 µg

Total annualized dose of systemic corticosteroid

3. BDA MDI 160/180 µg versus AS MDI 180 µg
4. BDA MDI 80/180 µg versus AS MDI 180 µg

Asthma Control Questionnaire-5 (ACQ-5) change from baseline responder analysis at Week 24

5. BDA MDI 160/180 µg versus AS MDI 180 µg
6. BDA MDI 80/180 µg versus AS MDI 180 µg

Asthma Quality of Life Questionnaire for 12 years and older (AQLQ+12) change from baseline responder analysis at Week 24

7. BDA MDI 160/180 µg versus AS MDI 180 µg

8. BDA MDI 80/180 µg versus AS MDI 180 µg

Statistical tests for the secondary analyses will be conducted at the 5% level of significance (2-sided). Inference for a test in the defined order is dependent on statistical significance having been achieved in the preceding tests, if this is not achieved then nominal p-values will be provided. As per the primary analysis, comparisons of BDA MDI 160/180 versus AS MDI will exclude the pediatric population, whilst comparisons of BDA 80/180 versus AS MDI will include all ages.

Statistical significance can only be claimed on the key secondary endpoints if a statistically significant treatment effect is observed on both BDA MDI 160/180 µg and BDA MDI 80/180 µg versus AS MDI for the primary endpoint of time to first severe exacerbation.

8.2 Sample size estimate

A sample size of 1000 adult and adolescent subjects per treatment group and observation of the 570 first severe exacerbation events provides this study with 87% power to observe a 25% reduction in the risk of severe exacerbation with at least 1 dose of BDA MDI versus AS MDI assuming the Hochberg procedure (Hochberg 1988) for multiple testing and a 2-sided significance level of 5%.

In addition, up to 100 subjects in the 4 to 11 year age group with moderate to severe asthma will be randomized with approximately 50 subjects randomized to the AS MDI group and 50 subjects randomized to the low dose BDA MDI group only.

8.3 Definitions of analysis sets

8.3.1 Full analysis set

The full analysis set (FAS) 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 in the FAS.

The efficacy and attributable estimand will include all data obtained up to pDBL, before subjects discontinue randomized treatment and/or before a change in maintenance therapy for lack of asthma control. The effectiveness estimand will utilize all observed data up to randomized treatment discontinuation, regardless of whether subjects experience a change in maintenance therapy for lack of asthma control. The de facto estimand will utilize all observed data, including postIP discontinuation data, regardless of a change in maintenance therapy.

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 more than 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 FAS.

8.5 Outcome measures for analyses

8.5.1 Primary efficacy analysis

The primary analysis will include all data obtained up to pDBL, before subjects discontinue randomized treatment and/or before a change in maintenance therapy for lack of asthma control and will use the FAS, in accordance with the primary estimand (Section 8.1.1).

8.5.1.1 Derivation of time to first severe asthma exacerbation

Time to first severe asthma exacerbation will be calculated as the time from randomization until the start date of the first severe asthma exacerbation:

Start date of first severe asthma exacerbation – Date of randomization (Visit 2) +1

Subjects not having any severe asthma exacerbation will be censored at the date of their latest follow-up or EOS, for subjects who discontinue IP/have a change in maintenance therapy for lack of asthma control, the earliest of either day of discontinuation or day there was a change to maintenance therapy.

8.5.2 Secondary efficacy analyses

The secondary analyses will include all data obtained up to the pDBL, before subjects discontinue randomized treatment and/or before a change in maintenance therapy for lack of asthma control and will use the FAS, in accordance with the primary estimand (see Section 8.1.1).

8.5.2.1 Derivation of annualized severe asthma exacerbation rate

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=∑ number of severe exacerbations*365.25/∑ follow-up*

where the summations are over all subjects within a treatment arm.

For subjects who do not discontinue IP or do not receive a change in maintenance therapy for lack of asthma control, *follow-up* is calculated as:

[Date of latest follow-up or EOS] – [date of randomization (Visit 2)] – [cumulative duration of severe exacerbation(s)] + 1.

Otherwise, follow-up is calculated as the date of earliest occurrence of either IP discontinuation or change in maintenance therapy for lack of asthma control:

[Date of IP discontinuation/change in maintenance therapy] – [date of randomization (Visit 2)] - [cumulative duration of severe exacerbation(s)] + 1.

8.5.2.2 Derivation of total systemic corticosteroid exposure

Total systemic corticosteroid (SCS) exposure reported as the total annualized dose will be calculated for each subject as the sum of the cumulative doses of corticosteroid divided by the duration of time (years) the subject was in the study, from randomization and up to treatment discontinuation.

Each SCS will be normalized to the equipotent dose of prednisone (mg) before calculating the annualized total dose.

8.5.2.3 Derivation of Asthma Control Questionnaire-5 variables

All 5 symptom questions are assessed on a 7-point scale (0=good control; 6=poor control). The overall score is the mean of the 5 symptom items. At least 4 out of the 5 symptom items are needed to provide an ACQ-5 score.

The minimal important difference (MID) in ACQ-5 score is estimated to be 0.5 (Juniper 2005). On the basis of the MID, responders at Week 24 are defined as subjects achieving a decline from baseline of at least 0.5:

- Responder: (Week 24 – baseline) ≤-0.5
- Nonresponder: (Week 24 – baseline) >-0.5

Subjects who discontinue treatment for any reason or receive a change in maintenance therapy for lack of asthma control before Week 24 will be classified as nonresponders. Baseline is defined as the most recent non-missing score before and including randomization (Visit 2).

A similar analysis will be conducted at Week 12. This will be considered an exploratory endpoint.

Additionally, changes from baseline ACQ-5 overall score at Week 12 and Week 24 will be categorized into the exploratory 3-level factor:

- Improvement: (Week 24 – baseline) $\leq$-0.5
- No Change: -0.5 < (Week 24 – baseline) <0.5
- Worsening: (Week 24 – baseline) $\geq$0.5

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

8.5.2.4 Derivation of Asthma Quality of Life Questionnaire +12 and Pediatric Asthma Quality of Life Questionnaire variables

As described in Section 5.1.2, there will be separate questionnaires for both adults and children. Both sets of questionnaires will be analyzed in a similar manner.

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 24 are defined as subjects achieving an increase from baseline of at least 0.5:

- Responder: (Week 24 – baseline) $\geq$0.5
- Nonresponder: (Week 24 – baseline) <0.5

Subjects who discontinue treatment before Week 24 for any reason will be classified as nonresponders. Baseline is defined as the most recent non-missing score before and including randomization (Visit 2).

A similar analysis will be conducted at Week 12. This will be considered an exploratory endpoint.

