Bond Avillion 2 Development LP

Clinical Study Protocol	
Drug Substance	Budesonide/Albuterol Sulfate (BDA)
Study Code	AV006
Version	2.0
Date	19 March 2021

A Phase I, Randomized, Open-label, Single-dose, 2-way Crossover Study to Compare the Pharmacokinetics of Budesonide Delivered by PT027 to Pulmicort Respules® in Children with Asthma Aged 4 to 8 Years (BLANC)

Sponsor:

Bond Avillion 2 Development LP

[redacted]

EudraCT number: 2020-006058-27

VERSION HISTORY

Version 2.0, 19 March 2021
Removal of sample taken at 420-minute post-dose, replaced by a sample to be collected at 720 minutes (12 hours) post-dose.
Version 1.1, 16 February 2021
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 Phase I, Randomized, Open-label, Single-dose, 2-way Crossover Study to Compare the Pharmacokinetics of Budesonide Delivered by PT027 to Pulmicort Respules® in Children with Asthma Aged 4 to 8 Years (BLANC)

Study centers and number of children planned

It is planned to randomize a sufficient number of children with asthma to obtain evaluable pharmacokinetic (PK) samples from 10 children aged 4 to 8 years, with at least 4 children aged 4 to 5 years. Children who do not complete both treatments (Treatment A and Treatment B) may be replaced. Approximately 3 study centers in Bulgaria and the United States (US) are anticipated to be included.

Phase of development

Phase I Pediatric

Study design

This will be a randomized, multicenter, open-label, single-dose, 2-way crossover study. The purpose of this study is to compare the systemic exposure of budesonide delivered by the combination inhaler (budesonide/albuterol sulfate [BDA] metered-dose inhaler [MDI]) to Pulmicort Respules®

To be eligible for the treatment period of the study, children with asthma will be required to meet all of the inclusion and none of the exclusion criteria.

At Visit 2, the children will be randomly assigned to a treatment sequence:

A/B: BDA MDI at Visit 2 and Pulmicort Respules at Visit 3

OR

B/A: Pulmicort Respules at Visit 2 and BDA MDI at Visit 3

The study will comprise:

- Screening (Visit 1): within 14 days prior to randomization.
- Two treatment days:
  - Visit 2/Randomization visit: children will be dosed with a single dose of BDA MDI or Pulmicort Respules (A/B or B/A) and blood will be drawn for PK sampling for up to 12 hours after dosing in alignment with the sampling schedule.
  - Visit 3 will occur not less than 2 and no greater than 14 days after dosing on Visit 2 (ie, washout of 2 to 14 days) during which children will be dosed with a single dose of BDA MDI or Pulmicort Respules (A/B or B/A) and blood will be drawn for PK sampling for up to 12 hours after dosing in alignment with the sampling schedule.
- A follow-up telephone call (TC) will occur 2 to 5 days after the last dose (Visit 3) for safety follow-up (or early withdrawal, if applicable).

Safety will be monitored by spontaneously reported adverse events (AEs)/serious AEs (SAEs) and physical examination findings. Vital signs (heart rate and blood pressure) will be assessed at the beginning (pre-dose) and the end (post-last PK sample) of each clinic visit to ensure the well-being of the children.

Objectives

Primary objective	**Primary endpoints**
To determine and compare the systemic exposure of budesonide after single-dose administrations of BDA MDI and Pulmicort Respules.	AUC0-t and Cmax
Secondary objective:	**Secondary endpoints:**
To determine and compare other PK parameters for budesonide delivered by BDA MDI and Pulmicort Respules	tmax, tlast, t½λz, λz, Clast, and AUC0-inf (if feasible)
Safety objective:	**Safety endpoints:**
To assess the safety and tolerability of BDA MDI and Pulmicort Respules	AEs/SAEs

AE: adverse event; AUC0-inf: area under the plasma concentration-time curve from time zero to infinity; AUC0-t: area under the plasma concentration-time curve from time zero to time of last quantifiable concentration; BDA MDI: budesonide/albuterol sulfate metered-dose inhaler; Clast: drug concentration at last observed timepoint; Cmax: maximum observed plasma concentration; PK: pharmacokinetic; SAE: serious adverse event. tlast: time of last quantifiable plasma concentration; tmax: time to reach maximum observed plasma concentration; t½λz: half-life associated with terminal slope (λz) of a semi-logarithmic concentration-time curve.

Target subject population

This study will be conducted in male and female children with asthma, 4 to 8 years of age, with at least 4 children aged 4 and 5 years. It is planned to randomize enough children with asthma to obtain evaluable PK samples from 10 children.

Duration of treatment

The randomized treatment period will start after a screening period of up to 14 days. The open-label treatment will occur with single dosing of either the test (Treatment A) or reference product (Treatment B) at Visits 2 and 3, which will be approximately 1 week apart. Visit 3 will occur not less than 2 and no greater than 14 days after dosing on Visit 2 (ie, washout of 2 to 14 days). The overall study duration for the children will take approximately 3 to 4 weeks.

Investigational Medicinal Products		
	Treatment A (test product) [a]	**Treatment B (reference product)** [b]
Formulation:	BDA MDI	Pulmicort Respules
Supplier:	[redacted]	[redacted]
Strength:	80/90 µg (budesonide/albuterol)	1 mg budesonide
Dose:	2 inhalations	1 ampoule
Route of administration:	Oral inhalation	Oral inhalation
Regimen:	Single dose – 2 inhalations	Single nebulization dose
Special handling requirements:	Prime per instructions. Contamination avoidance procedures.	Nebulization until sputtering with nebulization cup as empty as possible Contamination avoidance procedures.

BDA MDI: budesonide/albuterol sulfate metered-dose inhaler

Note: The IMPs (test product and the reference product) will be manufactured by [redacted]

The placebo MDI for the test product will be used for training purposes only during screening (Visit 1) and will be taken home for training as well.

A saline ampoule for the reference product will be used for training purposes only during screening (Visit 1).

Pharmacokinetic assessments

A total of 10 samples (~4 mL each) will be taken for determination of budesonide in plasma per treatment visit at pre-dose and at 10, 20, 40, 60, 120, 240, 360, 480 and 720 minutes after dosing.

Statistical methods

Presentation and analysis of pharmacokinetic data:

The PK analysis set will consist of all randomized children for whom at least 1 of the primary PK parameters can be calculated and who have no major protocol deviations impacting PK.

A listing of PK blood sample collection times, and all reportable budesonide concentrations will be provided for all children. Budesonide concentrations will be summarized by treatment using descriptive statistics.

Plasma samples will be analyzed using non-compartmental analysis (NCA) to determine the pharmacokinetics (AUC0-t, Clast, Cmax, tmax, tlast, λz, t½λz, and AUC0-inf [if feasible)]) of budesonide in plasma.

This study is descriptive. There are no predefined statistical hypotheses and/or decision rules. The relative exposure of budesonide between BDA MDI versus Pulmicort Respules will be based on estimates of the AUC0-t and Cmax.

The AUC0-t and Cmax for budesonide will be compared between treatments using a multiplicative (ie, log-transformation) analysis of variance (ANOVA) model with treatment, sequence, period, and subject within sequence as fixed factors. Geometric mean treatment ratios and 90% confidence limits will be calculated from the model. Half-life and tmax will be compared by means of descriptive statistics.

Presentation and analysis of safety and eligibility data:

The safety analysis set will include all children who received any amount of either IMP (BDA MDI or Pulmicort Respules, respectively). Safety data will be presented in data listings. Continuous safety variables will be summarized using descriptive statistics (n, mean, standard deviation, minimum, median, maximum) by treatment. Categorical variables will be summarized in frequency tables (frequency and proportion) by treatment. The analysis of the safety variables will be based on the safety analysis set.

Determination of sample size

For this study, no prospective calculations of statistical power have been made. Complete data from 10 children is considered sufficient to provide information on the PK in this population without exposing more children than necessary to the IMP.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation or special term	Explanation
AE	Adverse event
ANOVA	Analysis of variance
AUC0-inf	Area under the plasma concentration-time curve from time zero to infinity
AUC0-t	Area under the plasma concentration-time curve from time zero to time of last quantifiable concentration
BDA	Budesonide/albuterol sulfate
BDA MDI (PT027)	Budesonide/albuterol sulfate metered-dose inhaler
BMI	Body mass index
Clast	Drug concentration at last observed (quantifiable) concentration
Cmax	Maximum observed plasma concentration
CRF	Case report form
CRO	Clinical research organization
CSP	Clinical study protocol
CYP	Cytochrome P450
DDI	Drug-drug interaction
EC	Ethics Committee; synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
eCRF	Electronic case report form
EDC	Electronic data capture
EU	European Union
FEV1	Forced expiratory volume in 1 second
GCP	Good Clinical Practice
GINA	Global Initiative for Asthma
GMP	Good Manufacturing Practice
HFA	Hydrofluoroalkane
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
ICS	Inhaled corticosteroid
IMP	Investigational medicinal product
λz	Terminal elimination rate constant
LABA	Long-acting β2-agonist

Abbreviation or special term	Explanation
LAMA	Long-acting muscarinic antagonist
LAR	Legally authorized representative
LTRA	Leukotriene receptor antagonist
MDI	Metered-dose inhaler
MedDRA	Medical Dictionary for Regulatory Activities
NCA	Non-compartmental analysis
PK	Pharmacokinetic(s)
PRN	As-needed
QID	Four times a day
SABA	Short-acting β2-agonist
SAE	Serious adverse event
SAMA	Short-acting muscarinic antagonist
SAP	Statistical analysis plan
SOC	System Organ Class
SULT1A3	Sulfotransferase 1A3
TEAE	Treatment-emergent adverse event
t½λz	Half-life associated with terminal slope (λz) of a semi-logarithmic concentration-time curve
tlast	Time of last quantifiable plasma concentration
tmax	Time to reach maximum observed plasma concentration
TC	Telephone call
US	United States

1 INTRODUCTION

1.1 Background

Bond Avillion 2 Development LP (Sponsor) is developing budesonide/albuterol sulfate (PT027, a fixed-dose combination product; hereafter referred to as budesonide and albuterol sulfate metered-dose inhaler [BDA MDI]) pressurized inhalation suspension product in adults and children (≥4 years of age) with asthma. Please refer to the current Investigator's Brochure (IB) for additional information (1).

