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**Statistical Analysis Plan**

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

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Study Statistician



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Avillion Statistician



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## LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
ACQ-5	Asthma Control Questionnaire-5
ACQ-7	Asthma Control Questionnaire-7
AE	Adverse event
ALT	Alanine aminotransferase
AQLQ+12	Asthma Quality of Life Questionnaire for 12 years and older
AS MDI (PT007)	albuterol sulfate metered-dose inhaler
AST	Aspartate aminotransferase
AUC <sub>0-6hours</sub>	Area under the curve from 0 to 6 hours
BD MDI (PT008)	Budesonide metered-dose inhaler
BDA MDI (PE027)	Budesonide/albuterol metered-dose inhaler
β-hCG	β-human chorionic gonadotropin
BMI	Body mass index
ECG	Electrocardiogram
eCRF	Electronic case report form
eDiary	Electronic diary
EOT	End-of-treatment
FAS	Full Analysis Set

Abbreviation or special term	Explanation
FEV <sub>1</sub>	Forced expiratory volume in 1 second
GINA	Global Initiative for Asthma
ICH	International Conference on Harmonization
ICS	Inhaled corticosteroid
IDMC	Independent Data Monitoring Committee
IP	Investigational product
IPD	Important protocol deviation
LABA	Long-acting $\beta_2$ -agonist
MAR	Missing at random
MDI	Metered-dose inhaler
MID	Minimal important difference
MNAR	Missing not at random
OAE	Other significant adverse event
PAQLQ	Paediatric Asthma Quality of Life Questionnaire
PDV	Premature discontinuation visit
PEF	Peak expiratory flow
PFT	Pulmonary function test
prn	as needed
QID	four times daily
RM	Repeated measures
SABA	Short/rapid-acting $\beta_2$ -adrenoreceptor agonist
SAE	Serious adverse events
SDTM	Study Data Tabulation Model
TBL	Total bilirubin
TC	Telephone contact
TOEPH	Heterogeneous Toeplitz
ULN	Upper limit of normal



## AMENDMENT HISTORY

Date (version)	Brief description of change
16 <sup>th</sup> March 2021 (V2.0)	<p>Included text on decision following the second blinded sample size reassessment (section 1.3.1.3).</p> <p>In order to support the integrated summary of safety analyses, the total daily number of puffs of randomized treatment, grouped by actual treatment received and based on the safety analysis set will be displayed in summaries of exposure (see section 6.2.3).</p> <p>In order to support the integrated summary of safety analyses, additional adverse events summary tables will now be reported with incidence rates/event rates, as appropriate (see section 6.2.6.1).</p> <p>In order to support the integrated summary of safety, summaries of adverse events and serious adverse events will be reported within subgroups specified in section 6.2.8.2.</p> <p>Clarification added to section 6.2.7.11 for exploratory endpoints of night-time awakenings and asthma symptom score.</p>
28 <sup>th</sup> July 2021 (V3.0)	<p>Added the COVID-19 estimand.</p> <p>Added supportive analysis to the primary endpoint where the data collected following the onset of a COVID-19 related adverse event or dose interruption are excluded from the analysis.</p> <p>Derivation of stratification factors for patients aged 4 to 11 years added.</p> <p>Detailed methodology for handling duplicate patients.</p> <p>Clarified how the analyses populations will be used when making treatment group comparisons in sections 2.1, 6.2.5 and 6.2.7.</p>

## 1. STUDY DETAILS

### 1.1 Study objectives

#### 1.1.1 Primary objective

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

#### 1.1.2 Secondary objective

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

#### 1.1.3 Safety objective

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

### 1.1.4 Exploratory objective

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

## 1.2 Study design

This is a 12-week, randomized, double-blind, placebo-controlled, multicenter, parallel group, Phase III study. The purpose of this study is to compare 2 dose levels of BDA MDI compared to its constitute components BD MDI and AS MDI on improvement in lung function and asthma symptoms after 12 weeks of treatment. The subjects for the study are adults, adolescents, and children, aged 4 years and older, with symptomatic asthma currently being treated with short/rapid-acting  $\beta_2$ -adrenoreceptor agonist (SABA; eg, Ventolin) as needed (prn) alone or with low-dose inhaled corticosteroid (ICS) maintenance therapy plus SABA prn. Albuterol is a SABA, inducing airway smooth muscle relaxation and reducing or preventing bronchoconstriction. Albuterol has been approved in many countries in multiple formulations for treatment or prevention of bronchoconstriction.

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

This study is designed to investigate the benefit of 2 dose levels of BDA MDI [PT027] compared to its constituent components BD MDI [PT008] and AS MDI [PT007] based on improvement in lung function and asthma symptoms after 12 weeks of treatment.

See Figure 1 for a graphical presentation of the study schema, Table 1 for a list of study assessments and Table 2 for timed assessments at Visit 2 through to Visit 6.

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

Only Sponsor-provided investigational product (IP) and Sponsor-provided Ventolin to be used in response to asthma symptoms are allowed during the study. No other asthma medications are allowed during the study.

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

A randomization schedule will be generated by a designated statistical representative performing statistical support for the study. This schedule will be prepared before the start of the treatment period. Randomization for adults and adolescents will be centralized and stratified by pre-study background therapy consisting of either ICS or non-ICS (subjects not previously treated with ICS), by Asthma Control Questionnaire-7 (ACQ-7;  $\leq 1.5$ ,  $> 1.5$ ), and by age ( $\geq 12$  to 17,  $\geq 18$ ). Children aged 4 to 11 years will not be stratified. At randomization (Visit 2), adult and adolescent subjects (age  $\geq 12$  years) who meet the eligibility criteria will be randomly assigned to 1 of the following 5 treatment groups in a 1:1:1:1:1 ratio:

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

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

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

The study will consist of 3 periods:

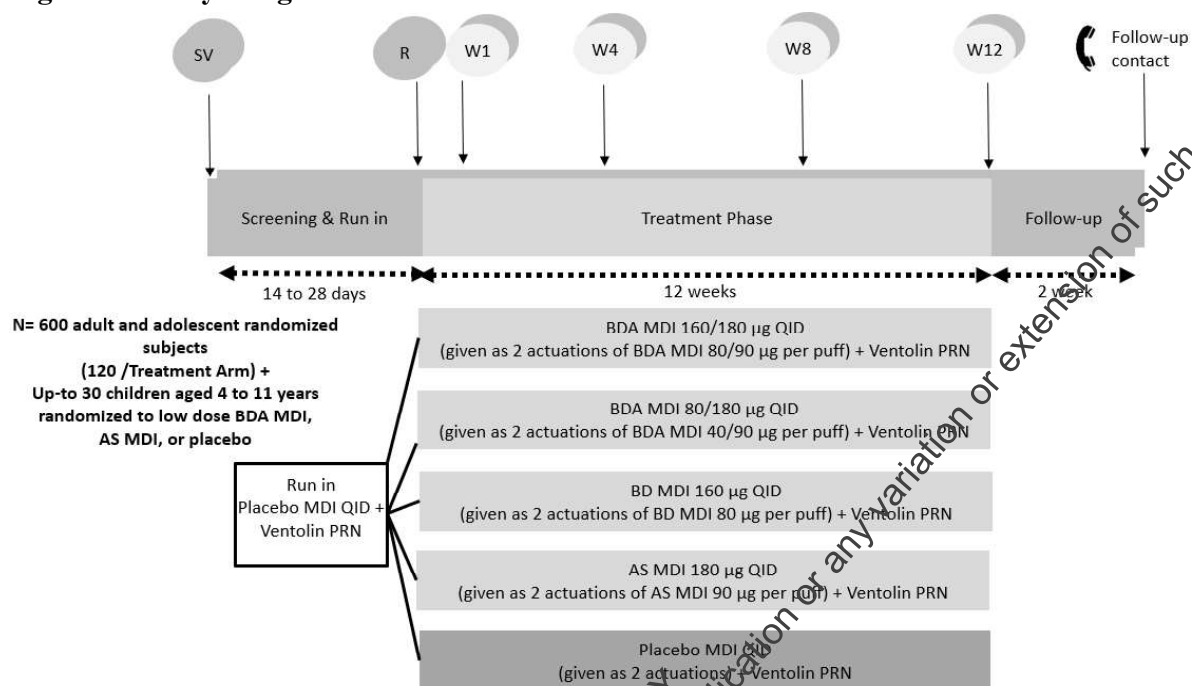
- Screening and run-in period (14 to 28 days).
- 12-week treatment period.
- Safety follow-up period: where a safety follow-up telephone contact will occur 2 weeks ( $\pm 4$  days) after the subject's last dose of treatment (end-of-treatment [EOT]) or premature discontinuation visit (PDV).

The treatment duration of 12 weeks has been set for each of the subjects, as this is an appropriate duration of time to evaluate lung function benefit in asthma subjects.

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

- Change from baseline in  $FEV_1$  AUC<sub>0-6</sub> hours over 12 weeks
- Change from baseline in trough  $FEV_1$  at Week 12

The end-of-study is defined as the last visit of the last subject undergoing the study, therefore will occur when the last subject has completed his or her post study follow-up telephone contact (TC). Subjects who discontinue randomized treatment will complete a PDV, and AE/SAE will be followed up if medically indicated.