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

8.5.3 Exploratory analyses

The exploratory analyses will include all data obtained up to the pDBL, before subjects discontinue randomized treatment and/or before a change in maintenance therapy for lack of asthma control and will use the FAS, in accordance with the primary estimand (see Section 8.1.1).

8.5.3.1 Derivation of deterioration of asthma variables

Time to first deterioration of asthma and the raw deterioration of asthma rate will be calculated in a similar way as to time to first severe asthma exacerbation (see Section 8.5.1.1) and the raw annualized severe asthma exacerbation rate (see Section 8.5.2.1).

8.5.3.2 Derivation of time to treatment discontinuation or change in maintenance therapy for lack of asthma control

Time to treatment discontinuation or change in maintenance therapy for lack of asthma control will be calculated as the time from randomization until the earliest of treatment discontinuation/change in maintenance therapy for lack of asthma control:

Date of IP discontinuation/change in maintenance therapy –date of randomization (Visit 2) +1

Subjects not having prematurely discontinued treatment or receiving a change in maintenance therapy will be censored at the latest follow-up or EOS.

8.5.3.3 Derivation of Asthma Control Test responder variable

The MID in ACT score is estimated to be 3 (Schatz 2009). On the basis of the MID, the responders at Week 24 are defined as subjects achieving an increase from baseline of at least 3:

- Responder: (Week 24 – baseline) ≥ 3
- Nonresponder: (Week 24 – baseline) < 3

Subjects who discontinue treatment for any reason or receive a change in maintenance therapy for lack of asthma control before Week 24 will be classified as nonresponders. Baseline is defined as the most recent non-missing score before and including randomization (Visit 2).

8.5.3.4 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

"As needed"-free days

- An "as needed"-free day is defined as a day and night with no use of IP

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 "as needed" medication

8.5.3.5 Inhaled corticosteroid exposure

Additional inhaled corticosteroid exposure from BDA MDI will be calculated as the total daily number of puffs of randomized treatment.

Background maintenance therapy will be categorized into [low, medium, high] daily steroid dose. Maintenance therapy categorizations will be based on prescribed daily dose of maintenance therapy steroids.

8.6 Methods for statistical analyses

All tests will be 2-sided and at 5% level of significance unless otherwise stated. Adjustment will be made using the Hochberg procedure (Hochberg 1988) for the primary endpoint treatment comparisons.

In addition to the analyses described below, all variables will be summarized descriptively where appropriate.

8.6.1 Analysis of the primary variable

The primary analysis will target the efficacy estimand in the FAS population. The primary variable, time to first severe asthma exacerbation, will be analyzed using a Cox proportional hazards regression model to compare treatment arms. The model will be adjusted for the randomization stratification factors (age group [≥ 4 to 11, ≥12 to 17, ≥18]); region (North America, Western Europe and South Africa [Region 1] and rest of world [Region 2]); and number of prior severe exacerbations (1, >1) in the 12 months prior to screening (Visit 1) plus any severe exacerbation event experienced during the screening period and key covariates of interest with more detail to be provided in the SAP. The summary measure to compare

treatments is the estimated hazard ratio which will be presented with the corresponding 95% confidence interval and p-value.

The planned treatment comparisons for the primary analysis are:

1 BDA MDI 160/180 µg versus AS MDI 180 µg (superiority, primary objective)
2 BDA MDI 80/180 µg versus AS MDI 180 µg (superiority, primary objective)

The comparison of BDA MDI 160/180 µg versus AS MDI 180 µg will exclude the pediatric subjects (subjects aged 4 to 11 years) as they will not be randomized to BDA MDI 160/180 µg. For this analysis the age covariate will only have the 2 levels ≥12 to 17 and ≥18. However, the primary analysis for comparison of BDA MDI 80/180 µg versus AS MDI 180 µg will include subjects from all age groups.

Formally, the null and alternative hypotheses for comparisons 1 and 2 are:

H_0: $Hazard\ ratio$ (BDA MDI versus AS MDI)=1,

H_A: $Hazard\ ratio$ (BDA MDI versus AS MDI)≠1

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. 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

Analysis of the secondary efficacy variables will be on the FAS population. For all secondary analyses the same treatment comparisons as for the primary analysis will be conducted (see Section 8.6.1). Please see the hierarchical testing strategy for secondary endpoints (see Section 8.1.2).

8.6.2.1 Severe asthma exacerbation rate

Analysis of severe asthma exacerbation rate will target the efficacy estimand in the FAS population. Annualized severe asthma exacerbation rate will be analyzed using negative binomial regression to compare treatment groups. The response variable in the model will be the number of severe asthma exacerbations. The model will adjust for (age group [≥ 4 to 11, ≥12 to 17, ≥18]); region (North America, Western Europe and South Africa [Region 1] and rest of world [Region 2]); and number of prior severe exacerbations (1, >1) in the 12 months prior to randomization) and key covariates of interest with more detail to be provided in the SAP.

The logarithm of the time at risk of experiencing an exacerbation will be used as an offset variable in the model. Time during an exacerbation or in the 7 days after an exacerbation will not be included in the calculation. From the negative binomial model, the annual severe asthma

exacerbation rates will be estimated, and the summary measure for the comparison of treatments will be the estimated rate ratio which will be presented with the corresponding 95% confidence interval and p-value.

The raw annualized exacerbation rate will also be summarized descriptively by treatment, using the derivation described in Section 8.5.2.1.

8.6.2.2 Asthma Control Questionnaire-5

The responder variable described in Section 8.5.2.3 at Week 24 will be analyzed using a logistic regression model to compare treatment groups. The model will be adjusted for the randomization stratification factors (age group [≥ 4 to 11, ≥12 to 17, ≥18]); region (North America, Western Europe and South Africa [Region 1] and rest of world [Region 2]); and number of prior severe exacerbations (1, >1) in the 12 months prior to screening (Visit 1) plus any severe exacerbation event experienced during the screening period and key covariates of interest with more detail to be provided in the SAP. From the logistic regression model, treatment effects will be estimated by odds ratios and their corresponding 95% confidence intervals and p-values.

The exploratory endpoint for responder analysis at Week 12 and 3 factor categorization of ACQ-5 (Improvement; No change; Worsening) at Week 12 and Week 24 will be analyzed using an ordinal logistic regression and adjusting for the similar covariates. Full details of these analyses will be provided in the SAP.

Analysis of change from baseline in ACQ-5 at Week 24 will target the efficacy estimand in the FAS population. The treatment effect for change from baseline in ACQ-5 will be estimated using a repeated measures analysis. All data up to Week 24 will be included in the model, with terms for treatment, visit, treatment*visit, and baseline ACQ-5. The model will also be adjusted for the randomization stratification factors (age group [≥ 4 to 11, ≥12 to 17, ≥18]); region (North America, Western Europe and South Africa [Region 1] and rest of world [Region 2]); and number of prior severe exacerbations (1, >1) in the 12 months prior to screening (Visit 1) plus any severe exacerbation event experienced during the screening period and key covariates of interest with more detail to be provided in the SAP. 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 compound symmetric variance-covariance matrix 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, including the EOS visit/PDV and the safety follow-up telephone contact.