Albuterol is a short/rapid-acting β2-agonist (SABA), inducing airway smooth muscle relaxation and reducing or preventing bronchoconstriction. Albuterol is approved in many countries in multiple formulations for treatment or prevention of bronchoconstriction, and is also known under the generic name of salbutamol. In clinical practice, albuterol is used as reliever therapy on an as-needed (PRN) basis (2).

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

Research studies have demonstrated that inhaled corticosteroid (ICS) agents potentiate the effects of SABAs in reducing airway smooth muscle tone (3) and can reverse adrenergic receptor tolerance and desensitization (4). 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 (5).

Combining albuterol with budesonide in the BDA MDI combination product should not only provide rapid bronchodilation, but also treat worsening airway inflammation by the addition of the budesonide component. Current treatment guidelines (2) recommend addition of low-dose ICS to SABA used as reliever medication as early as in Global Initiative for Asthma (GINA) step 1 asthma (previously treated with SABA PRN alone), broadening the range of asthma severity grades that would be treated by both ICS and β2-agonist. Anti-inflammatory and bronchodilation components used PRN in a fixed-dose combination are expected to result in overall better asthma control and decreased risk of experiencing asthma symptoms than bronchodilation alone.

1.2 Rationale for study design, doses and control groups

The BLANC study is a Phase I, randomized, multicenter, open-label, single-dose, 2-way crossover study to compare the pharmacokinetics (PK) of budesonide delivered by BDA MDI to Pulmicort Respules® in children with asthma aged 4 to 8 years. Avillion is obtaining safety and efficacy information for the intended PRN use of BDA MDI in patients with asthma aged

4 years and older in 2 ongoing Phase III pivotal studies: the MANDALA study, which investigates time to first severe exacerbation, and the DENALI study, which investigates change from baseline in forced expiratory volume in 1 second (FEV1) AUC0-6 hours over 12 weeks and change from baseline in trough FEV1 at 12 weeks.

For BDA MDI, a single dose of 160/180 µg (given as 2 inhalations of 80/90 µg [budenoside/albuterol respectively]) will be administered. The selection of dose is limited by the albuterol component to be given as a single dose and is chosen to be as high as possible for the budesonide component to ensure adequate PK measurements. A dose of 160/180 µg is considered relevant for budesonide PK measurements and safe for albuterol based on dosing recommendations for Proventil in children (6).

For Pulmicort Respules, a single dose of the highest recommended dose of 1 mg will be studied (7). This dose is known to be safe in this study's age group and is adequate to measure PK parameters of budesonide after a single dose.

Based on the known metabolic routes of budesonide and albuterol, the potential for a drug-drug interaction (DDI) between these 2 drugs is low. Budesonide is known to be a substrate of cytochrome P450 (CYP) 3A, and the effects of inhibitors of CYP3A on budesonide PK are well documented. Information available in the published literature indicates that the primary enzyme responsible for the metabolism of albuterol in humans is sulfotransferase 1A3 (SULT1A3); labelling for albuterol does not suggest any potential for metabolic DDI. The lack of a DDI between budesonide and albuterol was confirmed in Study D6930C00003, which was designed to demonstrate comparable systemic exposure between BDA MDI and the mono-components in healthy volunteers. This study also confirmed comparability of the formulation of the combination product BDA MDI versus the mono-products.

In the United States (US) development program for BDA MDI, Pulmicort Respules will be used as a reference product for the BDA MDI marketing application for children ages 4 and 5 years. It is therefore required that a scientific bridge be established between the test and reference products which can be obtained by determining the comparability of systemic budesonide exposure of both products. Avillion is proposing to enroll children 4 to 8 years of age with asthma in this study to facilitate the collection of sufficient PK data to adequately bridge BDA MDI to Pulmicort Respules.

13 Benefit/risk and ethical assessment

To mitigate any potential risks, all children will be closely monitored to ensure child safety. At study visits, children will only be discharged from the study center based on the Investigator's clinical judgment.

The study will be conducted in accordance with International Council for Harmonisation (ICH) guidelines. Permission from the research ethics committee (EC) will be sought and the study will start only after authorization. In the study, single-dose treatment and single-dose comparison with Pulmicort Respules is necessary to compare the systemic exposure in children between the ages of 4 to 8 years. When considering and assessing all non-clinical and clinical data available for the investigational medicinal products (IMPs), the Sponsor considers the risk and benefit profiles of the BLANC study to be acceptable.

1.4 Study design

This will be a randomized, multicenter, open-label, single-dose, 2-way crossover study. The Study Flow Chart is presented in Figure 1. The purpose of this study is to compare the systemic exposure of budesonide delivered by the combination inhaler (BDA MDI) to Pulmicort Respules.

To be eligible for the treatment period of the study, children with asthma will be required to meet all of the inclusion criteria and none of the exclusion criteria.

At Visit 2, the children will be randomly assigned to a treatment sequence:

A/B: BDA MDI at Visit 2 and Pulmicort Respules at Visit 3

OR

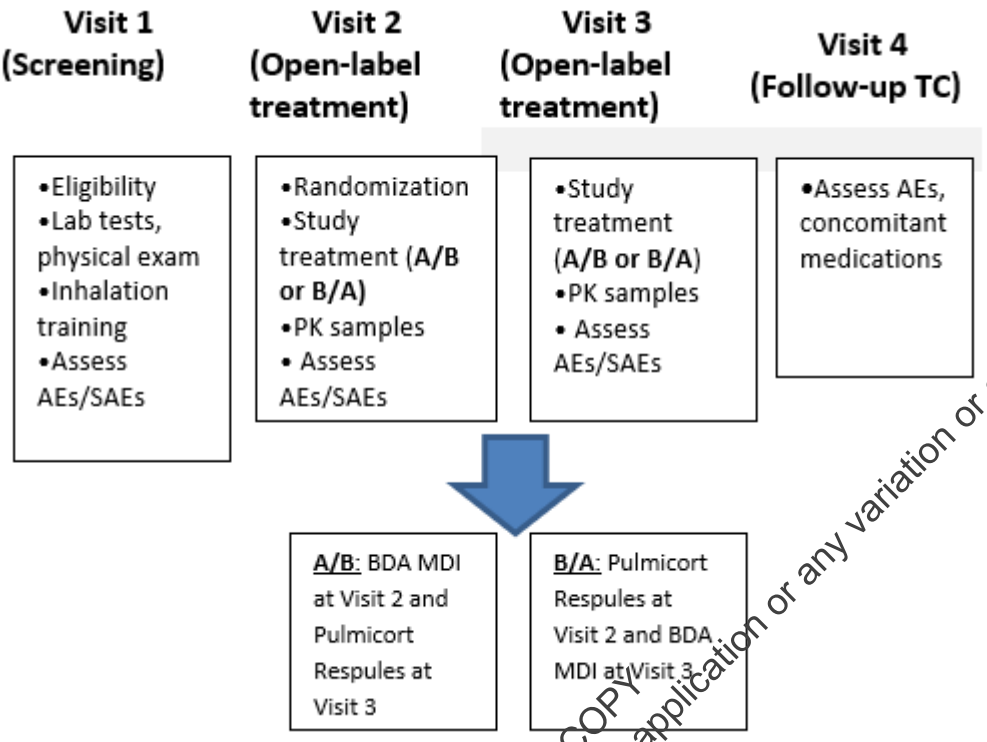
B/A: Pulmicort Respules at Visit 2 and BDA MDI at Visit 3

The study will comprise:

- Screening (Visit 1): within 14 days prior to randomization.
- Two treatment days:
  - Visit 2/Randomization visit: children will be dosed with a single dose of BDA MDI or Pulmicort Respules (A/B or B/A) and blood will be drawn for PK sampling for up to 12 hours after dosing in alignment with the sampling schedule.
  - Visit 3 will occur not less than 2 and no greater than 14 days after dosing on Visit 2 (ie, washout of 2 to 14 days) during which children will be dosed with a single dose of BDA MDI or Pulmicort Respules (A/B or B/A) and blood will be drawn for PK sampling for up to 12 hours after dosing in alignment with the sampling schedule.
- A follow-up telephone call (TC) will occur 2 to 5 days after the last dose (Visit 3) for safety follow-up (or early withdrawal, if applicable).