**Figure 1: Study design**

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

**Table 1 Study Assessments and Procedures**

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

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



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

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

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

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

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

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

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

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

<sup>h</sup> A serum pregnancy test ( $\beta$ -hCG) will be performed at Visits 1 and treatment discontinuation (EOT) or PDV; urine  $\beta$ -hCG test will be performed at Visits 2 and 4 (for women of childbearing potential only).

<sup>i</sup> Pre-bronchodilator (Visit 1/Visit 1a)/ Pre-dose (Visit 2 onwards) FEV<sub>1</sub> will be measured in the morning between 06:00 and 10:00 AM at the designated visits in Table 1, and within 1 hour of FEV<sub>1</sub> measured at Visit 2. Pre-bronchodilator FEV<sub>1</sub> of  $\geq$ 50 to  $<$ 85% predicted normal value for adults ( $\geq$ 18 years of age) and  $\geq$ 50 to  $<$ 90% predicted normal value for subjects aged 4 to 17 years after withholding SABA  $\geq$ 6 hours (at Visit 1 or Visit 1a if applicable). If subject took SABA within 6 hours in the morning of Visit 1, either the entire visit must be rescheduled or just PFT assessment rescheduled. At Visit 1, pre- and post- dose will be with respect to administration of Sponsor-provided bronchodilator (Ventolin). From Visit 2 onwards, pre- and post- dose measurements will be with respect to administration of IP.

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

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

<sup>l</sup> Ventolin usage to be reviewed at each collection/dispensing visit using eDiary. Replacement kit dispensed as required. The actuator should be cleaned once per week if used in the last 7 days according to instructions.

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

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

**Table 2 Timed assessments at Visit 2 through Visit 6**

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

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

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

- <sup>a</sup> This is not a timed assessment. Sites should plan to perform these activities to allow for collection of timed spirometry.
- <sup>b</sup> Questionnaires (ACQ-5, ACQ-7, AQLQ+12, and PAQLQ) are collected at all visits (except Visit 3 AQLQ+12, and PAQLQ).
- <sup>c</sup> Vital signs should be started (approximately 5 to 10 minutes) ahead of the specified time point to ensure spirometry will be conducted as close to the specified time points as possible.
- <sup>d</sup> Pre-dose vital signs (heart rate, blood pressure) will be collected twice, at least 5 minutes apart.
- <sup>e</sup> Pre-dose ECG will be collected at Visit 2, Visit 6, and PDV only, or as clinically indicated
- <sup>f</sup> All clinical laboratory tests (hematology and chemistry) will be assessed approximately 60 minutes prior to dosing at Visit 6 in advance of first spirometry measurement. Laboratory tests may be performed at all other visits as clinically indicated.
- <sup>g</sup> Every effort should be made to assess subjects pre-bronchodilator and post-dose FEV<sub>1</sub> at the same time throughout the study). Pre- bronchodilator FEV<sub>1</sub> will be measured in the mornings between 06:00 and 10:00 AM, and within 1 hour of FEV<sub>1</sub> measured at Visit 2. From Visit 2 onwards, pre- and post-dose measurements will be with respect to administration of IP (Table 4).

- h. At the start of each treatment visit, subjects must withhold all asthma medications, including Sponsor-provided Ventolin for at least 6 hours prior to start of test day procedures.*
- i. Dispense IP to subject for at-home use following the completion of all post-dose assessments. IP will not be dispensed at Visit 6.*

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### 1.3 Number of subjects

The target population for this study are male and female subjects  $\geq 4$  years of age with a diagnosis of asthma as defined by Global Initiative for Asthma (GINA) criteria. To be eligible for the study they must have been taking a stable dosing of asthma therapies (prn SABA or stable low-dose ICS in addition to prn SABA) for at least the last 30 days prior to Visit 1.

In line with the blinded sample size re-estimation (see section 1.3.1.2), the sample size of approximately 1000 adults and adolescent subjects with asthma will be randomized, with approximately 200 subjects per treatment group. In addition, up to 30 child subjects with asthma will be enrolled but will not receive high dose ICS and will be randomized 1:1:1 to receive low-dose BDA MDI 80/180  $\mu\text{g}$  QID, AS MDI 180  $\mu\text{g}$  QID, or placebo MDI. Approximately 2000 subjects will need to be screened, assuming an estimated screen failure rate of 50% prior to randomization.

Each subject must meet all the inclusion criteria and none of the exclusion criteria for this study. It must be noted that no study-related procedures may be performed before the subject has signed the Ethics Committee (EC) approved Informed Consent Form (ICF).

#### 1.3.1 Sample Size Calculation

##### 1.3.1.1 Initial assumptions and estimates

A blinded sample size re-estimation was performed once 44% of subjects had completed week 12. Based on the blinded estimate of variability, approximately 1000 subjects are required in order to demonstrate at least 90% power. Consequently, the total randomised adult and adolescent subjects has been increased to 1000 in order to ensure sufficient power. This section details the initial assumptions of variability prior to calculating the blinded sample size re-estimation. Please refer to section 1.3.1.2 for details on the sample size and power calculations following the blinded sample size re-estimation.

Prior to the blinded sample size re-estimation, randomization of approximately 120 subjects to each treatment group expected provide at least 93% probability to detect a 100 mL difference in the change from baseline in trough  $\text{FEV}_1$  at Week 12 for comparison of BD MDI versus placebo MDI, BDA MDI versus placebo MDI, or BDA MDI versus AS MDI. This calculation was based on a standard deviation of 210 mL obtained from the placebo MDI group of Study PT008001 and an assumed dropout rate of 10% and 15% for active and placebo treatment group, respectively, prior to Week 12.

Prior to the blinded sample size re-estimation, it was assumed that the sample size of 120 subjects per treatment group would also provide  $>99\%$  probability to detect a 130 mL difference in  $\text{FEV}_1 \text{ AUC}_{0-6 \text{ hours}}$  over 12 weeks for comparison of BDA MDI versus BD MDI (effect sizes for AS MDI or BDA MDI versus placebo MDI should be considerably larger).

This calculation assumed a 2% dropout prior to Week 1 and an effective standard deviation of 140 mL which was derived from the following: a per visit standard deviation of 200 mL (ProAir Respiclick Studies 301 and 304 and the AS MDI Dose-Ranging Study DC6930C00001), a correlation between visits of 65%, and projected subject completion of 4 out of 5 visits.

### 1.3.1.2 Results from the first blinded sample size re-estimation

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

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

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

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

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

### 1.3.1.3 Results from the second blinded sample size re-estimation

Randomization of approximately 200 subjects ( $\geq 18$  years of age) to each treatment group will provide 85% probability to detect a 100 mL difference in the change from baseline in trough FEV<sub>1</sub> at Week 12 for the comparison of BD MDI versus placebo MDI, BDA MDI versus placebo MDI, or BDA MDI versus AS MDI. This calculation is based on a standard deviation of 320 mL obtained from the blinded sample size re-estimation performed after 65% of subjects completed week 12. An overall dropout rate of 7% prior to Week 12 was calculated from this data.

Although the variability has slightly increased since the first blinded sample size estimation, the drop-out rate is lower than originally estimated. Whilst there is still at least 80% power, the sample size will not be further increased beyond 2000 subjects.

## 2. ANALYSIS SETS

### 2.1 Definition of analysis sets

#### 2.1.1 Full analysis set

The full analysis set (FAS) is defined as all subjects who are randomized, take at least 1 puff of randomized treatment and have at least one efficacy assessment. Subjects will be analyzed according to the treatment they were assigned to at randomization. Additionally, data suspected to be fraudulent will be reviewed on a case-by-case basis and may lead to exclusion from the full analysis set. Such exclusions will be fully documented and all data will be readily available in the SDTM and ADaM datasets.

For primary, secondary and exploratory efficacy analyses, a subpopulation of the FAS including patients aged 12 years and older will be used to make comparisons between the treatment groups. All efficacy analyses will be repeated on the FAS including all ages. Further details are provided in Section 6.

The efficacy and attributable estimand will include all data obtained before subjects discontinue randomized treatment, see section 6.1.1.

#### 2.1.2 Safety analysis set

The safety analysis set is defined as all subjects receiving at least 1 puff of randomized treatment. Subjects will be classified based on treatment they actually received. If a subject receives more than 1 randomized treatment, the subject will be summarized according to the treatment they received the most. All safety summaries will be based on the safety analysis set. Additionally, data suspected to be fraudulent will be reviewed on a case-by-case basis and may lead to exclusion from the safety analysis set. Such exclusions will be fully documented and all data will be readily available in the SDTM and ADaM datasets.

### 2.1.3 All patients enrolled

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

## 2.2 Protocol deviations

Important protocol deviations (IPDs) are defined as a subset of protocol deviations that may significantly affect the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being. All protocol deviations classified as important will be listed along with the full deviation term and coded term as collected in the Protocol Deviations CRF page. The important deviations will be summarised in terms of the number and percentage of subjects meeting the pre-defined protocol deviation coded term as defined in the Protocol Deviations CRF page. IPDs will be identified by the sponsor prior to the primary database lock and unblinding of the study results.