In all the scenarios above, baseline is defined as the most recent score before and including randomization (Visit 2).

8.6.2.3 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-5 (Section 8.6.2.2). The exploratory endpoint for responder analysis at Week 12 will also be analyzed in a similar way.

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 on AQLQ+12 and PAQLQ overall scores up to Week 24 will be estimated in the same way as ACQ-5, using a repeated measures analysis.

Change from baseline will also be described descriptively for all study visits, including the EOS visit/PDV and safety follow-up telephone contact for each of the domains and the overall scores.

In all the scenarios above, baseline is defined as the most recent score before and including randomization (Visit 2).

8.6.2.4 Total systemic corticosteroid exposure

The total systemic corticosteroid exposure as total annualized dose of SCS (mg/year) will be presented descriptively by treatment. A comparison in total annualized SCS dose between BDA MDI 80/180 vs AS MDI 180 and BDA MDI 160/180 vs AS MDI 180 will be analyzed using a Wilcoxon rank sum test and associated p-values will be presented along with the descriptive summary.

Additionally, the total SCS exposure will be summarized descriptively as the total number of days with SCS treatment due to asthma for all subjects. A similar descriptive summary will be done for all subjects who administered at least 1 dose of SCS during the study.

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. Adverse events will also be listed for each subject.

8.6.3.2 Vital signs

Change from baseline throughout the study will be assessed for resting pulse and blood pressure. Measurements should be taken in the sitting position after at least 10 minutes of rest.

Baseline is defined as the most recent non-missing measurement before and including randomization (Visit 2).

8.6.3.3 Clinical chemistry and hematology

Clinical chemistry, hematology; and morning serum cortisol assessments 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 and including randomization (Visit 2).

8.6.3.4 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 Deterioration of asthma

Annualized deterioration of asthma and time to first deterioration of asthma will be analyzed in the same way as the time to first severe asthma exacerbation (Section 8.6.1) and annualized severe asthma exacerbation rate (Section 8.6.2.1).

8.6.4.2 Prebronchodilator FEV_1

The treatment effect for change from baseline in FEV_1 (mL) will be estimated using a MMRM analysis. FEV_1 data from all visits up to Week 24 will be included in the model, with terms for treatment, visit and treatment*visit with baseline FEV_1 included as a covariate. The model will be adjusted for the randomization stratification factors (age group [≥ 4 to 11, ≥12 to 17, ≥18]); region (North America, Western Europe and South Africa [Region 1] and rest of world [Region 2]); and number of prior severe exacerbations (1, >1) in the 12 months prior to screening (Visit 1) plus any severe exacerbation event experienced during the screening period and key covariates of interest with more detail to be provided in the SAP. 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 compound symmetric variance- covariance matrix will be used instead. This model will be used to give assessments of the treatment effect as well as 95% confidence intervals at Week 12 and Week 24.

Baseline is defined as the most recent non-missing measurement before and including randomization (Visit 2).

8.6.4.3 Morning peak expiratory flow

The mean value of change from baseline in morning PEF data during treatment will be analyzed by analysis of covariance with treatment as a factor and, baseline morning PEF score as a continuous covariate. The model will also be adjusted for the randomization stratification factors (age group [≥ 4 to 11, ≥12 to 17, ≥18]); region (North America, Western Europe and South Africa [Region 1] and rest of world [Region 2]); and number of prior severe exacerbations (1, >1) in the 12 months prior to screening (Visit 1) plus any severe exacerbation event experienced during the screening period and key covariates of interest with more detail to be provided in the SAP. The summary measure for the comparison of treatments will be the estimated mean difference, presented with the corresponding 95% confidence interval.

Additionally a repeated measures 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 and associated p-value.

Change from baseline in morning PEF will also be summarized for each subject by treatment group using summary statistics.

For all scenarios above, baseline morning PEF is defined as the average during the 10 days prior to randomization (Visit 2) during run-in. Morning PEF will be captured via the eDiary.

8.6.4.4 Other eDiary variables

Evening PEF, reliever therapy use, asthma symptoms (day, night, and total), night-time awakenings due to asthma symptoms, symptom-free days, "as needed"-free days and asthma control days will be analyzed in the same way as the morning PEF.

Baseline is defined as the average during the 10 days prior to randomization (Visit 2) during run-in.

8.6.4.5 Time to treatment discontinuation or change in maintenance therapy for lack of asthma control

Time to treatment discontinuation or change in maintenance therapy for lack of asthma control will be analyzed as per the primary analysis described in Section 8.6.1.

8.6.4.6 Asthma Control Test

The ACT/C ACT will be summarized as per the secondary analysis of change from baseline and responder analysis in ACQ-5 in Section 8.6.2.2.

Baseline is defined as the most recent non-missing score before and including randomization (Visit 2).

8.6.4.7 Inhaled corticosteroid exposure

Inhaled corticosteroid exposure as mean daily number of puffs of randomized treatment will be summarized descriptively. Additionally, descriptive summaries of the main daily number of puffs will be further broken down into subgroups of background maintenance therapy prescribed use of [low, medium, high] daily dose.

8.6.5 Subgroup analysis

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

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8.6.6 Sensitivity analysis

8.6.6.1 Tipping point analysis

Multiple imputation tipping point analysis under the missing not at random assumption will be conducted. For subjects in the BDA MDI groups, this method will impute missing values post-study discontinuation/change in maintenance for lack of asthma control assuming they were more likely to have a severe asthma exacerbation event than as implied under the missing at random assumption. The tipping point analysis will look at by how much the event rate would need to increase for the result to become non-significant. The full details of the analysis will be specified in the SAP.

8.6.6.2 Attributable estimand

Analysis of the attributable estimand will be conducted using data obtained before subjects discontinue randomized treatment and/or before a change in maintenance therapy for lack of asthma control and will use the FAS. However, the data that is missing due to randomized treatment discontinuation and/or a change in maintenance therapy will be imputed on the basis of the 95th or 5th percentile of the AS MDI prn distribution if the reason is reasonably attributable to tolerability or lack of control. 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.

8.6.6.3 Effectiveness estimand

Analysis of the effectiveness estimand will be conducted in the FAS in which all observed data will be utilized regardless of whether subjects experience a change in maintenance therapy for lack of asthma control.

8.6.6.4 De facto estimand

Analysis of the de facto estimand will be conducted on the FAS in which all observed data will be utilized, regardless of whether subjects experience a change in maintenance therapy or are discontinued from randomized study treatment.