The overall study duration for the children will take approximately 3 to 4 weeks.
Safety will be monitored by spontaneously reported adverse events (AEs)/serious AEs (SAEs) and physical examination findings. Vital signs (heart rate and blood pressure) will be assessed at the beginning and the end of each clinic visit to ensure the well-being of the children.

Figure 1: Study Flow Chart



AE: adverse event; BDA MDI: budesonide/albuterol sulfate metered-dose inhaler; PK: pharmacokinetic; SAE: serious adverse event; TC: telephone call

2 STUDY OBJECTIVES

2.1 Primary objective

Primary objective:	Primary endpoints:
To determine and compare the systemic exposure of budesonide after single-dose administrations of BDA MDI and Pulmicort Respules.	AUC0-t and Cmax

2.2 Secondary objectives

Secondary objective:	Secondary endpoints:
To determine and compare other PK parameters for budesonide delivered by BDA MDI and Pulmicort Respules	tmax, tlast, t½λz, λz, Clast, and AUC0-inf (if feasible)

2.3 Safety objective

Safety objective:	Safety endpoints:
To assess the safety and tolerability of BDA MDI and Pulmicort Respules	AEs/SAEs

AE: adverse event; AUC0-inf: area under the plasma concentration-time curve from time zero to infinity; AUC0-t: area under the plasma concentration-time curve from time zero to time of last quantifiable concentration; BDA MDI: budesonide/albuterol sulfate metered-dose inhaler; Clast: drug concentration at last observed timepoint; Cmax: maximum observed plasma concentration; PK: pharmacokinetic; SAE: serious adverse event. tlast: time of last quantifiable plasma concentration; tmax: time to reach maximum observed plasma concentration; t½λz: half-life associated with terminal slope (λz) of a semi-logarithmic concentration-time curve.

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

Each child must meet all of the inclusion criteria and none of the exclusion criteria for this study. There can be no exceptions to this rule.

3.1 Inclusion criteria

For inclusion in the study, children should fulfill the following criteria:

1. Provision of informed consent prior to any study specific procedures. Children should provide assent to join the study, as applicable. The child's parent(s) or legally authorized representative (LAR) must sign the informed consent form (ICF). The LAR must be aged ≥18 years old.
2. Male or female aged between 4 and 8 years inclusive (not having reached his/her 9th birthday by the time of screening ([Visit 1]).
3. Weigh at least 14 kg or higher.
4. Clinician-diagnosed asthma of at least 3 months
5. Stable on treatment with albuterol PRN and/or ICS and/or leukotriene receptor antagonists (LTRAs) for 2 weeks prior to screening; children taking budesonide in any form at Visit 1 will be switched to another corticosteroid with a washout of budesonide of 3 to 7 days.
6. Demonstrate ability to correctly use the nebulizer and metered-dose inhaler (MDI) device without a spacer (according to the instructions in Section 4.2).
7. Willingness and ability of the child and parent(s)/LAR to comply with the demands of the study as described in the informed consent/assent.

3.2 Exclusion criteria

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

1. Inability to change from any budesonide therapy to another suitable corticosteroid.
2. History of life-threatening asthma defined as any asthma episode associated with loss of consciousness, intubation or admission to an intensive care unit.
3. Unstable asthma as judged by the Investigator (eg, any change in asthma therapy within 2 weeks prior to screening or use of more than 2 occasions of rescue medication (albuterol) per day within 1 week prior to screening (potential for rescreen).
4. Children receiving regular maintenance treatment with prohibited anti-inflammatory or long-acting bronchodilator asthma medication (inhaled, nebulized, oral, or systemic) within 1 month prior to Visit 1. Note: During the treatment period, children are not allowed to use any asthma treatments/medications (of any class) other than the IMPs and their background treatment (ie, SABA PRN alone and/or ICS and/or LTRAs) that was

started before screening. No child can be on other asthma maintenance therapies. See Section 4.11.2 for details.

5. More than 1 short course of oral/rectal/systemic corticosteroids within 6 months preceding screening (Visit 1), or any oral/rectal/systemic corticosteroids within 30 days prior to Visit 1.
6. Evidence of active concomitant pulmonary disease other than asthma (children with stable allergic rhinitis will be permitted, as long as, there are no changes in the treatment and the medications do not interfere with the analytical assay methods).
7. Upper respiratory infection involving antibiotic treatment not resolved within 14 days prior to Visit 1.
8. Children with a known or suspected hypersensitivity to albuterol/salbutamol, budesonide or any of the excipients used in the IMPs.
9. 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.
10. Systemic treatment with potent CYP3A4 inhibitors (eg, ketoconazole, itraconazole, and ritonavir).
11. Receipt of any other prohibited medication as detailed in Section 4.11.3.
12. Treatment with any investigational product within the last 30 days (or 5 half-lives, whichever is longer) of Visit 1.
13. Historical or current evidence of a clinically significant disease or congenital abnormality including, but not limited to the areas of cardiovascular, hepatic, renal, hematological, neuropsychological, endocrine, or gastrointestinal. Significant is defined as any disease or condition that, in the opinion of the Investigator, would put the safety of the child at risk through study participation, or that could affect the PK or safety analysis if the disease/condition exacerbated during the study.
14. Cancer not in complete remission for at least 5 years before Visit 1.
15. Hospitalization for psychiatric disorder or attempted suicide within 1 year of Visit 1.
16. History of psychiatric disease, intellectual deficiency, or other conditions if their magnitude limits the child's capacity to assent to the study.
17. Having a scheduled/planned hospitalization during the study.
18. Inability (and/or unwillingness) to abstain from protocol-defined prohibited medications during the study.
19. Use of drugs with enzyme-inducing properties such as St. John's Wort within 3 weeks prior to the first administration of the IMP.
20. Use of any herbal products by inhalation or nebulizer within 2 weeks of Visit 1 and/or the unwillingness to stop during the study duration.

21. Consumption of grapefruit or grapefruit juice, Seville oranges, quinine (e.g., tonic water) from 7 days prior to screening (Visit 1) until after the follow-up TC.
22. Current participation in any interventional study.
23. Previous enrollment in the present study or randomization in any other BDA MDI clinical study.
24. Immediate family member of the Sponsor or study center staff.

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

3.3 Subject enrollment and randomization

Approximately 3 study centers in Bulgaria and the US are anticipated to be included.

Approximately 28 children (4 to 8 years of age) will need to be screened, assuming an estimated screen failure rate of 50% prior to randomization in order for 14 to be randomized and 10 to complete. At least 4 children should be randomized in the age range of 4-5 years.

Children who do not complete both treatments (Treatment A and Treatment B) may be replaced.

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

Randomization codes will be assigned separately for the treatment sequence and entered by the Investigator or designee into the electronic case report form (eCRF). If a subject withdraws from participation in the study, then his/her enrollment/randomization code cannot be reused.

3.4 Procedures for handling incorrectly enrolled or randomized subjects

Children who fail to meet the eligibility criteria should not, under any circumstances, be enrolled, randomized, or receive the IMP. There can be no exceptions to this rule. There can be no waivers granted from the Sponsor for any child not meeting all of the inclusion criteria and none of the exclusion criteria.

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

3.5 Methods for assigning treatment groups

A randomization schedule will be generated by a designated statistical representative performing statistical support for the study. This schedule will assign children to a treatment sequence (**A/B** [BDA MDI at Visit 2 and Pulmicort Respules at Visit 3] or **B/A** [Pulmicort Respules at Visit 2 and BDA MDI at Visit 3]). This will be prepared before the first child is screened. The designated statistical representative will follow their established standard operating procedures regarding generation, security, and distribution of the randomization schedule.

Upon screening, each child will receive a screening number starting with the first child and continuing sequentially as required. This will be specific for each study center. Children who drop out of the clinical study before randomization will retain their screening number. Randomization will occur at Visit 2 after all pre-dose procedures have been performed and eligibility for randomization has been re-checked. Children will be assigned a unique randomization number in accordance with the randomization list generated for the study.

Randomization numbers will encode the child's treatment assignment (A/B or B/A). Randomized children who withdraw or are withdrawn from clinical study participation for any reason, regardless of whether IMP was administered or not, will retain their randomization number and the child will not be allowed to re-enter the study.

The Investigator or study center staff designee will enter the randomization number into the electronic data capture system (EDC). Once it has been determined that a child meets all eligibility criteria, the child's information will be entered into the EDC system.

3.6 Methods to minimize bias: randomization and blinding

This is an open-label study and not blinded. At Visit 2, the children will be randomly assigned to a treatment sequence (A/B or B/A).