A per protocol analysis excluding subjects with important protocol deviations is not planned. However, any subjects or site activity identified or suspected to be fraudulent (e.g. subjects who are enrolled on this clinical study more than once or another interventional clinical study, subjects re-enrolling onto the study or fabricated data) will be excluded from the analysis populations defined in section 2.1. Such instances will be reviewed on a case-by-case basis and fully documented by the Sponsor prior to unblinding.

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

An indication on whether protocol deviations are linked to COVID-19 will be recorded on the eCRF. Incidence of COVID-19 related protocol deviations will be also summarized.

Any miss-stratified patients will be identified as important protocol deviations. All patients who are randomized and are part of the full analysis set will be analyzed according to the strata they were allocated to in IVRS/IWRS, as opposed to their actual strata.

## 3. Demography and Subject Characteristics Variables

### 3.1 Demographics

The following demographic characteristics will be collected at Screening.

- Ethnicity\*
- Race\*

- Sex

\* Race and/or ethnicity will be collected depending on local regulations.

Additionally, age will be collected at randomization. The age group strata will be derived based on the age at randomisation and will be categorised as

- Children:  $\geq 4$  to 11
- Adolescents:  $\geq 12$  to 17
- Adults:  $\geq 18$ .

Subjects must meet the eligibility criteria, assessed during screening, to be randomized to treatment. The list of inclusion and exclusion criteria are provided in the protocol. Eligibility criteria not met are collected on the eCRF.

Vital signs collected at screening will include height (cm), weight (kg) and a derivation of body mass index (BMI) ( $\text{kg}/\text{m}^2$ ), as collected in the eCRF. BMI will be re-calculated based on the collected height and weight measurements recorded at screening to allow greater precision compared to the BMI collected on the eCRF, which was recorded to 0 decimal places. BMI will be re-calculated as  $[\text{weight (kg)}] \cdot [\text{height (m)}]^2$ .

The stratification factors which are recorded at randomization are the pre-study background therapy (ICS, non-ICS) and the subject's ACQ-7 score at randomization ( $\leq 1.5$ ,  $> 1.5$ ). The children ( $\geq 4$  to 11 years) are not stratified by their pre-study background therapy and ACQ-7 score in the randomization to treatment, frequencies shown are for informative purposes only. Country will also be collected at randomization and included in the Demographics SDTM dataset.

### 3.2 Medical, asthma and smoking history

Medical (including surgical), asthma (including exacerbations) and smoking history will be recorded on the eCRF at Visit 1. General medical history will be categorized into past and current medical history. Current medical history will be defined as a condition that is either classified as on-going, or ending after the first dose of randomized treatment.

Additionally, the time since diagnosis of asthma (years) will be calculated as

$$(\text{Date of randomization (Visit 2)} - \text{Date of diagnosis of asthma} + 1) / 365.25.$$

Partial dates for the above calculations will be handled as per section 4.1.8.



### 3.3 Concomitant medications

All concomitant medication will be recorded on the eCRF throughout the study. Disallowed medications will be identified by a physician on review of the data which will be completed prior to database lock. All identified medications which are disallowed will be considered for flagging as an IPD during the protocol deviation reviews, prior to database lock and unblinding.

### 3.4 Spirometry at study entry

Lung function measurements of FEV<sub>1</sub> (L), FVC (L), FEV<sub>1</sub>/FVC (%) will be recorded at screening and randomization. At screening, assessments are collected at pre-ventolin and post-ventolin timepoints. At randomization, the spirometry assessments are performed as per Table 4. The calculation for reversibility in FEV<sub>1</sub> is provided in section 4.1.3. The definition of baseline spirometry assessments are provided in Section 4.1.1.

## 4. PRIMARY AND SECONDARY VARIABLES

### 4.1 General Definitions

#### 4.1.1 Definition of baseline

The general definition for non-diary and non-spirometry data is defined as the most recent non-missing measurement before the first dose of the randomized treatment on the day of randomization. Unscheduled visits will not be used when assigning a baseline value.

Baseline FEV<sub>1</sub> and FVC will be taken as the average of the 60- and 30- minute pre-dose measures on the day of randomization (Visit 2). If either of the 60- or 30- minute pre-dose spirometry measures are missing, then the available non-missing pre-dose FEV<sub>1</sub> value will be used. If both the 60- and 30- pre-dose spirometry measurements are then the baseline FEV<sub>1</sub> measure will be missing.

For patient reported outcomes in the eDiary, baseline will be calculated as the mean over the last 10 days of the run-in period prior the first dose of randomized treatment. See section 4.1.6 for the derivation of daily scores from the eDiary.

Any exceptions to the above will be described in the relevant variable derivation section.

#### 4.1.2 Absolute and percent change from baseline

Absolute change from baseline outcome variables is computed as

$$\text{Absolute change from baseline} = (\text{post-randomization value} - \text{baseline value}).$$

Percent change from baseline is computed for FEV<sub>1</sub> on Day 1 for onset and duration of response and is computed as

$$\text{Percentage change from baseline} = [(post\text{-}randomization\ value - baseline\ value) / baseline\ value] * 100\%.$$

Please note that for symptom-free days and asthma control days the change from baseline is represented as the absolute change of percentages as opposed to the percent change from baseline (section 6.2.7.11).

If either the post-randomization value or the baseline value is missing, then the absolute or percent change from baseline value will also be set to missing.

### 4.1.3 Reversibility

The reversibility is calculated as follows:

$$\text{Reversibility} = [(Post\ FEV_1 - Pre\ FEV_1) / Pre\ FEV_1] * 100\%.$$

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

### 4.1.4 Study day calculation

Study day will represent the number of days since first dose of randomized treatment of an observation and will be calculated as:

Pre-dose study day = date of assessment – date of first dose of randomized treatment

Post-dose study day = date of assessment – date of first dose of randomized treatment + 1

If either the date of assessment or date of first dose of randomized treatment are missing, then the assigned study day will be missing.

### 4.1.5 Visit windowing

Visit windowing will be applied to spirometry assessments, laboratory measures, vital signs and ECG. The visit windows which will be applied to the scheduled study visits collected are as follows:

**Table 3 Visit windowing**

<i>Visit</i>	<i>Target Day</i>	<i>Adjusted windows for analyses (days):</i>
Baseline (Week 0)	1	1
Week 1	7	2 – 12 ( $\pm$ 5 days)
Week 4	28	21 – 35 ( $\pm$ 7 days)
Week 8	56	49 – 63 ( $\pm$ 7 days)
Week 12	84	70 – 98 ( $\pm$ 14 days)

Table 3 shows how the planned clinic visits will be assigned an appropriate scheduled visit from the VISIT module. If more than one scheduled visit occurs within the window, then the visit closest to the target day will be flagged for analysis. If there are two (or more) visits equidistant to the target day, then choose the most recent assessment to be used in analysis. Unscheduled visits are listed and will not be windowed, but will be considered in minimum/maximum on treatment results. Data collected at the PDV will be windowed to a visit as per Table 3.

Pulmonary function tests (PFTs) will be performed both before administration of randomized treatment (pre-dose) and following the morning dose of randomized treatment (post-dose). The timing of the PFTs carried out by the investigator are provided in Table 4. The assessment windows defined as per protocol will be used for guidance for the sites. No formal analysis windows are defined for serial spirometry measures; all spirometry assessments will be considered, and will be based on the actual clock time. Derivations based on post-dose serial spirometry will only be calculated if there is at least 1 non-missing FEV<sub>1</sub> result within 2 hours post-dose. More information on the derivation of serial spirometry endpoints is provided in Section 4.3.1.

**Table 4 Schedule of FEV<sub>1</sub> measurements at standard visits**

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

Abbreviation: min=minute; PFT=pulmonary function test

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

#### 4.1.6 Daily eDiary variables

The eDiary will be filled in by the subject twice daily, once in the morning upon awaking to record information relating to the previous night-time and once in the evening prior to bedtime and to record information relating to the daytime period.

For the purpose of analyses, daytime results recorded on the evening of day  $n$  and night-time results recorded on the morning of day  $n+1$  will correspond to the analysis day  $n$ . As such, daily totals for eDiary variables will be calculated as:

*Daily total for eDiary variable for analysis day  $n$  = (daytime result recorded in the evening on day  $n$ ) + (night-time result recorded in the morning on day  $n+1$ )*

This rule is not applicable to the assignment of daily lung function data (e.g. daily PEF) as these results do represent the timepoint at which they were recorded in the ed diary.

Where applicable, daily totals will only be calculated if both the daytime and night-time components are non-missing. The daily totals are calculated for; asthma symptom score, Ventolin reliever therapy inhalation, night-time awakenings, symptom free days and asthma control days.

#### 4.1.7 Treatment average

For ACQ-5, ACQ-7 and AQLQ variable summaries, the treatment average score will be calculated by averaging the overall scores collected during the randomized treatment period. The treatment average will also be calculated within each of the individual domain scores.

For daily eDiary variables, the treatment average will be calculated as the sum of all daily totals over the randomized treatment period and dividing by the number of evaluable days in the randomized treatment period. An evaluable day corresponds to the days where both the night-time result and the subsequent daytime result collected on the same day are non-missing. As the result recorded in the morning of study day 1 corresponds to pre-dose, this day will not be included in the treatment average calculations for daily total eDiary results.