8.6.6.5 COVID-19 pandemic impacts

As the trial is on-going during 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 IP.

As a minimum, the number of missed visits, premature withdrawals, and efficacy assessments not conducted 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 SAP, prior to database lock and unblinding.

Similarly, as a minimum, the number of scheduled safety assessments missed 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 scheduled 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 WEDC 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 if 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

All randomized subjects who do not prematurely discontinue will have a minimum of 24 weeks of treatment. The study treatment period will continue (extension phase) until the required 570 first severe exacerbation events, as defined per protocol, have been reached; and the last subject has completed 24 weeks of treatment. The EOS visit will be planned once the 570 first severe exacerbation events occur. If a subject's treatment is ≥24 weeks then the subject's EOS visit will occur at their next scheduled clinic visit. Once the PCD has been reached, any ongoing subject ≥24 weeks will return to complete their EOS visit at their next scheduled clinic visit. The safety follow-up telephone contact will occur 2 weeks (±4 days) after EOS or PDV, if applicable. The end of the study is defined as "the last visit of the last subject undergoing the study".

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

Adverse events and medical/surgical history will be classified according to the terminology of the latest version of the Medical Dictionary for Regulatory Activities at the time of database lock. Medications will be classified according to the World Health Organization Drug Dictionary. All coding will be performed by the Medical Coding Team at [redacted]

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

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

Serious adverse event reconciliation

Serious AE 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.

Primary outcome database lock

When all required 570 first severe exacerbation events have occurred and the last adult subject has completed 24 weeks of treatment and safety follow-up, the data cleaning should be completed for the primary outcome database lock. Database lock will occur once all data have been coded, validated, signed, and locked, and clean file has been declared. Data will be unblinded at the primary outcome database lock.

Final database lock

The study treatment period will continue for children (4 to 11 years) and adolescents (12 to 15 years) who have not completed 24 weeks of treatment by the time of the primary outcome database lock. The safety follow-up telephone contact will occur 2 weeks (±4 days) after EOS

or PDV, if applicable. Database lock will occur once 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, analyzed, and accurately reported according to the Clinical Study Protocol, GCP, guidelines of the ICH, and any applicable regulatory requirements. The investigator will contact the Sponsor immediately if contacted by a regulatory agency about an inspection at the center.

11 LIST OF REFERENCES

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12 SUMMARY OF CHANGES

12.1 Changes made to Version 3.0

Section	Changes made to Version 3.0, 21 July 2020 to develop global amendment, Version 4.0, 08April 2021
Cover page/Version History	Date and version changed; updated sponsor address; brief summary of amendment added.
Clinical Study Protocol Synopsis	Updated the estimated date of last subject completed from Q3 2021 to Q1 2022.
Clinical Study Protocol Synopsis 3.3 Subject enrollment and randomization; 8.2 Sample size estimate	Clarification that up to 100 subjects in the 4 to 11-year age group with moderate to severe asthma will be randomized.
Clinical Study Protocol Synopsis 1.2 Rationale for study design, doses, and control groups, 1.4 Study design; Table 1, footnote c; 4.2 Randomization/treatment period/extension phase	Clarification that the treatment period will continue until the last adult subject has completed 24 weeks of treatment.
Clinical Study Protocol Synopsis	Clarification that pediatric subjects will continue until 24 weeks of treatment have been reached for each pediatric patient, defined as the final completion date.
Clinical Study Protocol Synopsis; 8.5.1 Primary efficacy analysis	Clarification that the primary efficacy analysis will include all data up to the PCD.
Clinical Study Protocol Synopsis; 8.5.2 Secondary efficacy analyses	Clarification that the secondary efficacy analysis will include all data up to the PCD.
1.2 Rationale for study design; doses, and control groups; 1.4 Study design	Clarification that not all pediatric subjects will have 24 weeks of treatment at time of PCD.

Section	Changes made to Version 3.0, 21 July 2020 to develop global amendment, Version 4.0, 08April 2021
3.1 Inclusion criteria #6	Clarification that subjects aged ≥12 years of age must demonstrate reversibility at Visit 1. Added the following sentence: Subjects aged 4 to 11 years of age will perform the reversibility test, but do not require demonstration of reversibility during Visit 1 and may enroll, provided documented historical reversibility within 1 year is available. Subjects aged 4 to 11 years who previously failed inclusion criterion 6 will be permitted to rescreen. Each subject may re-screen only once.
3.1 Inclusion criteria #17, subbullet ii	Added additional forms of birth control: a condom with spermicide, intrauterine device (IUD), or intrauterine hormone-releasing system (IUS).
4.1 Screening and run-in period	Updated that subjects aged 4 to 11 years of age who previously failed inclusion criterion 6 will be permitted to rescreen.
4.2 Randomization/treatment period/extension phase	Added that children and adolescents ongoing in treatment after the PCD will continue in follow-up until they have completed 24 weeks of treatment.
5.2.1 Laboratory safety assessments	Added serum cortisol assessments along with those for chemistry and hematology.
New section: 8.1.2 Primary outcome analysis (subsequent heading numbering updated)	Primary outcome database lock (pDBL) will commence once all randomized adults (≥18 years) have attended their EOS visit at the PCD. The analyses of primary, secondary, exploratory, and safety objectives will include all data up to the pDBL, which may include data for children (4 to 11 years) who are still on-going in the trial and have not yet completed the 24-week treatment period.

Section	Changes made to Version 3.0, 21 July 2020 to develop global amendment, Version 4.0, 08April 2021
	A final data base lock will occur after the pDBL, once all children have completed the EOS visit and safety follow-up. Patient level listings of data for children who were on-going at the pDBL will be reported at the final database lock. No efficacy analyses will be conducted on data collected following the pDBL.
8.3.1 Full analysis set	Clarification that efficacy and attributable estimand will include all data obtained up to pDBL.
8.5.3 Exploratory analyses	Clarification that the exploratory analyses will include all data obtained up to pDBL.
8.5.3.5 Total inhaled corticosteroid exposure; 8.6.4.7 Total inhaled corticosteroid exposure	Headings revised: 8.5.3.5 Inhaled corticosteroid exposure 8.6.4.7 Inhaled corticosteroid exposure Text revised to describe categories for maintenance therapy in addition to methods used to calculate and analyze inhaled corticosteroid exposure.
8.6.6 Primary outcome analysis	Section removed; subsequent heading numbering updated
9.3 Study timetable and end-of-study	Updated that all randomized subjects who do not prematurely discontinue will have a minimum of 24 weeks of treatment. Deleted text defining PCD. Once the PCD has been reached, any ongoing subject **≥24 weeks** will return to complete their EOS visit at their next scheduled clinic visit
9.4 Data management	Revised to clarify that when the last adult subject has completed 24 weeks of treatment and safety follow-up,

Section	Changes made to Version 3.0, 21 July 2020 to develop global amendment, Version 4.0, 08April 2021
	the data cleaning should be completed for the primary outcome database lock. Final database lock revised to clarify that study treatment period will continue for children (4 to 11 years) and adolescents (12 to 17 years) who have not completed 24 weeks of treatment by the time of the primary outcome database lock.
Throughout document	Additional nonsubstantial changes for administrative, typographical, and/or grammatical corrections were made.