The Investigator(s) will:

1. Obtain signed informed assent from the child and informed consent from the child's parent(s) or LAR before any study-specific procedures are performed.
2. Assign potential subject a screening number.
3. Determine subject eligibility (see Sections 3.1 and 3.2).
4. Re-check eligibility and subsequently randomize the child at Visit 2.

Children will not have a direct access to data recorded or reported by the children.

3.7 Restrictions

Study restrictions are detailed in Section 4.11.

3.8 Criteria for study withdrawal

At any time, children may withdraw from the study (ie, study procedures/visits) at their own request or their parent/LAR's request for any reason, without prejudice. Children may also be withdrawn from the study upon request of the Investigator, or by the Sponsor at any time or for any reason. Some reasons for study withdrawal include:

An AE or other unacceptable toxicity considered to jeopardize the safety of a child participating in the study.

Children who suffer 1 severe exacerbation or worsening of asthma that in the Investigator's opinion could affect short-term disease course or the study assessments will be discontinued if the Sponsor and the Investigator decide that it is in the best interest of the child to withdraw from the study.

General or specific change(s) in the child's condition that renders(s) him/her ineligible for further participation according to the inclusion/exclusion criteria.

- Non-compliance: in the opinion of the Investigator, the child is non-compliant with the requirements of the Clinical Study Protocol (CSP) (eg, post-enrollment eligibility violation).
- Lost to Follow-up: the child 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 child).
- Intercurrent illness: a condition, injury, or disease unrelated to the primary diagnosis that becomes apparent during treatment and necessitates the child's termination from the study, eg, a symptomatic lower respiratory tract infection that puts the child at potential risk and interferes with the child's ability to carry out the required procedures.

If a child is withdrawn from the study for any reason, the study center must immediately notify the medical monitor. The date and the reason for study withdrawal must be recorded on the eCRF. The child will be asked to complete the safety follow-up (or early withdrawal) TC. The TC will occur 2 to 5 days after the last study dose, as indicated in the Schedule of Assessments (Table 2).

Children who complete both visits will have a follow-up TC and children who withdraw between Visit 2 and Visit 3 will have a withdrawal TC.

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

Once a child is withdrawn from the study, the child may not re-enter the study. If a child withdraws from participation in the study, then his/her enrollment/randomization code cannot be reused. Withdrawn children will be replaced if there are not enough evaluable PK samples.

3.8.1 Screen failures

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

Children who are screen failures may be rescreened once if temporary reasons for the original screen failure (eg, respiratory infections, asthma exacerbations, episodes of unstable asthma) have resolved. These should be at the Investigator's discretion and in discussion with the medical monitor.

3.9 Discontinuation of the study

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

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

Regardless of the reason for termination, all data available for the child 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 children's interests.

4 TREATMENTS

4.1 Identity of the test and reference products

The BDA MDI is formulated as both micronized budesonide and micronized albuterol co-suspended with spray-dried porous particles in a hydrofluoroalkane (HFA) propellant (Table 1). The co-suspension formulation ensures that children receive a consistent delivery of the drug from each actuation of the MDI.

Pulmicort Respules is a sterile suspension for inhalation via jet nebulizer and contains the active ingredient budesonide (micronized) and the inactive ingredients disodium edetate, sodium chloride, sodium citrate, citric acid, polysorbate 80, and water for injection. Pulmicort Respules should be administered from jet nebulizers at adequate flow rates via mouthpieces (instructions for Pulmicort Respules will be provided separately).

Table 1: Investigational medicinal product strength and dosage form

	Investigational Medicinal Products	
	Treatment A (test product) [a]	**Treatment B (reference product)** [b]
Formulation:	BDA MDI	Pulmicort Respules
Supplier:	[redacted]	[redacted]
Strength:	80/90 µg (budesonide/albuterol)	1 mg budesonide
Dose:	2 inhalations	1 ampoule
Route of administration:	Oral inhalation	Oral inhalation
Regimen:	Single dose – 2 inhalations	Single nebulization dose
Special handling requirements:	Prime per instructions. Contamination avoidance procedures.	Nebulization until sputtering with nebulization cup as empty as possible. Contamination avoidance procedures.

BDA MDI: budesonide/albuterol sulfate metered-dose inhaler

Note: The IMPs (test product and the reference product) will be manufactured by [redacted]

[a] The placebo MDI for the test product will be used for training purposes only during screening (Visit 1) and will be taken home for training as well.

A saline ampoule for the reference product will be used for training purposes only during screening (Visit 1).

4.2 Nebulization inhalation and metered-dose inhaler device technique

A jet nebulizer (with mouthpiece for adequate flow rates) will be connected to a compressor and will be used to deliver Pulmicort Respules to each child. The brand of jet nebulizer will be standard across all study sites. Further details will be provided in the Site Manual.

The children will be provided with detailed instructions on the use of the placebo MDI device and Pulmicort Respules nebulization. All children must demonstrate adequate MDI and nebulizer administration techniques in order to be randomized as determined by the Investigator.

4.2.1 Nebulization inhalation technique

Correct nebulization inhalation technique will be defined as follows:

As determined by the Investigator:

- No pauses during nebulization
- No leakage around the mouthpiece
- No breathing through the nose (a nose clip will be used if the child will accept it)
- Calm and even breathing (tidal breathing)

Nebulizer device and inhalation training will be conducted at screening (Visit 1). The children will receive placebo MDI for additional training at home.

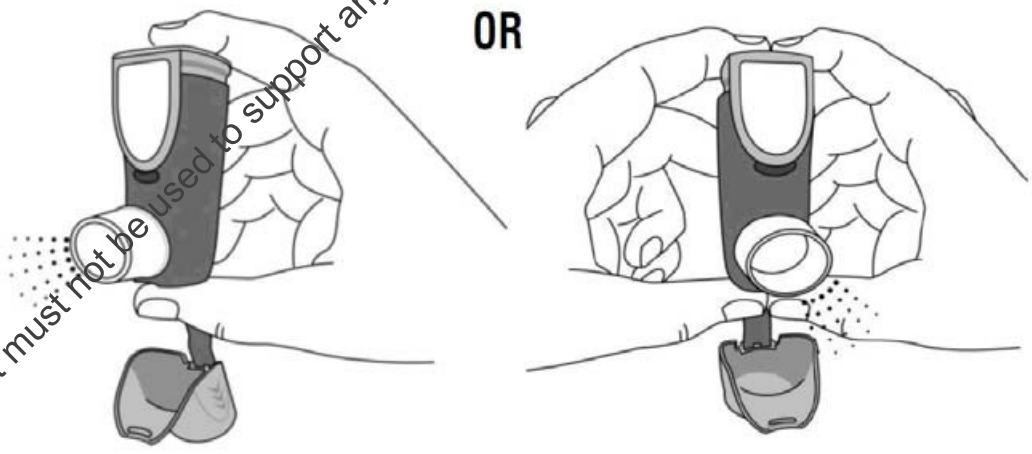
4.2.2 Metered-dose inhalation technique

Using the MDI

1. The MDI should be held upright with the mouthpiece at the bottom and the actuation counter at the top as pictured in Figure 2.

Note: The patient can be supported by an adult for performing correct inhalation (examples: shaking the MDI, actuating the MDI, etc).

Figure 2: How to Hold the Metered-dose Inhaler



2. Shake the MDI for 5 to 10 seconds.

3. Breathe out fully through your mouth, expelling as much air from your lungs as possible. Tilt your head back slightly, placing the mouthpiece into your mouth, holding the MDI with the mouthpiece down, and closing your lips around it, as presented in Figure 3. To allow the medication to enter your lungs, keep your tongue flat on the bottom of your mouth.

Figure 3: How to Use the Metered-dose Inhaler

4. While breathing in deeply and slowly through your mouth, fully depress the top of the actuation counter with your index finger. Immediately after the spray is delivered, release your finger from the canister. When you have breathed in fully, remove the MDI from your mouth and close your mouth.

NOTE: an audible "click" **may** be heard which is advancement of the actuation counter and considered normal.

5. Hold your breath as long as possible, up to 10 seconds, and then breathe normally.
6. Repeat steps #2 to #5 for the second inhalation to complete the full dose.
7. After you finish taking 2 inhalations, rinse your mouth with water. Spit out the water. Do not swallow it.
8. Place the dust cap back onto the device.

<u>Training with the placebo MDI (Children)</u>

Placebo MDI and inhalation training will be conducted at screening (Visit 1).

After demonstrating correct inhalation technique, the child will receive placebo MDI for training at home. Children should use the placebo MDI with an adult's help, as instructed by study center staff. Children should practice with the placebo MDI as appropriate, with 2 actuations per training inhalation, to be able to demonstrate adequate MDI inhalation technique at the randomization visit.

4.3 Supply of test and reference products

The test product (BDA MDI) will be supplied by [redacted] The reference product (Pulmicort Respules) will be supplied by [redacted] Both products will be labelled with a study-specific label.

Dispensing and retention of reserve samples of the test and reference products will be performed in accordance with the Compliance Policy for the Quantity of Bioavailability and Bioequivalence Samples Retained Under 21 CFR 320.38(c) Guidance for Industry.