#### 4.1.8 Imputation rules

In order to classify adverse events and concomitant medications as occurring during the run-in period (prior to randomization), during the randomized treatment period (on-treatment), or post randomized treatment discontinuation, a conservative imputation rule will be applied in the instances where partial start and/or stop dates are recorded. The date imputation algorithm should be performed in the following sequence:

##### Partial end date

1. If missing day [--/mm/yyyy] then impute as the minimum (end of the month, treatment discontinuation /completion date).
2. If missing month [--/--/yyyy] then impute as minimum ([31/12/yyyy], treatment discontinuation/ completion date).
3. If completely missing, then impute as date of treatment discontinuation/ completion.

##### Partial start date

4. If missing day [--mm/yyyy] then impute as the minimum of:
  - Start of the month [01/mm/yyyy] unless mm/yyyy is same as first dose of randomized treatment then impute as the date of first dose of randomized treatment;
  - End date of medication/ event (after partial date handling has been applied).
5. If missing month [--/--/yyyy] then impute as the minimum of:
  - Start of the year [01/01/yyyy]
  - End date of medication/ event (after partial date handling has been applied).
6. If completely missing, then impute as the minimum of:
  - Date of first dose of randomized treatment;
  - End date of medication/ event (after partial date handling has been applied).

The raw, original dates will be presented in any listings produced. The intention for date imputation is to facilitate a programmatic decision making process to classify on-treatment observations.

For responder analysis variables of ACQ-7, AQLQ+12 and FEV<sub>1</sub> on Day 1, a non-responder imputation will be carried out for missing endpoints. Further details will be provided in the relevant endpoint derivation sections.

The dual primary endpoints of trough FEV<sub>1</sub> and change from baseline FEV<sub>1</sub> AUC<sub>0-12</sub> hours will be imputed under a MNAR assumption under the supportive analysis conducted in accordance of the attributable estimand. Please see section 6.2.9 for more detail of these imputation methods.

#### 4.1.9 Spirometry assessments

Spirometry assessments will be collected at each study visit and provided by ERT. For each planned timepoint in the serial spirometry, multiple efforts will be performed by the subject. Of all efforts made at a planned time point, the best effort will be identified and included in the SDTM data. The primary, secondary and exploratory spirometry analyses, with the exception of time to onset and duration of response FEV<sub>1</sub> endpoints (section 6.2.5.1), the best efforts and their associated times of collection will be used in the analyses and derivation of endpoints. For the analysis of time to onset and duration of response endpoints, derivations will consider all spirometry efforts collected.

#### 4.1.10 Derived stratification factors for patients aged 4 to 11 years

Patients aged  $\geq 12$  years old will be stratified according to their background therapy (ICS; non-ICS) and ACQ-7 score at baseline ( $\leq 1.5$ ;  $> 1.5$ ). This information will be collected on the eCRF for this age range. However, since this information will not be available for patients ages  $< 12$  years it will be derived based on concomitant medication and baseline ACQ-7/ACQ-IA results available in the database. This is required such that patients aged  $< 12$  years contribute to statistical analyses adjusted by these strata.

Baseline ACQ-7 will be calculated at baseline for all patients and the category ( $\leq 1.5$ ;  $> 1.5$ ) will be assigned to patients aged  $< 12$  years. Patients aged  $\geq 12$  years will use the strata allocated at randomization.

Background study medication (ICS; non-ICS) will be derived for patients aged  $< 12$  years based on data available in the prior/concomitant medications module. Background maintenance ICS will be identified as records satisfying the following criteria:

- Prior medication (starts and/or ends prior to first dose of randomized treatment)
- Therapy reason (as recorded on eCRF) = 'Asthma Maintenance'

- ATC 5<sup>th</sup> level classification codes of:
  - R03BA
  - R03AK
  - R01AD
  - R03AL

Patients aged <12 years without concomitant medication records satisfying this criteria will be classified into the “non-ICS” population.

## 4.2 Treatment exposure

The exposure to the study medication is the total duration (days) from the first dose to the last dose (inclusive) of the randomized study drug and is calculated as:

$$\text{Date of last dose of randomized study drug} - \text{Date of first dose of randomized study drug} + 1$$

## 4.3 Primary Efficacy Measure

### 4.3.1 Dual-primary efficacy endpoints

The primary efficacy analysis comprises dual-primary endpoints of change from baseline in FEV<sub>1</sub> AUC<sub>0-6 hours</sub> over 12 weeks and change from baseline in trough FEV<sub>1</sub> at Week 12. Baseline FEV<sub>1</sub> will be taken as the average of the 60- and 30-minute pre-dose spirometry measures on or before randomization (Visit 2).

### 4.3.2 Derivation for FEV<sub>1</sub> AUC<sub>0-6 hours</sub>

FEV<sub>1</sub> AUC<sub>0-6 hours</sub> will be calculated for the changes from the baseline (randomization visit) using the trapezoidal rule and will be normalized by dividing by the time from dosing to the last measurement included (typically 360 minutes).

$$AUC_{0-6 \text{ hours}} = \frac{1}{t_N - t_1} \times \sum_{i=1}^N \frac{(y_{i-1} + y_i) \times (t_i - t_{i-1})}{2}$$

For FEV<sub>1</sub> change from baseline results  $y_i$  recorded  $t_i$  minutes after the morning dose (actual clock time) at  $i = 1, 2, \dots, N$  actual timepoints. If all timepoints are available, then  $N = 10$  according to Table 4. Only FEV<sub>1</sub> results of ‘acceptable’ or ‘borderline acceptable’ (investigator assigned) quality will be used in the derivation of FEV<sub>1</sub> AUC<sub>0-6 hours</sub>. If an FEV<sub>1</sub> result is missing or recorded in the database, but assigned an ‘unacceptable’ quality grade at the scheduled assessment, then the assessment will be excluded from the calculation of FEV<sub>1</sub> AUC<sub>0-6 hours</sub>. To calculate FEV<sub>1</sub> AUC<sub>0-6 hours</sub>, there must be at least 1 non-missing post-dose FEV<sub>1</sub> within 0 to 2 hours post-dose. Missing FEV<sub>1</sub> post-dose measures will not be imputed.

### 4.3.3 Derivation for trough FEV<sub>1</sub>

At each of the post-randomization visits, trough FEV<sub>1</sub> will be taken as the average of the 60- and 30-minute pre-dose spirometry measures prior to dosing of randomized treatment.

In subjects with only 1 evaluable pre-dose assessment, the trough FEV<sub>1</sub> will be calculated from the single measurement. If both pre-dose assessments are unevaluable, then the trough FEV<sub>1</sub> will be missing. The 60- and 30- minute pre-dose assessments with an assigned quality grade of 'unacceptable' will be not be used in the calculation of trough FEV<sub>1</sub>.

## 4.4 Secondary Efficacy Measures

### 4.4.1 Derivation for time to onset (15% increase in FEV<sub>1</sub>) on Day 1 and duration of effect on Day 1

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

*Time of first 15% increase in percentage change from baseline in FEV<sub>1</sub> – Time of dosing on Day 1 (randomization, Visit 2)*

The time to event is only calculated for those patients who have an observed percentage of at least 15%.

The duration of effect will be calculated for each subject as the period, in minutes, in which the post-dose FEV<sub>1</sub> is at least 15% higher than baseline. If the subject does not achieve a 15% increase from baseline FEV<sub>1</sub> within the first 30 min of their post-dose assessments on day 1, the duration of effect will be zero. If a 15% increase is observed and is sustained until the last post-dose assessment of FEV<sub>1</sub> on day 1, the duration will be calculated up to the last available assessment. If a subject has multiple periods of effect throughout the Day 1 FEV<sub>1</sub> profile, only the first continual period of effect will be considered in the analyses.

When identifying the 15% increase from baseline FEV<sub>1</sub>, only acceptable and borderline acceptable spirometry assessments will be considered when deriving the above endpoints. Unacceptable quality FEV<sub>1</sub> measurements should be considered as unevaluable. The time to onset and duration of effect will be primarily calculated based on all effort results provided by the patient and included in the SDTM. Additionally, patients will be categorized into those who achieve a 15% increase in FEV<sub>1</sub> within the 30-minute post-dose on Day 1:

- Responder  $\geq 15\%$  change from baseline in maximum FEV<sub>1</sub> within 30 minutes post-dose.



- Non-responder <15% change from baseline in maximum FEV<sub>1</sub> within 30 minutes post-dose.

The maximum FEV<sub>1</sub> will be based on the non-missing spirometry assessments up to 30 minutes post-dose and assigned a quality grade of acceptable or borderline acceptable. If all post-dose measurements are missing or assigned an unacceptable quality up to 30-minutes post-dose on Day 1, then the patient will be categorized as a non-responder.