12.2 Changes made to Version 2.0

Section	Changes made to Version 2.0, 29 July 2019 to develop global amendment, Version 3.0, 21 July 2020
Version History	Date and version changed; brief summary of amendment added.
Clinical Study Protocol Synopsis	Updated the estimated date of last subject completed from Q3 2020 to Q3 2021.
1.3 Benefit/risk and ethical assessment	Added justification to continue study enrollment and treatment during the COVID-19 pandemic.
1.5.2 Adjudication committee	Clarification that the committee will adjudicate "after medical monitoring review."
2.2 Secondary Objective and Clinical Study Protocol Synopsis	Updated a secondary endpoint to total "systemic" corticosteroid exposure over the treatment period.
2.4 Exploratory Objective Clinical Study Protocol Synopsis	Addition of 2 additional exploratory endpoints:

Section	Changes made to Version 2.0, 29 July 2019 to develop global amendment, Version 3.0, 21 July 2020
	• ACQ-5 change from baseline and responder (3-factor) analysis at Week 12 and Week 24 • Inhaled corticosteroid exposure over the treatment period
3.1 Inclusion criteria (item 2) and Clinical Study Protocol Synopsis	Removed the inclusion of children ≥6 years of age in Italy. Removed the inclusion of adolescent subjects ≥12 years of age in Spain.
3.1 Inclusion criteria (item 4)	Clarification that subjects on ICS alone or in combination with LABA are allowed to have additional maintenance medication; specified leukotriene "receptor antagonists" are allowed.
3.1 Inclusion criteria (item 5)	Updated to reflect predicted normal FEV_1 values of ≥40 to ≤90% for adults and ≥60% for subjects aged 4 to 17. Specified that subjects 4 to 17 years of age who previously failed this inclusion criteria due to the previous upper FEV_1 limit are permitted to re-screen once.
3.1 Inclusion criteria (item 7)	Clarification that subjects aged 4 to 11 will be eligible if they provide 2 acceptable/repeatable measurements for spirometry.
3.1 Inclusion criteria (item 17)	Removal of the reference to ≥50 years of age as part of the definition of menopausal women.
3.2 Exclusion criteria (item 25)	Specification that subjects are excluded if they had been previously "randomized" in this study or another PT007 or PT027 study.
3.3 Subject enrollment and randomization and Clinical Study Protocol Synopsis	Updated the number of subjects screened from 4300 to 6000.

Section	Changes made to Version 2.0, 29 July 2019 to develop global amendment, Version 3.0, 21 July 2020
3.5 Methods for assigning treatment groups, 7.2 Dose and treatment regimens, and Clinical Study Protocol Synopsis	Removed reference to screening Visit 1a. Added clarification that randomization stratification will include the number of prior severe exacerbations (1, >1) in the 12 months prior to screening (Visit 1) "plus any severe exacerbation event experienced during the screening period."
3.11 Screen failures	Modification to allow for rescreening once in children and adolescents who failed because they did not meet the now obsolete upper FEV_1 % predicted limit.
4 Study plan and timing of procedures (Table 1)	Footnote f and applicable "X" indicators were removed due to country specific changes. Subsequent footnote marker letters were updated. Footnote h (previously footnote i) was updated to remove Italy and add Argentina as requiring additional pregnancy testing. Footnote m (previously footnote n) updated to reflect predicted normal FEV_1 values of ≥40 to <90% for adults and ≥60% for subjects aged 4 to 17.
4.1 Screening and run-in period 4.2 Randomization/ treatment period/extension phase, and 5.3.1 Physical examination	Italy-specific information regarding full examinations and pregnancy testing was removed.
5.1.8.2 COVID-19 and Pulmonary Function Testing	Addition 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. Proper cleaning and hygiene guidance is to be followed.
5.2.1 Laboratory safety assessments (Table 2)	Removed Italy and added "Argentina" to footnote a (pregnancy testing requirements).

Section	Changes made to Version 2.0, 29 July 2019 to develop global amendment, Version 3.0, 21 July 2020
5.3.2 Concomitant medications	Updated to indicate that previous medications should be recorded if they were taken within 3 months before screening. Added that asthma medication history will be recorded for 12 months before screening.
6.3.9 COVID-19 Adverse Events	Added to provide instructions on how to manage AEs and SAEs related to the COVID-19 pandemic.
7.8.1 Maintenance therapies	Addition to allow subjects receiving maintenance allergy immunotherapy (AIT) to continue their AIT. Specified that the initiation of AIT during the study is not allowed.
7.8.3 Prohibited medications	Clarification that polyclonal antibody therapy is prohibited but the use of intra-ocular monoclonal or polyclonal antibody therapy is allowed. Clarification that the use of specific cardio-selective beta-blockers in low daily doses, eg, metoprolol in doses up to 100 mg/d, are allowed.
8.1.2 Type 1 error control and Clinical Study Protocol Synopsis	Added information about hierarchical testing procedures to control the type-1 error in secondary endpoint analyses. Details regarding testing procedures, the order of testing for secondary endpoints, and when statistical significance can be claimed, are provided.
8.3.1 Full analysis set	Clarification that the effectiveness estimand will utilize all observed data up to randomized treatment discontinuation, regardless of whether subjects experience a change in maintenance therapy for lack of asthma control. Added that the de facto estimand will utilize all observed data, including post-IP discontinuation data, regardless of a change in maintenance therapy.
8.3.2.1 Derivation of annualized severe asthma exacerbation rate	Updated the calculations of follow-up and IP discontinuation/change in maintenance therapy to