4.4 Dose and treatment regimens

At screening (Visit 1), assenting children and consenting parents (or LAR) will be assessed to ensure that the child meets eligibility criteria. At this visit, nebulizer device and inhalation training will be conducted.

At Visit 2, eligible children will be randomized to either the A/B or B/A treatment sequence.

Handling instructions for the BDA MDI and Pulmicort Respules will be available for each study center throughout the study (Sections 4.2 and 4.10).

4.5 Labelling

Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines.

The labels will fulfil GMP Annex 13 requirements for labelling. Label text will be translated into local language.

The address and telephone number of the main contact for information on the product, clinical study and emergency contact will be provided to the child in the form of a leaflet or card which provides these details. The child must be informed to keep this in their possession at all times.

Test Product (BDA MDI) labelling:

Each kit will contain an MDI device, wrapped in a foil bag held within a carton.

Each kit will also contain the following labels:

- Cannister label (single panel, English only)
- Actuator label (single panel, dual language)
- MDI device shield label (single panel, English only)
- Foil bag label (single panel, dual language)
- Carton label (single panel, dual language)

Reference Product (Pulmicort Respules) labelling:

Each kit will contain a strip of five Respules, packaged within a foil envelope within a carton.

Each kit will also contain the following labels:

- Foil envelope label (single panel, local language)
- Carton label (single panel, local language)

Both the test and reference product labels will include the following information:

- Name of Sponsor (Bond Avillion 2 Development LP – Clinical Development Company: [redacted])
- Name of drug, IMP dosage form, route of administration, and quantity of dosage units
- Storage conditions
- Study Trial Reference
- Kit ID number, Batch number
- Directions for use
- The name of the Investigator, where applicable (this will be added on the label manually when the IMP is administered)
- Randomization number (this will be added on the label manually when the IMP is administered)
- The period of use, eg, expiry date

The label will include the following standard statements:

- "For clinical trial use only." (or the required local statement)
- "Keep out of reach of children"

4.6 Drug accountability, dispensing, and destruction

The test and reference products for this clinical study will be used only as directed in the CSP.

In accordance with Good Clinical Practice (GCP), each study center will account for supplies of IMP. Details of receipt, storage, assembly/dispensing and return will be recorded.

All unused supplies of IMP will either be destroyed or returned at the end of the study in accordance with instruction by the Sponsor.

4.7 Storage

All test and reference products should be kept in a secure place under appropriate storage conditions.

Due to regional differences in regulatory requirements and standards, each countries' permitted storage conditions are detailed in the local language of the carton label.

Test Product (BDA MDI 80/90 µg) should be stored as below:

For US: Store between 20° to 25°C, excursions permitted up to 30°C (86°F).

For European Union (EU): Store between 15° to 25°C

Reference Product (Pulmicort Respules) should be stored as below:

For US: Store at controlled room temperature 20° to 25°C (68° to 77°F [see USP])

For EU: Do not store above 30°C

Temperature readings of the storage area (minimum/maximum) should be recorded on every working day at a minimum.

4.8 Compliance

The administration of all test and reference products will be captured and recorded in the appropriate sections of the eCRF, as applicable. The IMP accountability will be recorded in the eCRF. Compliance will be assured by direct supervision and witnessing of IMP administration. Device and nebulization inhalation training is discussed in Section 4.2.

4.9 Accountability

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

4.10 Metered-dose inhaler handling

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

The importance of the device priming requirements should be emphasized. Priming of the test product MDI must occur.

4.11 Concomitant and other treatments

4.11.1 Investigational medicinal product

During the study, subjects are not allowed to use any asthma medication other than the IMPs and their background treatment (ie, SABA PRN alone and/or ICS and/or LTRA) that was started before screening (with the exception of budesonide) and continued as part of their asthma treatment (see Section 3.1). Non-asthma medications which are necessary for the subject's wellbeing and which do not affect the participation or results of the study are allowed at the investigator's discretion. All such medication should be recorded in the appropriate sections of the subject's eCRF.

4.11.2 Permitted asthma therapies

Short-acting beta agonists taken PRN and/or low-to-medium dose ICS and/or LTRAs are the only permitted therapies to be used as asthma therapy on-study as specified in Section 3.2. No child can be on any other asthma maintenance therapies.

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

4.11.3 Prohibited medications

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

- Oral, parenteral, or rectal corticosteroids (except if required to treat severe asthma exacerbation) during and at least 30 days prior to Visit 1.
- Any other asthma medication except Sponsor-provided test product or Pulmicort Respules during Visits 2 and/or 3 and the permitted SABA PRN alone and/or ICS and/or LTRA treatment that was started before screening and continued as part of maintenance treatment (see Section 3.1), regular SABA use (eg, four times a day [QID]) is not permitted.
- Inhaled disodium cromoglycate or inhaled nedocromil sodium
- 5-lipoxygenase inhibitors (ie, zileuton)
- Inhaled short-acting anticholinergics (or short-acting muscarinic antagonists [SAMA], ie, ipratropium)
- Inhaled long-acting muscarinic antagonists (LAMA)
- Inhaled LABA
- Phosphodiesterase-4 inhibitors (ie, roflumilast)

- Xanthine and theophylline
- Omalizumab, benralizumab, mepolizumab, reslizumab, dupilumab, or any other monoclonal or polyclonal therapy for any reason during the study or within 3 months or 5 half-lives before Visit 1, whichever is longer; (locally administered biologics, eg, intra-ocular, are allowed)
- Beta-2-adrenergic blockers, including eye-drops; (For the purpose of this study, metoprolol is considered to have beta-2-adrenergic receptor blocking ability.)
- Drugs with enzyme-inducing properties such as St. John's Wort within 3 weeks prior to the first administration of the IMP.
- Systemic treatment with potent CYP3A4 inhibitors (eg, ketoconazole, itraconazole, and ritonavir).

4.11.4 Food and beverage restrictions

Children should abstain from consumption of grapefruit or grapefruit juice, Seville oranges, quinine (eg, tonic water) from 7 days prior to screening on Day 1 until after the follow-up TC.

Children may eat a light breakfast at home prior to the clinic visits.

5 STUDY PLAN AND TIMING OF PROCEDURES

Table 2 presents study assessments and procedures.

General Considerations

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

- Site personnel will remind/instruct children not to take any prohibited asthma medications during the study. Non-asthma medications which are necessary for the child's well-being and which do not affect the participation in or results of the study, are allowed. All such medication should be recorded in the child's eCRF.
- Children must not ingest/consume xanthine and/or xanthine analogue (caffeine)-containing foods and beverages for at least 6 hours prior to each study visit and for the duration of each study visit. Examples of such products include coffee, tea, chocolate, and cola. Decaffeinated beverages are acceptable.
- To minimize diurnal variance, study centers should make every effort to assess children at the same time throughout the study.

Table 2: Schedule of assessments

	Screening Period	Open-label Treatment Period		Follow-up or early withdrawal
Visit	1	2	3	4 - TC
Day	Starting from Day -14	0	7 to 14 days after V2	2 to 5 days after V3
Informed consent/assent	X			
Eligibility criteria	X			
Re-check eligibility criteria		X		
Randomization		X		
Routine clinical procedures				
Medical/surgical history	X			
Demography	X			
Physical examination	X			
Height, weight, and BMI	X			
Routine safety measurements				
Laboratory assessments (including local laboratory clinical chemistry, hematology, and urinalysis) [a]	X			
AEs and concomitant medications	X	X	X	X
Seated vital signs (blood pressure and heart rate) [b]	X	X	X	
Placebo MDI training [c]	X			
Nebulization training	X			
Randomized IMP		X	X	
Blood sampling for PK - Timepoints		A total of 10 samples will be taken per treatment visit at pre-dose and at 10, 20, 40, 60, 120, 240, 360, 480 and 720 min after dosing.		

AE: adverse event; BMI: body mass index; IMP: investigational medicinal product; MDI: metered-dose inhaler; min: minute; PK: pharmacokinetic; TC: telephone call; V: Visit.

a Laboratory assessments (clinical chemistry, hematology and urinalysis) will be performed according to Section 6.3.1.

b Vital signs will be assessed at the beginning (pre-dose) and the end (post-last PK sample) of each study visit.

c Training for placebo MDI will occur at Visit 1 and the placebo MDI will go home with the child for additional training prior to randomization.

5.1 Screening period

Screening (Visit 1) will take place within 14 days prior to Randomization. During screening, assenting children and consenting parent(s) (or LAR) are assessed to ensure that the child meets eligibility criteria. Procedures will be performed according to study assessments and procedures presented in Table 2. Children who do not meet all of the inclusion criteria and none of the exclusion criteria must not be randomized into the study.

5.1.1 Visit 1

Standard demographic data and other characteristics will be recorded and will include age, gender, race, and ethnicity according to local regulations.

If a child has COVID-19 at Visit 1, the child should not attend the visit. The study center should take adequate measures (See Appendix D COVID-19 Emergency Measures Permitted to Ensure Subject Safety).