#### 4.4.2 Derivation of Trough FEV<sub>1</sub> at Week 1

The secondary efficacy endpoint of trough FEV<sub>1</sub> will be derived in the same manner as the dual-primary endpoint of trough FEV<sub>1</sub> at Week 12 (Section 4.3.3)

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

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

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

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

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

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

## 5. EXPLORATORY EFFICACY MEASURES

### 5.1 Derivation of severe exacerbation endpoints

The raw annualized severe asthma exacerbation rate will be calculated according to the following formula:

$$\text{Annualized severe exacerbation rate} = \frac{\sum \text{number of severe exacerbations} * 365.25}{\sum \text{follow-up}}$$

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

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

*Date of treatment completion - date of first dose of randomized treatment + 1.*

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

*Date of randomized treatment discontinuation - date of first dose of randomized treatment + 1.*

Date of randomized treatment completion and premature discontinuation will be collected on the eCRF.

## 5.2 Derivation of deterioration of asthma variables

The subject will use the eDiary for daily symptom reporting, entering symptoms twice daily. In particular the subject will record their daytime symptoms (0=No asthma symptoms; 1=You were aware of your asthma symptoms but you can easily tolerate the symptoms; 2=Your asthma was causing you enough discomfort to cause problems with normal activities; 3=You were unable to do your normal activities because of your asthma), night-time symptoms (0=No symptoms; 1= You were aware of your asthma symptoms but you can easily tolerate the symptoms; 2= your asthma was causing you enough discomfort to cause problems with sleep; 3=You were unable to sleep because of your asthma), and their rescue medication use (0, ..., 99 puff(s)).

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

- PEF: a decline of at least 20% from baseline in either the morning or evening result
- Ventolin reliever therapy use: >4 puffs per day and at least twice as frequent than recorded at baseline (per day)
- Symptoms: night-time score that is greater than baseline and at least 2 OR a daytime score that is greater than baseline and 3 (most severe outcome)
- Severe asthma exacerbation<sup>1</sup>

Ventolin reliever therapy use and symptom scores will be recorded in the eDiary. Baseline reliever therapy use will be calculated as the average number of puffs per day during the last 10 days of the run-in period.

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

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

If the above criteria are met for  $\geq 2$  consecutive days, it will be considered as one deterioration of asthma until the criteria are no longer met or becomes unevaluable. Typically, the date in which the criteria is no longer met will determine the end date of a deterioration of asthma. If the number of days separation between two asthma deteriorations are less than 3 consecutive days, then they will be classed as a single asthma deterioration.

Missing eDiary results will not be considered as a deterioration of asthma.

<sup>1</sup>Severe asthma exacerbations will also be considered to be deterioration of asthma and included in the analyses of this endpoint. Severe exacerbations will be recorded on the Severe Exacerbation module and 1 record corresponds to 1 severe exacerbation.

The deterioration of asthma rate will be calculated in a similar way as the raw annualized severe asthma exacerbation rate (Section 5.1).

### 5.3 Derivation of peak FEV<sub>1</sub>

Peak FEV<sub>1</sub> is derived as the maximum FEV<sub>1</sub> post-dose assessment of randomized treatment in the 6-hour profile period with an assigned quality grade of acceptable or borderline acceptable. Following this, the change from baseline to peak FEV<sub>1</sub> will be calculated at each visit by computing the difference between the peak and baseline FEV<sub>1</sub> values. Baseline FEV<sub>1</sub> is calculated as described in Section 4.3.1.

### 5.4 Derivation of peak expiratory flow

The best of 3 PEF measurements will be recorded by the subject in the morning and before going to bed in the evening prior to taking any asthma therapy and will be captured in the eDiary

Morning and evening peak expiratory flow will be grouped into 4-weekly averages across the 12-week randomized treatment period. The 4-weekly time intervals are defined as 28-day long periods starting from the date of first dose of randomized treatment. The following Table 5 illustrates how the periods will be assigned using the study day of each record (See section 4.1.4 for the calculation of study day).

**Table 5 4-Weekly Time Intervals**

<i>Period</i>	<i>Start Day</i>	<i>End Day</i>
Period 1	Day 1 (Date of randomization)	Day 28
Period 2	Day 29	Day 56 (Day 29 + 27)
Period 3	Day 57	Day 84 (Day 57 + 27)

Only PEF measurements prior to the last dose of randomized study drug will contribute to the period averages.

Additionally, overall averages of morning and evening PEF measurements will be calculated across the randomized treatment period, from first dose of randomized study treatment to the last dose of study treatment. PEF measurements after the last dose of study drug will not contribute to the average.

Only non-missing records will be considered in the 4-weekly and overall randomized treatment period averages and the denominator will be equal to the number of non-missing PEF measurements in the average calculation. A minimum of 5 days of non-missing PEF results are required to derive a 4-weekly average. A minimum of 15 non-missing PEF days are required to derive the overall randomized treatment period average.

In addition, following a review of ERT's production processes, ERT have identified irregularities that may impact a few AM3 devices, causing a higher frequency of inadequate efforts or false readings of the PFT signal leading to abnormally high PEF values (i.e. 700L/min and above). Such cases have been investigated and concluded that the abnormal measurements are due to manufacturing issues with the AM3 device. All PEF data will be provided in the SDTM, but a flag assigned by ERT which will indicate whether the PEF result was estimated from a faulty AM3 device. These unreliable results will be considered as unacceptable quality PEF measurement and excluded from the analyses. The faulty devices have been recalled and are to be exchanged.

## **5.5 Derivation of Asthma Control Questionnaire – 7 exploratory variables**

The changes from baseline ACQ-7 overall score at Week 12 will be categorized into the following 3-level factor:

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

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

## 5.6 Derivation of Asthma Control Questionnaire – 5 variables

Derivations for responder status for ACQ-5 will be performed as described in Section 5.2. At least 4 out of the 5 symptom items are needed to provide an overall ACQ-5 score.

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

AQLQ+12 consists of 32 questions in 4 domains and PAQLQ consists of 23 questions in 3 domains. Both are assessed on separate 7-point Likert scales from 1 to 7, with higher values indicating better health-related quality of life.

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

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

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

## 5.8 Derivation of Ventolin therapy variables

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

Total daily number of puffs will be calculated for each subject as the sum of the cumulative number of puffs of Ventolin therapy divided by the number of evaluable days the subject has until treatment discontinuation. An evaluable day is a day in which the subject has a complete diary entry on the number of puffs of Ventolin they have taken.

Total daily number of puffs will be further characterized within 4-weekly time intervals throughout the randomized treatment period. The 4-weekly time intervals will be calculated in the same manner as for peak expiratory flow (Section 5.3).

The average number of puffs for each 4-weekly, and overall average across the randomized treatment period will only consider evaluable eDiary days, where a record of Ventolin administrations is provided. Days with missing data will not contribute to the numerator or denominator of the average calculations.

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

## 5.9 Derivation of other eDiary variables

### Asthma symptom score

Asthma symptom score, a 4-point scale ranging from 0 (no asthma symptoms) to 3 (most severe asthma symptoms), will be collected twice daily in the morning and evening in the eDiary. Please refer to section 4.1.6 for the assignment of study day, and the derivation of the total symptom score. The average day, night and total asthma symptom score will be calculated over the randomized treatment period, and in 4-weekly intervals as per daily PEF (section 5.4).

### Night-time awakenings

Night-time awakenings will be collected every morning in the eDiary. Please refer to section 4.1.6 for the assignment of study day. The percentage of night-time awakenings will be calculated over the randomized treatment period, and in 4-weekly intervals as per daily PEF (section 5.4).

### Symptom-free days

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

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

The percentage of symptom free days will be calculated for each subject as the number of symptom-free days during the randomized treatment period divided by the number of evaluable days during the randomized treatment period. For both the denominator and numerator, the randomized treatment period is defined from the date of first dose to the date of last dose of randomized treatment.

For the asthma symptom score component, it is important to consider the daytime and night-time score separately. For example, a daytime score  $> 0$ , but missing night-time score would correspond to a day with symptoms and vice versa.

An unevaluable symptom-free day occurs when it cannot be unequivocally determined whether an analysis day was symptom free. Table 6 illustrates the daily status of a symptom-free day when there are missing components to the endpoint:

**Table 6 Missing data**

<i>Number of missing datapoints</i>	<i>Condition</i>	<i>Daily status</i>
0	Sum of datapoints > 0	Not Symptom-free
	Sum of datapoints = 0	Symptom-free
1	Sum of non-missing datapoints > 0	Not Symptom-free
	Sum of non-missing datapoints = 0	Not evaluable
2	No non-missing datapoints	Not evaluable

\* No night-time awakenings would contribute 0 to the sum of datapoints.

### **Asthma control days**

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

- A day and night with no asthma symptoms (ie, asthma symptom score=0)
- A night with no awakenings due to asthma symptoms
- A day and night with no use of prn Ventolin therapy (not including unscheduled use of investigational product)

The percentage of asthma control days will be calculated as done for symptom-free days.

### **Overall eDiary compliance**

Overall eDiary compliance during the randomized treatment period is calculated as:

$$\text{Overall eDiary compliance (\%)} = \frac{(\text{Actual number of entries})}{(\text{Expected number of entries})} * 100(\%)$$

Where the total expected compliance is:

$$\text{Total expected compliance} = (\text{Number of days in the treatment period} - 1) * 2$$

As subjects are expected to fill in the eDiary once in the morning and once in the evening, each day.

Additional information which the output provides is the percentage of subjects which have a compliance rate of  $\geq 80\%$ .