Section	Changes made to Version 2.0, 29 July 2019 to develop global amendment, Version 3.0, 21 July 2020
	exclude the cumulative duration of severe exacerbation(s).
8.5.2.2 Derivation of total systemic corticosteroid exposure, 8.6.2.4 Total systemic corticosteroid exposure, and Clinical Study Protocol Synopsis	Updated headings with "systemic" and replaced previous text regarding inhaled corticosteroid exposure. Specified methods to calculate and analyze total SCS exposure.
8.5.2.3 Derivation of Asthma Control Questionnaire-5 variables	Definition added for 3-level factor categorization (Improvement, No Change, and Worsening) for changes from baseline in the ACQ-5 overall scores at Weeks 12 and 24.
8.5.3.5 Total inhaled corticosteroid exposure and 8.6.4.7 Total inhaled corticosteroid exposure	Addition of sections to specify methods used to calculate and analyze total inhaled corticosteroid exposure.
8.6 Methods for statistical analyses	Removed reference to "2" primary comparisons and replaced with primary "endpoint treatment" comparisons.
8.6.1 Analysis of the primary variable	Specification that analyses would target the efficacy estimand in the FAS population. Added statement that 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. A sensitivity analysis will be conducted based on subjects' actual strata to assess the impact of miss-stratification on the model results.
8.6.1 Analysis of the primary variable, 8.6.2.2 Asthma Control Questionnaire-5, 8.6.4.2 Prebronchodilator FEV_1, and 8.6.4.3 Morning peak expiratory	Specified that the models for analyses of variables would be adjusted for the number of prior severe exacerbations (1, >1) in the 12 months prior to screening (Visit 1) "plus any severe exacerbation event

Section	Changes made to Version 2.0, 29 July 2019 to develop global amendment, Version 3.0, 21 July 2020
flow, and Clinical Study Protocol Synopsis	experienced during the screening period", and removed references to Visit 1a.
8.6.2 Analysis of the secondary efficacy variables	Specified that analyses would be conducted on the FAS population. Referenced Section 8.1.2 for hierarchical testing strategy for secondary endpoints.
8.6.2.1 Severe asthma exacerbation rate	Specification that analyses would target the efficacy estimand in the FAS population. The number of prior severe exacerbations in the 12 months prior to "randomization" was updated as a key covariate of interest.
8.6.2.2 Asthma Control Questionnaire-5	Addition of information for analysis of the 3-factor categorization of ACQ-5 using ordinal logistical regression. Specification that the analysis of change from baseline in ACQ-5 at Week 24 will target the efficacy estimand in the FAS population.
8.6.2.2 Asthma Control Questionnaire-5 and 8.6.2.3 Asthma Quality of Life Questionnaire +12 and Pediatric Asthma Quality of Life Questionnaire	Updated methods of analysis from MMRM to repeated measures analyses.
8.6.4.3 Morning peak expiratory flow	Addition of a repeated measures analysis of 4-weekly time intervals.
8.6.6 Primary outcome analysis	Removed "and final analysis" from heading.

Section	Changes made to Version 2.0, 29 July 2019 to develop global amendment, Version 3.0, 21 July 2020
	Clarification of the following: when subjects will return for their EOS visits, when data cleaning should be done, and when the primary (final) analysis will occur.
8.6.7.5 COVID-19 pandemic impacts	Addition to describe statistical methods that will be used to evaluate the impact of the COVID-19 pandemic on efficacy and safety variables.
11 List of References	Addition of reference to the American Academy of Allergy Asthma and Immunology for information regarding COVID-19 and Asthma. For Investigator Brochure reference, updated edition and date.
Appendix N, COVID-19 emergency measures permitted to ensure subject safety	Addition of 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 IP to subjects, laboratory testing, and spirometry testing are provided.
Throughout document	Updated study drug to "IP" for consistency. Additional nonsubstantial changes for administrative, typographical, and/or grammatical corrections were made.

12.3 Changes made to Version 1.0

Section	Changes made to Version 1.0, 11 Oct 2018 to develop global amendment, Version 2.0, 29 July 2019
Version History	Date and version changed, brief summary of amendment added.

Clinical Study Protocol Synopsis, 1.4 Study design, 3.3 Subject enrollment and randomization, 4 Study plan and timing of procedures (footnote b in Table 1), 4.1 Screening and run-in period	Updated the number of study sites/centers from 333 to 380 and an estimated screen failure rate to a range of 30% to 50%. Clarification on the timeframe (Visit 1 and Visit 1a) and possible extension of the screening period due to administrative reasons or a severe asthma exacerbation event (to a maximum of 9 weeks). Clarification on the use of patients' usual as-needed (prn) inhaled products and Sponsor-provided Ventolin (prn or prior to exercise) during screening. Addition of the de facto estimand as a treatment policy strategy defined in the draft International Conference on Harmonization (ICH) E9 addendum.
1 Introduction	Statement clarifying that albuterol is also known under the generic name of salbutamol (the international non-proprietary name).
1.2 Rationale for study design, doses, and control groups	Provided justification of the proposed doses for albuterol and budesonide based on the approved label for Proventil and the dose-ranging Study PT008001, respectively.
Clinical Study Protocol Synopsis, 1.4 Study design, 5.1.1.6.2 Symptom Reporting, 6.5 Overdose, and 7.2 Dose and treatment regimens	Clarification of the maximum daily dosing recommendation for subjects and notification/eDiary alert to medical monitors and investigators of any increased IP dosage in order to closely monitor treatment use with potential worsening asthma status.
1.5.2 Adjudication committee	Clarification on adjudication committee events-recording and case definition of "worsening of asthma" which would necessitate adjudication committee review.
Clinical Study Protocol Synopsis and 3.1 Inclusion criteria (item 2)	Specifying the inclusion of subjects 4 years of age in all countries with the exception of Italy, Serbia, Spain, Germany, Slovakia, and Ukraine.

	Specifying the inclusion of children ≥6 years of age only in Italy. Specifying the inclusion of adolescent subjects ≥12 years of age only in Serbia and Spain. Specifying the inclusion of adult subjects ≥18 years of age only in Germany, Slovakia, and Ukraine.
3.1 Inclusion criteria (item 4)	Additional clarification that up to 20% of all randomized patients will be permitted to have an additional maintenance medication (theophylline, leukotriene, or LAMA, in addition to either ICS alone or ICS/LABA fixed dose combination).
3.1 Inclusion criteria (item 5)	Clarification that if FEV_1 values are not within the permitted range at Visit 1, 1 re-test is required at Visit 1a before advancing to Visit 2 or being considered as a screen failure.
3.1 Inclusion criteria (item 6)	Clarification that if reversibility is not demonstrated at Visit 1, 1 retest for reversibility testing is required at Visit 1a before advancing to Visit 2 or being considered as a screen failure
3.1 Inclusion criteria (item 12)	Additional specification that the use of spacers are prohibited.
3.1 Inclusion criteria (items 15 and 18)	Addition of definition of complete abstinence (and that is an acceptable method of contraception only if it is consistent with the preferred and usual lifestyle of the subject); definition of double-barrier birth control; clarification on surgical sterility by vasectomy (for males); definition of postmenopausal status; addition of bilateral salpingectomy to the definition of surgical sterility; and clarification that contraceptive methods may only be recommended for adolescents who are already sexually active, and that the use of hormonal contraceptives must always be in consultation with a gynecologist (for females).