A standard medical, disease, and surgical history will be obtained with review of the inclusion and exclusion criteria with the child. Other study procedures carried out during this period will include physical examination (with height, weight, and body mass index [BMI]), concomitant medications review, seated vital signs (blood pressure and heart rate), training with placebo MDI and nebulization, AEs assessment/review, blood samples for hematology and clinical chemistry, and urine samples for urinalysis. See sections 4.2, 6.3 and 6.4 for details on assessments.

5.2 Randomization/treatment period

Procedures will be performed according to study visit assessments presented in Table 2. The Open-label Treatment Period consists of 2 visits (Visit 2 and Visit 3). Children meeting all of the inclusion criteria and none of the exclusion criteria will be randomized at Visit 2.

5.2.1 Visit 2 and 3

At Visit 2, eligibility criteria will be re-checked. Eligible children will then be randomized (1:1) to treatment sequence A/B or treatment sequence B/A at Visit 2. Pharmacokinetic samples will be taken up to 12 hours after dosing in alignment with the sampling schedule. Other study procedures carried out during this period will include seated vital signs (blood pressure and heart rate), AEs assessment/review, and concomitant medications review.

Table 3: Treatment sequence

Treatment sequence	Visit 2	Visit 3
A/B	BDA MDI 160/180 µg (given as 2 actuations of BDA MDI 80/90 µg)	1 mg Pulmicort Respules
B/A	1 mg Pulmicort Respules	BDA MDI 160/180 µg (given as 2 actuations of BDA MDI 80/90 µg [budesonide/albuterol])

BDA MDI: budesonide/albuterol sulfate metered-dose inhaler

For the test product, after the BDA MDI is primed and ready for use, the Investigator will provide the test product to the child (written instructions will be provided in the study manual). The test product will be administered in the study center.

For the reference product, one dose is removed from the foil envelope and added to the jet nebulizer to be ready for use. The reference treatment will then be provided to the child in the study center. A manual with instructions on delivering the Pulmicort Respules will be provided.

The exact date and start time of BDA MDI and Pulmicort Respules will be recorded in the eCRF in addition to the exact date and time of PK sampling.

In order to reduce the possibility of contamination of blood samples via hands, clothes, furniture, etc., precautions must be taken to avoid the possibility of contamination. BDA MDI activation and Pulmicort Respules nebulization must take place in a separate room from all other activities. The persons entering the room must wear appropriate protective gear (coats, gloves, caps, and shoes). Protective clothing must be discarded prior to leaving the room.

Children must be instructed to wash their hands (soap and water) and faces (with at least two wet tissues (discard after washing), prior to leaving the room. The staff and parent(s) must remove/discard the face mask worn to protect the face and then wash their hands with soap and water. Cross contamination between multiple children being dosed must be considered as well for study center staff and additional precautions taken per the study center's normal practice.

All handling of the nebulizers must be done in the nebulization room.

Additionally, children must rinse their mouths twice with tap water directly after taking the BDA MDI or receiving nebulization.

5.3 Follow-up period or early withdrawal

The planned end of study will occur upon completion of Visit 4. The follow-up TC will occur 2 to 5 days after Visit 3.

Procedures will be performed according to study visits and procedures presented in Table 2.

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

Children who complete both visits will have a follow-up TC and children who withdraw between Visit 2 and Visit 3 will have a withdrawal TC.

See Sections 3.8 and 3.9 for details on study withdrawal procedures.

6 MEASUREMENTS AND METHODS OF ASSESSMENTS

6.1 Appropriateness of Measurements

Standard measures to assess PK and safety apply during the study. For the single doses of BDA MDI and Pulmicort Respules, no safety issues are expected.

For timing of assessments, refer to Table 2.

6.2 Pharmacokinetic Assessments

Venous blood samples (~4 mL each) to determine plasma budesonide concentration will be collected at Visit 2 and Visit 3. A total of 10 samples will be collected at each visit, the pre-dose sample within 30 minutes prior to dose administration and then at 10, 20, 40, 60, 120, 240, 360, 480 and 720 minutes after dosing of the BDA MDI (Treatment A) and after the start of inhalation of the Pulmicort Respules (Treatment B).

The blood samples will be collected, labeled, processed, stored, and shipped as detailed in the Laboratory Manual. The date and actual sampling times will be recorded on the appropriate eCRF.

The reference time for blood sampling will be at the start of inhalation as captured in the eCRF. In total, 40 mL of blood will be collected from each child at each visit for analysis of budesonide in plasma.

6.3 Safety assessments

6.3.1 Laboratory assessments

Samples for determination of clinical chemistry, hematology, and urinalysis will be taken at Visit 1 as indicated in Table 2. Total blood volume, including PK sampling, is summarized in Table 5.

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

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

The following laboratory variables in Table 4 will be measured:

Table 4: Laboratory variables

Hematology/Hemostasis (whole blood)	**Clinical Chemistry (serum or plasma)**
Basophils (%)	Albumin
Basophils Abs	Alanine transaminase
Eosinophils (%)	Alkaline phosphatase
Eosinophils Abs	Aspartate transaminase
Hemoglobin	Bilirubin, total
Hematocrit	Calcium, total
Mean Corpuscular Hemoglobin	Chloride
Mean Corpuscular Hemoglobin Concentration	Cholesterol, total
Mean Corpuscular Volume	Creatinine
Monocytes (%)	Creatine kinase
Monocytes Abs	Gamma-glutamyl transpeptidase
Neutrophils (%)	Glucose (random)
Neutrophils Abs	Magnesium
Red blood cells (erythrocytes)	Phosphate
White blood cells (leukocytes)	Potassium
Platelet count	Protein, total
Lymphocytes Abs	Sodium
Lymphocytes (%)	Triglycerides
Urine*	
Urine blood	
Leukocyte esterase	
Urine protein	
Urine glucose	
Nitrite	

Abs: absolute

*If leukocyte esterase is detected, the site should send the sample for culture. If abnormal levels of blood or protein are detected, the sample should be sent for microscopic examination.

Table 5: Total blood volume

	Volume per Sample	Number of Samples	Total
Clinical chemistry	~0.5 mL	1	0.5
Hematology	~0.5 mL	1	0.5
Pharmacokinetics	~4 mL	20	80 mL
TOTAL			81 mL

Approximately 20-30 mL urine per sample will be taken for urinalysis.

6.3.2 Physical examination

A complete physical examination will be performed at Visit 1 (if applicable) as indicated in Table 2. This will include an assessment of the following items: height in centimeters and weight (kilograms) and BMI (kg/m^2) (at Visit 1 only), 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.

6.3.3 Vital signs

Vital signs will include measurements of blood pressure (mmHg) and heart rate (beats/min), while the child is seated.

Blood pressure measurements (systolic blood pressure and diastolic blood pressure) should be taken in the sitting position after at least 10 minutes of rest.

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

6.3.4 Adverse event assessments

Adverse events will be collected from time of signature of ICF/assent form through to the follow-up timepoint, as described in Section 7.3.

6.4 Other assessments

6.4.1 Concomitant medications

The collection and recording of all concomitant medications, including all pre-enrollment asthma therapies will be performed as indicated in Table 2. Permitted and restricted concomitant medications are further described in Section 4.11.

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

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

7 SAFETY REPORTING AND MEDICAL MANAGEMENT

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

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

7.1 Definition of adverse event

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

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

7.2 Definition of serious adverse event

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

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

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

7.3 Recording of adverse events

7.3.1 Period for collection of adverse events

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

7.3.2 Follow-up of unresolved adverse events

Any AEs that are unresolved at the child'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. [redacted] and the Pharmacovigilance Department representative retains the right to request additional information for any child with ongoing AE(s)/SAE(s) at the end of the study (after the child's follow-up TC) and capture that information in the eCRF, if judged necessary.

7.3.3 Variables

The following variables will be collected for each AE:

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

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

- Date AE met criteria for SAE
- Date the Investigator became aware of SAE
- Reason why the AE is considered serious
- Treatment given for the SAE
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Whether an autopsy is performed
- Causality assessment in relation to study procedure(s)
- Causality assessment to other medication
- Description of AE

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 7.2. 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 7.2. 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 7.2.

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

7.3.4 Causality collection

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

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

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

7.3.5 Adverse events based on signs and symptoms

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

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

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

7.3.6 Adverse events based on examinations and tests

The results from the CSP mandated and repeat/unscheduled measurements for laboratory tests, vital signs (ie, blood pressure and heart rate) and other assessments will be summarized

in the Clinical Study Report. Deterioration from baseline in these parameters should therefore only be reported as AEs if they fulfill any of the AE criteria or are the reason for discontinuation from the study or are considered "clinically significant."

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

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

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

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

7.4 Reporting of serious adverse events

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

If any SAE occurs during the course of the study, then investigators or other study center personnel should inform the Clinical Research Organization (CRO) within 1 day ie, immediately but **no later than 24 hours** of when he/she becomes aware of it.

The Principal Investigator will review each SAE and evaluate the intensity and the causal relationship of the event to IMP. All SAEs will be recorded from signing of the ICF/assent until the End-of-study Visit. Serious AEs occurring after the End-of-study Visit and coming to the attention of the Principal Investigator must be reported only if there is (in the opinion of the Principal Investigator) reasonable causal relationship with the IMP.