## 5.10 Safety variables

### 5.10.1 Vital signs

The following vital signs measurements will be conducted at the visits as shown in Table 1 and for timed assessments at Visit 2 and Visit 6. Measurements should be taken in the sitting position after at least 10 minutes of rest:

- Pulse rate (beats/min)
- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)

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

### 5.10.2 Adverse events (including Serious Adverse Events)

#### 5.10.2.1 Definition of adverse event

An AE is the development of any untoward medical occurrence in a 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 randomized treatment has been administered.

#### 5.10.2.2 Definitions of serious adverse event

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

- Death
- Immediately life-threatening
- Requires in-subject 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

All SAEs will be identified by the investigator and entered in the eCRF. The 'Serious?' field will be set to 'Y'.



### 5.10.2.3 Collection of AEs and SAEs

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

The following variables will be collected for each AE:

- AE term (verbatim)
- The date when the AE started and stopped
  - YYYY/MMM/DD
- Maximum intensity
  - Mild
  - Moderate
  - Severe
- Serious
  - Yes or no
- Investigator causality rating against the randomized treatment
  - Yes or no
- Action taken regarding randomized treatment
  - Dose not changed
  - Drug interrupted
  - Drug permanently discontinued
  - Not applicable
- Outcome
  - Recovered/resolved
  - Recovering/resolving
  - Recovered/resolved with sequelae
  - Not recovered/not resolved
  - Fatal

### 5.10.2.4 Definition of adverse event leading to discontinuation of investigational product (DAE)

Adverse events where “Action taken, Randomized Treatment” is answered “Drug permanently discontinued” will be defined as DAEs and reported separately (in addition to being reported as general AEs).

### 5.10.2.5 Adverse events data handling

Adverse events will be reported as starting during the run-in period if the AE start date is on or after the first date of run-in medication (Ventolin), and prior to the first dose of randomized medication.

Adverse events will be considered as starting during the treatment period if the onset date is on or after the first dose of randomized treatment and onset is no later than the last day of randomized treatment.

Adverse events will be considered as starting during the follow-up period if the onset date is after the last day of randomized treatment.

If an AE has a missing onset date, then, unless the stop date of the AE indicates otherwise, this will be considered as starting during the randomized treatment period. Similarly, if an AE has a partial onset date, then unless the partial onset date or the stop date indicates otherwise, this will be considered as starting during the randomized treatment period.

Please refer to Section 4.1.8 for the imputation rule to programmatically determine the classification of AEs when there are partial start and/or stop dates are recorded.

### **5.10.3 Laboratory Safety Variables**

The following laboratory variables described in Table 7 will be measured throughout the course of this study:

**Table 7 Laboratory Safety Variables**

<i>Hematology/Hemostasis (whole blood)</i>	<i>Clinical Chemistry (serum or plasma)</i>
<b>Complete Blood Count (CBC)</b>	Albumin
Hemoglobin	Alanine transaminase (ALT)
Hematocrit	Alkaline phosphatase (ALP)
Mean Corpuscular Hemoglobin (MCH)	Aspartate transaminase (AST)
Mean Corpuscular Hemoglobin Concentration (MCHC)	Bilirubin (total)
Mean Corpuscular Volume (MCV)	Calcium (total)
Red blood cells (erythrocytes)	Chloride
White blood cells (leukocytes)	Cholesterol (total)
	Creatinine
<b>Differential:</b>	Creatine kinase
Basophils (absolute)	Gamma-glutamyl transpeptidase
Basophils (%)	Glucose (random)
Eosinophils (absolute)	Magnesium
Eosinophils (%)	Phosphate
Lymphocytes (absolute)	Potassium
Lymphocytes (%)	Protein, total
Monocytes (absolute)	Sodium
Monocytes (%)	Triglycerides
Neutrophils (absolute)	Urea
Neutrophils (%)	Serum $\beta$ -hCG pregnancy (Visit 1 and treatment discontinuation [EOT or PDV])
<b>Platelet:</b>	
Platelet count	
<b>Urine</b>	
Urine $\beta$ -hCG pregnancy (Visits 2 and 4)	

Abbreviations: ALT=alanine transaminase; ALP=alkaline phosphatase; AST=aspartate transaminase;  $\beta$ -hCG= $\beta$ -human chorionic gonadotropin; CBC = Complete Blood Count; EOT=end-of-treatment

### Hy's Law

Cases where a subject shows elevation in liver biochemistry may require further evaluation and occurrences of AST and/or ALT  $\geq 3 \times \text{ULN}$  combined with TBL  $\geq 2 \times \text{ULN}$  may need to be reported as SAEs.

The following criteria will be used to identify potential Hy's Law cases:

**Part 1**

Bilirubin (total)  $\geq 2 \times$  Upper limit of the normal reference range

**Part 2**

Alanine transaminase  $\geq 3 \times$  Upper limit of the normal reference range

Aspartate transaminase  $\geq 3 \times$  Upper limit of the normal reference range

At least 1 criteria must be met from both Part 1 and Part 2 to be classified as a potential Hy's law case. Potential Hy's Law cases can occur at any time during the study, all timepoints, including unscheduled assessments will be considered for meeting the criteria.

**5.10.4 Resting 12-lead electrocardiogram**

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

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

**5.11 Other variables****5.11.1 Concomitant medications**

The collection and recording of all concomitant medications, including all pre-enrollment asthma therapies, will be performed at the visits detailed in Table 1.

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

If a concomitant medication is recorded with partial start date and/or end date of administration, a conservative approach will be considered such that unless it can be unequivocally determined that the medication started and ended prior to the first dose of randomized study drug, based on available information from the partial date(s), the medication will be classified as concomitant. To facilitate this decision-making process programmatically, the imputation process defined in section 4.1.8 will be considered.

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

### 5.11.2 Discontinuation of investigational product

Subjects may be withdrawn from the study at any time at their own request, their parent/legal representative's request, upon request of the investigator, or by the Sponsor at any time. The subject is free to discontinue treatment at any time for any reason, without prejudice to further treatment. Reasons for discontinuation of randomized treatment collected on the eCRF include:

- Subject Decision
- Adverse Event
- Severe non-compliance to protocol
- Condition under investigation worsened
- Lack of Therapeutic Response
- Development of study specific discontinuation criteria
  - A severe exacerbation event
  - Pregnancy
- Subject lost to follow-up
- Completed
- Other

Subjects who discontinue randomized treatment prior to the end of the 12-week treatment period will be withdrawn from the study and asked to complete a PDV and the presence of any AEs. If possible, they will be seen and assessed by an investigator(s) and followed up if medically indicated.

### 5.11.3 Study Withdrawal

Patients who discontinue treatment prior to the end of the 12-week treatment period will be withdrawn from the study. The following criteria are recorded when a subject is discontinued from the study:

- Adverse Event
- Completed
- Death
- Lost to Follow-Up
- Protocol Deviation
- Screen Failure
- Withdrawal by Subject
- Withdrawal by Parent/Guardian
- Other (specify)

### 5.11.4 Screen Failures

Screen failures are subjects who do not fulfill the eligibility criteria for the study, and therefore must not be randomized. These subjects, who have a reason for not enrolling to the study, should be recorded as a 'Screen Failure' on the disposition eCRF page. Subjects who are screen failures will not be rescreened.

### 5.11.5 Compliance of study medication

The administration times and number of puffs of randomized study treatment will be recorded in the eDiary daily. The compliance of randomized study treatment will be calculated as

$$\text{Overall compliance} = \frac{\text{Actual number of puffs}}{\text{Expected number of puffs}} \times 100\%$$

Where the expected number of puffs would be as follows:

$$\begin{aligned} \text{Expected number of puffs} &= [4 (\text{doses per day}) * 2 (\text{puffs per dose}) \\ &\quad * (\text{days in the randomized treatment period})] - 6 \end{aligned}$$

Subjects are expected to take 1 dose of randomized study drug on their last scheduled visit, therefore the final 3 doses (6 puffs) are subtracted from the final day of the randomized treatment period. This is due to the final PFT being on week 12 and the PFT should not occur after 10:00 am.

Any missing eDiary data for randomized treatment administration will be assumed to be zero doses when calculating overall compliance.

Ventolin will be dosed prn; therefore, compliance will not be applicable.

## **6. ANALYSIS METHODS**

### **6.1 Statistical Considerations**

All personnel involved with the analysis of the study will remain blinded until database lock and identification of protocol deviations are identified.

Analyses described within this Statistical Analysis Plan will be performed by [REDACTED]

#### **6.1.1 Estimands**

Three estimands are of interest in this study:

The primary estimand of interest is the efficacy estimand, defined as the effect of the randomized treatment in all subjects assuming continuation of randomized treatment for the duration of the study, regardless of actual compliance. This estimand could be considered as a while-on-treatment strategy or a hypothetical strategy as defined in the draft International Conference on Harmonization (ICH) E9 Addendum. Subjects who prematurely discontinue randomized treatment will also be discontinued from the study. For the primary, secondary and exploratory endpoint missing data will be assumed to be missing at random (MAR) under the efficacy estimand. Further details are provided in section 6.2.