3.2 Exclusion criteria (item 1)	Additional specification regarding regular or occasional use of oxygen.
3.2. Exclusion criteria (item 4)	Addition of dupilumab as an example of prohibited medication.
3.2 Exclusion criteria (item 21)	Additional specification that currently pregnant females will also be excluded from study participation.
3.2. Exclusion criteria (new item 26)	Addition of new exclusion criterion #26: subjects who experience >1 asthma exacerbation during the screening period.
3.7 Methods for unblinding	Clarification that unblinding should be based on the investigator's clinical judgment (when the appropriate management and welfare of the subject requires knowledge of the treatment allocation) and that it is not required, for the investigator to inform the Sponsor or Sponsor's designee before unblinding.
3.8 Restrictions	Addition of dupilumab as an example of prohibited medications and other investigational treatments (other than the study drugs).
3.9 Treatment discontinuation by subject and/or Sponsor, 6.3.8 Hy's Law, and Appendix E Hy's Law	Clarification that in case of elevated liver enzymes AST and/or ALT ≥3×ULN and total bilirubin ≥2×ULN, the use of the IP will be suspended until the liver test values return to the normal range, and that if the liver enzyme values become elevated again after the recommencement of the IP, the subject will be discontinued from IP and withdrawn from the study.
3.9 Treatment discontinuation by subject and/or Sponsor, 4 Study plan and timing of procedures (footnote e in Table 1), 4.6 Follow-up	Additional clarification on PDV procedures (including potential follow-up TC) for subjects who discontinue treatment prior to EOS for any reason; and if the PDV is performed at least 14 days after the last study drug dose.
4 Study plan and timing of procedures (footnote f and i in Table 1), 4.1 Screening and run-in period, 4.2 Screening and	Additional assessments applicable to Italy ONLY; in Italy, a full physical examination will be performed at all visits with additional pregnancy testing to be

enrollment period, 5.2.1 Laboratory safety assessments (Table 2 notes), 5.3.1 Physical examination	conducted at monthly time points in women of childbearing potential.
1.3 Benefit/risk and ethical assessment, 4 Study plan and timing of procedures (footnote g in Table 1), 4.1 Screening and enrollment period, 4.2 Randomization/treatment period/extension phase, 4.3 End-of-study visit, 4.4 Unscheduled visit and premature discontinuation visit, 5.2 Safety assessments, 5.2.1 Laboratory safety assessments (Table 2), 5.3.1 Physical examination and 8.6.3.3 Clinical chemistry and hematology	Addition of height assessments for all subjects at V1 and additional height assessments for subjects <18 years of age. Additional morning serum cortisol assessments for all subjects at specified visits (Screening, Week 24, EOS and PDV). Clarification that assessments of height will continue in accordance with a subject's age at the time of signed informed consent/assent.
4 Study plan and timing of procedures (footnote i in Table 1) and 5.2.1 Laboratory safety assessments (Table 2)	Addition of urine pregnancy assessments to safety measurements for all women of childbearing potential throughout the duration of the study (unless otherwise specified).
4 Study plan and timing of procedures	Clarification on time points for dispensing and collection of eDiary.
4 Study plan and timing of procedures	Addition of dispensing Ventolin at V1.
5.1.1 Asthma exacerbation definition	Clarification of deterioration of lung function with examples for clarity and consistency.
5.1.1.5 Onset and duration of asthma exacerbations	Distinction on reporting severe asthma exacerbations as separate or singular events, based on successive SCS use within 7 days (or more).
8.1.1.6.1 Severe asthma exacerbation eCRF	Clarification on the appropriate reporting of severe asthma exacerbations during the screening period.

5.1.1.6.2 Symptom reporting	Clarification on the appropriate reporting of asthma signs or symptoms.
5.1.2.1 Asthma Quality of Life Questionnaire+12	Clarification that the AQLQ+12 will be used in subjects 12 years and older.
5.1.2.2 Pediatric Asthma Quality of Life Questionnaire	Clarification that the PAQLQ will be self-administered in subjects aged 7 to 11 years.
5.1.8.1 Reversibility Test	Clarification that prebronchodilator PFTs should be performed after at least 15 minutes of rest, and before administration of Ventolin. Removed wording that the confirmation of the FEV_1 measurements should be entered into the eCRF to confirm eligibility. Other than overall eligibility confirmation, there is no specific confirmation relating to this (other than overall eligibility confirmation).
5.2.3 Vital sign measurements and 8.6.3.2 Vital signs	Correction of blood pressure measurement to be taken in the seated position (and not supine).
5.3.2 Concomitant medications	Update of timeframe for concomitant medications to include those taken beginning within 12 months before screening.
6.4 Reporting of serious adverse events	Provision of additional reporting responsibility of Sponsor for serious unexpected adverse drug reactions related to IP.
6.5 Overdose, 6.7 Medication error	Clarification on the appropriate collection/recording/reporting of an Overdose/Medication Error with or without an associated AE/SAE.
7.8.1 Maintenance therapies and 7.8.2 Medications that may affect reversibility and FEV_1 testing	Modification to remove the advance notification for investigators to notify the Sponsor with regards to any proposed maintenance therapy changes.
7.8.3 Prohibited medications	Clarification/correction that inhaled short-acting anticholinergics (or short-acting muscarinic antagonists [SAMA]).

	Additional clarification that inhaled long-acting anticholinergics (or LAMA), except those that were started before screening and continued as part of maintenance treatment are prohibited. Correction to reflect that nonglucocorticoid nasal sprays are not prohibited.
Clinical Study Protocol Synopsis, 8.1.1 Estimands and 8.6.7.4 De facto estimand	Addition of the de facto estimand as a treatment policy strategy defined in the draft ICH E9 addendum and specification of population analyses.
8.5.2.2 Derivation of total corticosteroid exposure, 8.6.2.4 Total corticosteroid exposure	Change in how ICS and SCS are to be analyzed: ICS to be summarized as a mean daily dose; SCS to be summarized by duration of administration.
Appendix D, Additional safety information	Adjustment to reflect reporting investigators are highly encouraged to express their clinical opinion when presented with limited or insufficient information in the causality assessments. Further, that if the causality assessment cannot be made, these serious adverse events will be considered to be "related".
Appendix F Asthma Quality of Life +12 Questionnaire	Updated to April 2008 version.
Appendix G Pediatric Asthma Quality of Life Questionnaire	Updated to January 2001 version.
Appendix H Asthma Control Questionnaire-5 and -7	Updated to December 2002 version (and July 2011 version of the Interviewer-administered ACQ).
Throughout document	Nonsubstantial changes for administrative, typographical and/or grammatical corrections.

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.

[redacted]

APPENDIX B, PRIMARY INVESTIGATOR SIGNATURE PAGE

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

[redacted]

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

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.