The Principal Investigator is responsible for providing notification to the CRO/Sponsor of any SAE, whether deemed IMP-related or not, that a child experiences during their participation in study within 24 hours of becoming aware of the event.

As a minimum requirement, the initial notification should provide the following information:

- Study number
- Subject number
- Sex
- Date of birth
- Name of Principal Investigator and full study center address
- Details of SAE
- Criterion for classification as 'serious'
- The IMP name, or code if unblinded, and treatment start date
- Date of SAE onset
- Causality assessment (if sufficient information is available to make this classification).

The CRO/Sponsor will request clarification of omitted or discrepant information from the initial notification. The Principal Investigator or an authorized delegate is responsible for emailing or faxing the requested information to the CRO/Sponsor within 24 hours of the request.

Initial reports of SAEs must be followed later with detailed descriptions, including clear photocopies of other documents as necessary (eg, hospital reports, consultant reports, autopsy reports), with the child's personal identifiers removed. All relevant information obtained by the Principal Investigator through review of these documents will be recorded and faxed to the Sponsor within 24 hours of receipt of the information. If a new SAE Report Form is faxed, then the Principal Investigator must sign and date the form. The CRO/Sponsor may also request additional information on the SAE, which the Principal Investigator or an authorized delegate must fax to the Sponsor within 24 hours of the request. Contact information for the appropriate safety reporting service will be provided in the Site Manual.

7.5 Follow-up of adverse events

All AEs experienced by a subject, irrespective of the suspected causality, will be monitored until the event has resolved, until any abnormal laboratory values have returned to baseline or stabilized at a level acceptable to the Principal Investigator and Medical Monitor, until there is a satisfactory explanation for the changes observed or until the subject is lost to follow-up.

7.6 Overdose

Acute overdosage with inhaled budesonide, even in excessive doses, is not expected to be a clinical problem.

For the purpose of this study, an accidental or deliberate intake of treatment of more than 2 actuations of the BDA MDI or more than 1 Respule of Pulmicort during Visits 2 and 3 is defined as an overdose and must be reported as such as described below.

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

The maximum daily dosage of IMP should not exceed 2 actuations per visit. If an overdose of IMP occurs in the course of the study which has an associated SAE, then the Investigator or other study center personnel will inform the CRO immediately, or **no later than 24 hours** of when he or she becomes aware of it.

In the event of a suspected overdose, the Investigator should:

1. Contact the [redacted] Medical Monitor immediately.
2. Closely monitor the child for AE/SAE and laboratory abnormalities until the IMP can no longer be detected systemically (at least 6 weeks).
3. Obtain a plasma sample for PK analysis within 7 days from the date of the last dose of IMP if requested by the Medical Monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF.

Decisions regarding dose interruptions will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the child.

For overdoses associated with an SAE, the standard SAE reporting timelines apply, see Section 7.4.

7.7 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 test product or the reference product that either causes harm to the child or has the potential to cause harm to the child.

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 center staff or child.

A medication error includes situations where an error:

- occurred
- was identified and intercepted before the child received the drug

- did not occur, but circumstances were recognized that could have led to an error

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

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

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

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

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

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

If a medication error occurs during the course of the study which has an associated SAE, then the Investigator or other study center personnel will inform the CRO **immediately, or no later than 24 hours** of when he or she becomes aware of the medication error.

The CRO will work with the Investigator to ensure that all relevant information is provided to CRO representative. For medication errors associated with an SAE, the standard SAE reporting timelines apply, (see Section 7.4).

7.8 Management of test product-related toxicities

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

8 STATISTICAL METHODS

8.1 Statistical considerations

Analyses will be performed by the Sponsor or its representatives. Comprehensive analysis plans will be written for PK and statistical analyses separately, and any subsequent amendments will be documented, with final amendments completed before the database lock.

8.2 Sample size estimate

No prospective calculations of statistical power have been made. Complete data (evaluable data from both Treatment A and Treatment B) from 10 children is considered sufficient to provide information on the PK in this population without exposing more children than necessary to the IMP. Considering potential dropouts, approximately 14 children will be randomized. Results will be interpreted in the perspective of the explorative nature of the study.

8.3 Definitions of analysis sets

8.3.1 Pharmacokinetic analysis set

The PK analysis set will consist of all randomized children for whom at least 1 of the primary PK parameters can be calculated and who have no major protocol deviations impacting PK.

Children who do not provide evaluable data for both treatments (Treatment A and Treatment B) will be excluded from the statistical analysis, which is the analysis of variance (ANOVA).

Any excluded cases will be documented together with the reason for exclusion.

8.3.2 Safety analysis set

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

8.3.3 All subjects enrolled analysis set

The all subjects enrolled analysis set will be defined as all children who provide informed assent and whose parent(s) or LAR(s) have provided informed consent. This analysis set will be used for descriptive summaries of disposition.

8.3.4 All subjects randomized analysis set

The all subjects randomized analysis set will be defined as all children who have been randomized to a treatment sequence. This analysis set will be used for listings of demographic variables and listings and descriptive summaries of prior and concomitant medications.

8.4 Violations and deviations

Important protocol deviations will be listed and summarized by randomized treatment groups.

All children 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 children failing any of the inclusion/exclusion criteria and will be based on the full analysis set.

8.5 Subject disposition

Summaries of subject disposition will include the following information: Number of children enrolled, screen failed, randomized, number and percentage of randomized children treated, not treated, who completed the study, and the number and percentage of randomized children who were withdrawn (including reasons for withdrawal). Disposition data will be presented by planned treatment sequence and overall based on the all subjects enrolled analysis set.

Randomized children who are excluded from the analysis sets (as defined in Section 8.3) will be listed and will include the planned treatment sequence and reason for exclusion.

8.6 Demographic and baseline characteristics

Demographic variables (age, gender, race, ethnicity, height, weight, and BMI) will be listed by child, for all randomized children.

Demographic characteristics (age, gender, race, and ethnicity) and subject characteristics (height, weight, and BMI) will be summarized by treatment sequence and overall based on the children in the safety analysis set. The denominator for percentages will be the number of children in the safety analysis set.

Medical history data will be listed by child including planned treatment sequence, visit, description of the disease/procedure, Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC), MedDRA Preferred Term, start date and stop date (or ongoing if applicable).

8.7 Prior and concomitant medication

Prior medications are those that started and stopped prior to the first dose of randomized treatment; all medications taken after first dose of randomized treatment are considered as concomitant (including medications that started prior to dosing and continued after).

Prior and concomitant medication will be summarized separately by coded preferred term (according to the WHODrug dictionary) and planned treatment sequence. Prior and concomitant medication will be listed by child and will include the following information: planned treatment sequence, reported name, coded preferred term, the route of administration, dose, frequency, start date/time and indication. Descriptive summaries and listings of prior and concomitant medication will be based on the all subjects randomized analysis set.

8.8 Pharmacokinetic analysis methods and parameters

A listing of PK blood sample collection times, and all reportable budesonide concentrations will be provided for all children. Budesonide concentrations will be summarized by treatment using descriptive statistics.

Plasma samples will be analyzed using non-compartmental analysis (NCA) to determine the PK (AUC0-t, Clast, Cmax, tmax, tlast, λz, t½λz, and AUC0-inf [if feasible]) of budesonide in plasma.

This study is descriptive. There are no predefined statistical hypotheses and no predetermined tests or decision rules. The relative exposure of budesonide between BDA MDI versus Pulmicort Respules will be based on estimates of the AUC0-t and Cmax.

The AUC0-t and Cmax for budesonide will be compared between treatments using a multiplicative (ie, log-transformation) ANOVA model with treatment sequence, period, and subject within sequence as fixed effects. Geometric mean ratios between test (BDA MDI) and reference (Pulmicort Respules) treatments and 90% confidence limits will be calculated from the model. Half-life and tmax will be compared by means of descriptive statistics.

A detailed PK analysis plan will be prepared prior to database lock.

8.9 Safety analysis

Continuous safety variables will be summarized using descriptive statistics (n, mean, standard deviation, minimum, median, maximum) by treatment. Categorical variables will be summarized in frequency tables (frequency and proportion) by treatment. The analysis of the safety variables will be based on the safety analysis set and will be reported using the actual treatment associated with the observed data.

8.9.1 Laboratory assessments

The clinical chemistry, hematology, and urinalysis assessments will be listed by treatment sequence and visit including repeat/unscheduled measurements.

The listings will include the following information: test name, date of measurement, reference range, result and clinical significance, as determined by the Investigator.

8.9.2 Physical examination

The results of the physical examination conducted at Visit 1 will be documented in medical history for each child.

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

Results of height, weight, and BMI will be listed by child, treatment sequence and visit, and summarized with other demographics and baseline characteristics data.

8.9.3 Vital signs

Vital signs of heart rate (beats/min), systolic blood pressure (mmHg) and diastolic blood pressure (mmHg) will be listed by treatment sequence and visit including the date/time of the assessment, and repeat/unscheduled measurements.

Descriptive statistics of heart rate, systolic blood pressure and diastolic blood pressure collected at Visit 2 and 3 will be summarized by treatment group and timepoint (pre-dose and post-last PK assessment).