The second estimand of interest is the attributable estimand, defined as the effect of treatment in subjects attributable to the randomized treatment. For this estimand, discontinuation of randomized treatment for reasons such as tolerability or lack of efficacy is considered a negative outcome. This estimand is a mixture of composite and hypothetical strategies as defined in the draft ICH E9 addendum. Further details are provided in section 6.2.9.

The third estimand of interest is the COVID-19 estimand. This estimand is supportive to the efficacy estimand, defined as the effect of the randomized treatment in all subjects assuming continuation of randomized treatment for the duration of the study in the absence of COVID-19 impacts. The dual-primary endpoints for the study will be analyzed under the COVID-19 estimand. COVID-19 related treatment emergent adverse events can be identified through a pre-defined list of preferred terms in MedDRA. Dose interruptions are investigator identified breaks in medication that are collected in the eCRF, the investigator will also flag whether or not the interruption was related to COVID-19 in the eCRF.

### 6.1.2 Discontinuation of randomized treatment due to lack of efficacy

The attributable estimand will consider missing data when the primary reason for discontinuation is due to tolerability or lack of efficacy a negative outcome in the analyses. The primary reason for treatment discontinuation will be collected on the eCRF. The following reasons for discontinuation will be indicative of a lack of asthma control:

- Subject decision (where specific reasons are):
  - Subject perceives the investigational product to be ineffective
  - Subject wishes to take a treatment that is not allowed in this study
  - Subject perceives the logistics to be unacceptable
- Adverse event related to treatment<sup>1</sup>
- Condition under investigation worsened
- Lack of therapeutic response
- Development of study specific discontinuation criteria (where specific reasons are):
  - A severe exacerbation event

Death due to asthma<sup>11</sup> Reasons for discontinuation that are attributable to lack of efficacy will be reviewed by the Sponsor and finalized prior to database lock and unblinding of the study.

### 6.1.3 Type I error control

The Type I error for the primary analysis will be controlled using a sequential testing strategy, such that to reject a null hypothesis  $H_{0_m}$  of a pre-defined order  $1, \dots, m, \dots, n$ , the null hypotheses,  $H_{0_1}$  to  $H_{0_{m-1}}$  must all be rejected beforehand. Please see Section 6.2.4 for further details about the dual primary endpoint analyses and the implementation of this multiple testing strategy.

## 6.2 Analysis methods

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

When appropriate, statistical analysis models will be adjusted to include the stratification factors used at randomization. All patients who are randomized and are part of the full analysis set will be analyzed according to the strata they were allocated to in IVRS/IWRS.



Any patients who are miss-stratified will be identified as important protocol deviations and listed in the CSR.

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

Unless otherwise stated, descriptive summaries of continuous endpoints will include: The number of evaluable subjects in the analysis (n); Mean; Standard Deviation; Median; Minimum; Maximum. Summaries of categorical endpoints will include the absolute counts and percentage, with the denominator used in the percentage calculation clearly defined in the footnote of the table. Unless stated otherwise, the denominator will be the number of subjects in the analysis set used for the descriptive summary.

### 6.2.1 Subject Disposition

Subject disposition will be summarised for all subjects who have been enrolled and have provided informed consent. The number of subjects who were enrolled, run-in and not run-in will be summarised. The number and percentage of subjects will be presented by the following categories; randomized, not randomized (and reasons), randomized who received study treatment, randomized who did not receive study treatment (and reasons), completed, and discontinued the study (and reasons). If the reason for premature discontinuation is "Development of study specific discontinuation criteria" the specify field, which contains standard text, will be reported as a sub-field in the summary table. For categories that are post-randomization, summaries will be further split by treatment group.

A separate table will present the number and percentage of subjects randomized to each treatment group, by country and centre. This table will be based on the FAS.

### 6.2.2 Demographic and Baseline Characteristics

The summary of demographic and baseline characteristics will be performed on the full analysis set. Summary statistics will be repeated for FAS patients aged  $\geq 12$  years. Demographic characteristics of age (years), sex, race and ethnic group will be summarized by treatment group (including total across treatment).

Patient height (cm), weight (kg) and BMI ( $\text{kg/m}^2$ ) will be summarized by treatment group (including total across treatment).

Lung function endpoints of FEV<sub>1</sub> (L), FVC (L), FEV<sub>1</sub>/FVC (%) and reversibility (%) will be summarized at screening and baseline descriptively, within treatment group and across treatment groups. Pre- and post-bronchodilator will be presented at screening in these descriptive summaries. Summary statistics will be presented for the FAS (all ages) and repeated for FAS patients aged  $\geq 12$  years.

ACQ-5, ACQ-7, AQLQ+12, PAQLQ and PEF recorded at baseline will be summarized descriptively, within treatment group and across treatment groups. Summary statistics will be presented for the FAS (all ages) and repeated for FAS patients aged  $\geq 12$  years.

Medical (past and current) and surgical histories will be summarised by MedDRA preferred term within MedDRA system organ class.

Smoking status will be summarised categorically as the number of subjects who have never smoked, are current smokers or are former smokers and grouped by randomized treatment group. Nicotine pack years, e-cigarette pack years and total (nicotine + e-cigarette) pack years will be summarised as a continuous endpoint by randomized treatment group.

Additionally, asthma history variables collected on the eCRF will be summarised descriptively. Time since diagnosis of asthma will be summarised as a continuous scale and present the median, minimum and maximum result by treatment group.

### 6.2.3 Treatment Exposure

The duration of treatment will be summarised as the period in days from the date of first dose to the date of last dose of randomized study treatment, inclusive:

Duration of exposure = Date of last dose of randomized treatment – Date of first dose of randomized treatment + 1.

This summary of duration of exposure will be based on the safety analysis set. Additionally, the total daily number of puffs of randomized treatment will be summarised descriptively and based on the safety analysis set. For exploratory efficacy analyses of reliever therapy use, please refer to section 6.2.7.10.

### 6.2.4 Analysis of the dual-primary endpoints

The dual-primary endpoints, change from baseline in  $FEV_1$  AUC<sub>0-6 hours</sub> over the 12-week period, and change from baseline in trough  $FEV_1$  at week 12 will each be analyzed using a repeated measures (RM) linear model to compare treatment groups. The model will include baseline  $FEV_1$ , percentage reversibility to Ventolin, and age as continuous covariates, and visit, treatment, the treatment-by-visit interaction, and Pre-study background therapy (ICS, non-ICS) as categorical covariates. Under the efficacy estimand, only windowed data (Section 4.1.5) prior to treatment discontinuation will be included in the primary analysis. The presentation of analysis results will include the least squares mean estimates for each treatment and the least squares mean differences between the treatment groups, along with associated 95% confidence intervals and p-values.

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

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

$H_0$ : Difference between treatments = 0,

$H_A$ : Difference between treatments  $\neq$  0.

Change from baseline in  $FEV_1$  AUC<sub>0-6 hours</sub> over 12 weeks:

1. AS MDI 180  $\mu$ g QID versus placebo MDI QID
2. BDA MDI 160/180  $\mu$ g QID versus placebo MDI QID
3. BDA MDI 160/180  $\mu$ g QID versus BD MDI 160  $\mu$ g QID

Change from baseline in trough  $FEV_1$  at Week 12:

4. BD MDI 160  $\mu$ g QID versus placebo MDI QID
5. BDA MDI 160/180  $\mu$ g QID versus placebo MDI QID
6. BDA MDI 160/180  $\mu$ g QID versus AS MDI 180  $\mu$ g QID

Statistical testing for BDA 80/180  $\mu$ g will proceed in a similar manner as for BDA 160/180  $\mu$ g, as shown below:

Change from baseline in trough  $FEV_1$  at Week 12:

7. BDA MDI 80/180  $\mu$ g QID versus placebo MDI QID
8. BDA MDI 80/180  $\mu$ g QID versus AS MDI 180  $\mu$ g QID

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

The comparison of BDA MDI 160/180  $\mu$ g versus AS MDI 180  $\mu$ g will exclude the child subjects aged 4 to 11 years as they will not be randomized to BDA MDI 160/180  $\mu$ g.

The above tests in steps 1 to 8 will exclude children (age 4 to 11 years). The analysis will be repeated to include children, but will be considered a supportive analysis of the dual primary endpoint.

The comparisons of BDA MDI 80/180 µg QID versus placebo MDI QID and BDA MDI 80/180 µg QID versus BD MDI 160 µg QID for FEV<sub>1</sub> AUC<sub>0-6 hours</sub> over 12 weeks are not included in the Type I error control procedure as they redundantly evaluate the contribution of albuterol to the combination, which is already captured in Steps 2 and 3. However, these comparisons will be reported for completeness.

The associated p-values for the treatment differences will be presented for all comparisons as per the 8-step testing strategy defined above. In the primary results table there will be an accompanying column to aid interpretation of each hypothesis test with respect to the overall type-I error control being used.

FEV<sub>1</sub> AUC<sub>0-6 hours</sub> over 12 weeks will be calculated using an appropriate contrast. Two-sided p-values and point estimates with two-sided 95% confidence intervals will be calculated for each pairwise treatment contrast. An example SAS code is provided below.

```
proc mixed data = <<input datasets>> alpha = 0.05;
  class avisit ICS trtp usubjid;
  model CHG = trtp avisit trtp*avisit ICS blfev revl age/ddfm = kr;
  repeated avisit / type = UN subject = usubjid;
  lsmeans trtp trtp*avisit/diff cl;
run;
```

Abbreviations: age = age; avisit = visit; ICS = inhaled corticosteroid treatment; trtp = treatment group; usubjid = subject id no. chg = change from baseline in primary endpoint; blfev = baseline FEV<sub>1</sub>; revl = percentage reversibility to Ventolin.