The below defines the minimally acceptable documentation for inclusion criteria:

1 Signed and dated notes from a referring physician, including name and dose of the ICS/ICS/LABA inhaler (or names and doses, if used as separate inhalers).

2 Evidence of prescriptions for ICS/LABA medications that demonstrate coverage for the duration specified in inclusion criteria.

Low, Medium, and High Doses of Inhaled Corticosteroids

Adults and adolescents (12 years and older)			
	Daily dosage (µg)		
DRUG	**LOW**	**MEDIUM**	**HIGH**
Beclometasone dipropionate (CFC)[a]	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)[a]	100-200	>200-400	>400
Beclometasone dipropionate (HFA)	50-100	>100-200	>200
Budesonide (DPI)	100-200	>200-400	>400
Budesonide (nebules)	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
Triamcinolone acetonide	400-800	>800-1200	>1200

Abbreviations: CFC=chlorofluorocarbon propellant; DPI=dry powder inhaler; HFA=hydrofluoroalkane propellant; NA=not applicable

[a] 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)[a] (age group with adequate safety and effective data)
Beclometasone dipropionate (HFA)	200 (ages ≥5 years)
Budesonide nebulized	500 (ages ≥1 year)
Fluticasone propionate (HFA)	100 (ages ≥4 years)
Mometasone furoate	110 (ages ≥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

[a] Subjects 5 years and younger meeting GINA step 3 eligibility should be treated with double low-dose ICS or Low dose ICS + LTRA (Global Initiative for Asthma [GINA] 2018).

APPENDIX D, ADDITIONAL SAFETY INFORMATION

Further guidance on the definition of a serious adverse event (SAE)

Life -threatening

"Life -threatening" means that the subject was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the subject's death. "Life-threatening" does not mean that 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 a serious AE, 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 judgment 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 judgment 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 rechallenge.
- 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 judgment. With limited or insufficient information in the case, it is highly encouraged for the reporting investigator to express his/her clinical opinion. If (despite all efforts) the causality assessment cannot be made, these SAEs will be considered to be "related".

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

APPENDIX E, HY'S LAW

Introduction

This Appendix describes the process to be followed to identify and appropriately report cases of Hy's Law (HL). 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 aspartate aminotransferase (AST) and/or alanine transaminase (ALT) ≥ 3×ULN and total bilirubin (TBL) ≥ 2×ULN, IP will be suspended until the liver test values return to the normal range. If the AST, ALT or TBL 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 (PHL) criteria at any point during the study.

The investigator participates, with the Sponsor's clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether 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 AE and SAE according to the outcome of the review and assessment in line with standard safety reporting processes.

Definitions

Potential Hy's Law

AST and/or ALT ≥3× ULN **combined with** TBL ≥2×ULN at any point during the study after the start of IP irrespective of an increase in alkaline phosphatase (ALP).

Hy's Law

AST and/or ALT ≥3×ULN **combined with** TBL ≥2×ULN, where no other reason, other than the IP, can be found to explain the combination of increases, eg, elevated ALP 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 ≥3×ULN
- AST ≥3×ULN
- TBL ≥2×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 labs and whether these constitute an AE. Where an AE is entered due to elevations of local labs, the AE will be queried in the eCRF and elevated local lab 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 (See section below on "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 Hy's Law lab 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 the section "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 the section "Actions required when Potential Hy's Law criteria are met before and after starting IP".

If No: follow the process described in the section "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 M, SPIROMETRY ASSESSMENT CRITERIA

Acceptable Versus Usable Tests

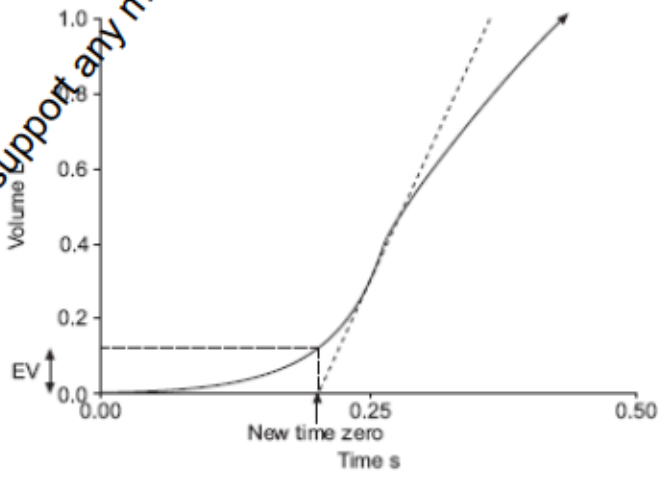
Acceptable **Tests must meet the following criteria:**

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

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

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

Figure 1 Example of a Usable Spirogram



EV=back extrapolation volume

The expanded version of the early part of a subject's volume-time spirogram, illustrating back extrapolation through the steepest part of the curve, where flow is 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 PEF.

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_1 must be within 0.150 L of each other

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

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

Post-dose assessments

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

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

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

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

APPENDIX N, 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:

Delayed Visits	○ 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. ○ If a return to lockdown is announced or the site is on lockdown and cannot process a visit, if possible, visits should be re-scheduled to earlier/later as required to safeguard subjects and site staff. ○ Randomization: If a subject is in screening and cannot complete the randomization 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 >28 days due to COVID-19, the following safety measurements should be repeated in advance of randomization: safety laboratory assessments, ECG, vital signs, concomitant medications, and medical/surgical history. ○ Visit 6/Week 24: 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.

Remote Visits	○ Where subjects have COVID-19 infection, the site is on lockdown, 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. ○ Before a remote visit is performed, 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 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. ○ If a remote visit is completed and it is considered appropriate and safe to continue IP, this could be dispatched direct to the subject by courier. ○ 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". ○ Remote Closeout Visits where necessary for sites that have no enrolled patients.
Subject Discontinuation	○ 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 and consent should be requested to perform continued remote follow-up of the subject "off treatment on-study" in line with global amendment 1.
Shipment of Drug from Site to Subjects	○ 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's medical records and preferably confirmed in writing via an email or other written means (eg, via post).

Safety Labs	○ Where central analysis is not possible, local testing is permitted. Lab normal ranges would need to be made available. ○ 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 the subject's next clinic visit if possible.
Spirometry	○ The investigator should request confirmation from the subjects 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.
Subjects with confirmed COVID-19 infection	○ 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. ○ The investigator should determine whether the subject's IP should continue, be interrupted, or stopped in accordance with the Clinical Study Protocol. ○ 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. ○ For new subjects previously identified as COVID-19 positive, a retest must be performed after resolution of symptoms (if present). The subject can only be considered for enrollment 4 weeks after having a negative result.