8.9.4 Adverse events

All AEs will be coded using the MedDRA dictionary and will be listed for each child by treatment sequence assigned. A treatment-emergent adverse event (TEAE) is defined as an AE with onset (start date/time) on or after the first dose of randomized IMP at Visit 2. Any AEs occurring in the washout between successive treatment periods will also be regarded as treatment-emergent and assigned to the treatment administered in the period prior to the washout. Additional details on assigning an AE to a treatment period based on AE start and end dates will be further detailed in the statistical analysis plan (SAP).

Adverse events will be summarized by Preferred Term and SOC using MedDRA dictionary. Furthermore, children with SAEs, AEs that led to death, and AEs that led to withdrawal will be summarized and listed separately.

Adverse events that occur before dosing will be reported separately.

9 STUDY AND DATA MANAGEMENT

9.1 Training of study center staff

An EDC system will be used for data collection and query handling. The Investigator will ensure that data are recorded on the eCRFs as specified in the CSP and in accordance with the instructions provided.

Before the first child is entered into the study, a designated representative will review and discuss the requirements of the CSP and related documents with the investigational staff and also train them in any study specific procedures and the EDC DataLabs system(s) utilized.

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

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

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 eCRFs. A copy of the completed eCRFs will be archived at the study center.

Hematology, chemistry, and urinalysis will be done by the study center's local laboratory and PK assessments will be done by a central laboratory.

9.2 Monitoring of the study

During the study, the Sponsor or a designated representative will have regular contacts with the study center, 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 CSP, that data are being accurately and timely recorded in the eCRFs, that biological samples are handled in accordance with the Laboratory Manual and that IMP accountability checks are being performed.
- Perform source data verification (a comparison of the data in the eCRFs with the child's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent/assent of participating children. This will require direct access to all original records for each child (eg, clinic charts).
- Ensure all SAEs and AEs have been captured and reported correctly, providing oversight of child safety while on-study.

- Verify the correct storage, handling, administration, and return of all test and reference products.

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

9.2.1 Source data

Source documents provide evidence for the existence of the child and substantiate the integrity of the data collected. Source documents are filed at the Investigator's study center.

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

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

9.2.2 Study agreements

The Investigator(s)/the participating center(s) should comply with all the terms, conditions, and obligations of the CSP for this study.

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

9.2.3 Archiving of study documents

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

9.3 Study timetable and end of study

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

The study may be terminated at individual centers if the study procedures are not being performed according to 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 either the test or reference product.

9.4 Data management

All subject data relating to the study will be recorded in eCRFs unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the case report form (CRF).

Guidance on completion of eCRFs will be provided in the CRF Completion Instructions document.

The Investigator must permit study-related monitoring, audits, EC review, and Regulatory Agency inspections and provide direct access to source data documents.

Monitoring details describing strategies, including definition of study critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.

The Sponsor or designee is responsible for the data management of this study, including quality checking of the data.

The Sponsor assumes accountability for actions delegated to other individuals (eg, contract research organizations).

Records and documents, including signed ICF/assent, pertaining to the conduct of this study must be retained by the Investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

All data generated by the study center personnel will be captured electronically at each study center using eCRFs. Data from external sources (such as laboratory data) may be imported into the database. Once the eCRF clinical data have been submitted to the central server at the independent data center, corrections to the data fields will be captured in an audit trail. The reason for change, the name of the person who performed the change, together with the time and date will be logged to provide an audit trail.

If additional corrections are needed, the responsible monitor or data manager will raise a query in the EDC application. The appropriate staff at the study center will answer queries sent to the Investigator. The name of the staff member responding to the query, and time and date stamp will be captured to provide an audit trail. Once all source data verification is complete and all queries are closed, the eCRF pages will be frozen.

The specific procedures to be used for data entry and query resolution using the EDC system/eCRF will be provided to study centers in a training manual. In addition, study center personnel will receive training on the EDC system/eCRF.

Serious adverse event reconciliation

The SAE reconciliation reports are produced and reconciled in accordance with the safety and medical management plans for the study.

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 data standards, if applicable.

Final database lock

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

10 ETHICAL AND REGULATORY REQUIREMENTS

10.1 Ethical conduct of the study

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

10.2 Subject data protection

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

Children 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 child identifiable will not be transferred. Children must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law(s). The level of disclosure must also be explained to the child. Children 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 CSP, including the final version of the ICF/assent and any other written information and/or materials to be provided to the children. The Investigator will ensure the distribution of these documents to the applicable EC, and to the study center staff.

The opinion of the EC should be given in writing. The Investigator should submit the written approval to the Sponsor or designee before enrollment of any child into the study.

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

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

If required by local regulations, the CSP should be re-approved by the EC annually.

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

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

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

10.4 Informed consent/assent

The Investigator(s) at each center will:

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

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

Study procedures will not be changed without the mutual agreement of the Principal Investigator and the Sponsor.

If there are any substantial changes to the CSP, then these changes will be documented in a new version of the CSP.

The new version of the CSP 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 CSPs.

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

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

10.6 Audits and inspections

Authorized representatives of the Sponsor, a regulatory authority, or an EC may perform audits or inspections at the center, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, data were recorded, analyzed, and accurately reported according to the CSP, 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

1. Investigator Brochure Edition 2.0. Budesonide/Albuterol Sulfate Pressurized Inhalation Suspension (BDA MDI, PT027); Budesonide Pressurized Inhalation Suspension (BD MDI, PT008); Albuterol Sulfate Pressurized Inhalation Suspension (AS MDI, PT007), 20 September 2019.

2. Global Initiative for Asthma. Global strategy for asthma management and prevention. 2020. Available from: https://ginasthma.org/gina-reports/.

3. Mendes ES, Horvath G, Campos M, Wanner A. Rapid corticosteroid effect on β(2)-adrenergic airway and airway vascular reactivity in patients with mild asthma. J Allergy Clin Immunol. 2008;121(3):700-704.

4. Cooper PR, Panettieri RA. Steroids completely reverse albuterol-induced β2-adrenergic receptor tolerance in human small airways. J Allergy Clin Immunol. 2008;122(4):734-740.

5. Mendes ES, Cadet L, Arana J, Wanner A. Acute effect of an inhaled glucocorticosteroid on albuterol-induced bronchodilation in patients with moderately severe asthma. Chest. 2015;147(4):1037-1042.

6. [redacted] Prescribing Information for Proventil HFA. https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/020503s046lbl.pdf

7. [redacted] Prescribing Information for Pulmicort Respules. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020929s052lbl.pdf

12 LIST OF APPENDICES

APPENDIX A AVILLION PROTOCOL SIGNATURE PAGE

[redacted]

[redacted]

[redacted]

APPENDIX B PRIMARY INVESTIGATOR SIGNATURE PAGE

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

Principal Investigator's Name (print)

Principal Investigator's Signature

Date

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

APPENDIX C ADDITIONAL SAFETY INFORMATION

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

Life-threatening

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

Hospitalization

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

Important medical event or medical intervention

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

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

Angioedema not severe enough to require intubation but requiring intravenous hydrocortisone treatment

Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine

Intensive treatment in an emergency room or at home for allergic bronchospasm

Blood dyscrasias (eg, neutropenia or anemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalization

Development of drug dependency or drug abuse

A guide to interpreting the causality question

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

Time Course. Exposure to suspect drug. Has the subject actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?

Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?

No alternative cause. The AE cannot be reasonably explained by another cause/etiology such as, the underlying disease, other drugs, and other host or environmental factors.

Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

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

Is this a recognized feature of overdose of the drug?

Is there a known mechanism?

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

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

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

APPENDIX D COVID-19 EMERGENCY MEASURES PERMITTED TO ENSURE SUBJECT SAFETY

The following activities are 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.

COVID-19 tests for subjects or caregiver/ parent may be conducted proactively prior to inclusion or site visits at any point throughout the study in accordance with local and national guidance. This will be documented as an unscheduled procedure with a positive result recorded as an AE. Any patients that undergo COVID-19 tests as part of an adverse event investigation will have the results recorded via the AE process.

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 study center staff or enables an on-site subject visit. • If a return to lockdown is announced or the study center is on lockdown and cannot process a visit, if possible, visits should be rescheduled to earlier/later as required to safeguard subjects and study center staff. • Randomization: If a subject is in screening and cannot complete the randomization visit within 14 days due to local COVID-19 lockdown restrictions, the screening period may be extended to a maximum of 6 weeks. In the event of an extension to the screening period >14 days due to COVID-19, the following safety measurements should be repeated in advance of randomization: safety laboratory assessments, vital signs, concomitant medications, and medical/surgical history.
Subject Discontinuation	• Refer to Section 3.9.

Subjects with Confirmed COVID-19 Infection	• If a subject has confirmed COVID-19 this is to be reported as an AE/SAE. It should be discussed with the medical monitor prior to determining if/when to withdraw the subject. • 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 14 days after a negative test. • For new subjects previously identified as COVID-19 positive, a re-test must be performed after resolution of symptoms (if present). The subject can only be considered for enrollment 2 weeks after having a negative result.