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

A supportive analysis will be performed where data collected post a COVID-19 related treatment emergent adverse event, or a COVID-19 treatment interruption will be excluded from the dual primary endpoint derivation.

Forest plots of the dual primary endpoint analyses under the efficacy estimand will be programmed and show the LS means differences and associated 95% confidence intervals for the treatment group comparisons specified in the 8-step testing sequence.

### 6.2.5 Analysis of the secondary efficacy variables

For all secondary analyses the same treatment comparisons as for the primary analysis will be conducted (Section 6.2.4), will be conducted on the FAS  $\geq 12$  years and will be repeated on the FAS including all ages.

#### 6.2.5.1 Median time to onset (15% increase in FEV<sub>1</sub>) and duration of response

The median time to onset (defined as 15% increase in FEV<sub>1</sub>) over the pre-treatment value at randomization (Visit 2) will be compared among treatment groups using a Wilcoxon rank sum test. Confidence intervals for the median treatment difference will be calculated using the Hodges-Lehmann method. Only the patients who achieve the 15% increase in FEV<sub>1</sub> within 30 minutes post-dose will be included in the analysis.

For these secondary analyses, all efforts from the serial spirometry will be used (see 4.1.9). Additionally, the proportion of patients achieving a 15% increase in FEV<sub>1</sub> within 30 minutes post-dose on Day 1 will be analyzed using a logistic regression model with treatment and pre-study background therapy (ICS, Non-ICS) as categorical covariates, and baseline FEV<sub>1</sub> score and age as continuous covariates. The odds ratios and corresponding 95% confidence interval along with p-values will be estimated from the model.

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

#### 6.2.5.2 Asthma Control Questionnaire

The primary analyses of ACQ-7 will be conducted in subjects that are uncontrolled at baseline (i.e., baseline ACQ-7  $\geq 1.5$ ) as these are the subjects capable of demonstrating a clinically meaningful response with treatment. Only data from first dose up to the last dose of randomized treatment will contribute to analyses of ACQ-7. The analysis of ACQ-7 in the population of patients indicating partially controlled to uncontrolled asthma at baseline (ACQ-7  $\geq 0.75$ ) will be considered as an exploratory analysis (section 6.2.7.7).

The responder variable described in Section 4.4.3 at Week 12 will be analyzed using a logistic regression model with treatment and previous ICS use (Yes/No) as categorical covariates, and baseline ACQ-7 score, baseline post-dose percent predicted FEV<sub>1</sub> and age as continuous covariates. From the logistic regression model treatment effects will be estimated by odds ratios and corresponding 95% confidence interval along with p-values.

Subjects who discontinue treatment for any reason will be classified as non-responders. The frequency and percentage of responders will be summarized descriptively for all study visits.

The treatment effect for change from baseline in ACQ-7 will be estimated using a repeated measures analysis. All data up to Week 12 will be included in the model, with terms for age, treatment, visit, treatment\*visit, prior ICS use (Yes/No), baseline ACQ-7 score and baseline

post-dose percent predicted FEV<sub>1</sub>. Visit will be fitted as a categorical variable, and the variance-covariance matrix will be assumed to be unstructured. If the procedure does not converge, then a heterogeneous TOEPH will be used instead. This model will be used to give an overall assessment of the treatment effect as well as 95% confidence intervals. Data post-discontinuation of randomized treatment will not contribute to the analyses.

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

## 6.2.6 Analysis of safety variables

The safety analyses will include all data obtained before subjects discontinue randomized treatment and will use the safety analysis set. Adverse events obtained post-treatment discontinuation, occurring in the safety follow-up will be reported separately. Safety data collected during screening will be listed.

### 6.2.6.1 Adverse events

Adverse events will be summarized by treatment group, system organ class and preferred term assigned to the event by the Medical Dictionary for Regulatory Activities, using the most recent version available at the time of database lock. The following summaries will be included:

- Number of subjects with any AE in any category for both randomized treatment period and run in period.
- Adverse events in the randomized treatment period by SOC and PT, which will include the number of subjects with any AE; number of subjects with SAE; number of SAE; number of subjects with AE leading to discontinuation; AE's assessed by sponsor to be significant.
- Incidence rates will be provided by SOC and PT for all subjects with AEs and SAEs during the randomized treatment period.
- Event rates will be provided by SOC and PT for all AEs and SAEs during the randomized treatment period.<sup>2</sup>
- Adverse events in the run in period by SOC and PT, which will include the number of subjects with any AE.
- Number of subjects with AE with outcome of death by SOC and PT.
- Adverse events with outcome of death.

- The most common AEs, defined as preferred terms accounting for at least 2% of all AEs within any treatment group.<sup>1</sup>
- Non-serious adverse events accounting for at least 2% of subjects.<sup>1</sup>
- Number of subjects with AE's during the randomized treatment period, by preferred term and maximum reported intensity.<sup>1</sup>
- Number of subjects with AE's during the randomized treatment period, by preferred term and relationship to IP, as assessed by the investigator.<sup>1</sup>
- Serious adverse events during the entire study
- Adverse events leading to discontinuation of randomized treatment.<sup>1</sup>
- Number of patients with SAE during the randomized treatment period, by system organ class and preferred term.<sup>1</sup>

<sup>1</sup>AEs occurring during the randomized treatment period will include the incidence rate. The incidence rate is defined as the number of subjects who have experienced the event per 100 subject treatment years.

<sup>2</sup>Number of events and event rates for AEs and SAEs will also be presented. Event rates are defined as the total number of events across all subjects in the treatment group per 100 subject treatment years.

All adverse events, including adverse events occurring during the follow-up period will be listed for each subject.

#### 6.2.6.2 Vital signs

Absolute values and changes from baseline in vital signs variables (Section 5.10.1) will be descriptively summarized by visit and treatment group whilst also being listed by subject. Visit windows will be applied to the vital signs as per section 4.1.5.

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

#### 6.2.6.3 Clinical chemistry and hematology

Absolute values and changes from baseline in clinical chemistry and haematology parameters will be summarized by treatment group and visit and will also be listed by subject. Absolute values will be compared to the relevant reference range and classified as low (below range), normal (within range or on limits) or high (above range). All values (absolute and change) falling outside the reference ranges will be flagged. Additionally, shift tables presenting the

shift from baseline reference range indicator (Low; Normal; High) to the minimum and maximum on-treatment result will be summarized descriptively by randomized treatment group and laboratory parameter.

Baseline is defined as the most recent non-missing measurement before and including randomization (Visit 2). Visit windows will be applied to the central laboratory descriptive summaries labs as per section 4.1.5.

Subjects with cases meeting potential Hy's Law criteria (see Section 5.10.3) will be additionally listed. Scatter plots grouped by randomized treatment will show the maximum post-baseline ALT and bilirubin concentrations, as multiples of the ULN, on the x and y-axis respectively. Reference lines of ALT (multiple of ULN) = 3 and bilirubin (multiple of ULN) = 2 representing the threshold criteria for Hy's Law (Section 5.10.3) will be added to the figure.

#### **6.2.6.4 Electrocardiogram**

ECG parameters will be summarized by treatment group and visit and will also be listed by subject. Visit windows will be applied to ECG descriptive summaries as per section 4.1.5.

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

#### **6.2.6.5 Concomitant medication**

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

Listings will be grouped by prior medication, medication occurring during the randomized treatment period. Concomitant medication listings will be split into those taken in response to an adverse event, those taken in response to a severe exacerbation and an overall listing of concomitant medication.

### **6.2.7 Analysis of exploratory variables**

The exploratory analyses will include all data obtained before subjects discontinue randomized treatment and will use the FAS for patients aged  $\geq 12$  years, in accordance with the primary estimand (Section 6.1.1). As per the primary analysis, the exploratory efficacy analyses will be repeated on the FAS including all ages.

#### **6.2.7.1 Trough FEV<sub>1</sub> at individual time points**

The analyses specified in Section 6.2.4 for trough FEV<sub>1</sub> will be used to present the least squares mean estimates for each treatment and the least squares mean differences between the treatment groups at each scheduled visit, along with associated 95% confidence intervals and



p-values. Descriptive summaries of absolute values and changes from baseline trough FEV<sub>1</sub> will also be presented.

#### 6.2.7.2 FEV<sub>1</sub> AUC<sub>0-6 hours</sub> at individual time points

The analyses specified in Section 6.2.4 for FEV<sub>1</sub> AUC<sub>0-6 hours</sub> will be used to present the least squares mean estimates for each treatment and the least squares mean differences between the treatment groups at each scheduled visit, along with associated 95% confidence intervals and p-values. Descriptive summaries of FEV<sub>1</sub> AUC<sub>0-6 hours</sub> will also be presented.

Additionally, the mean change from baseline FEV<sub>1</sub> will be plotted at each post-baseline timepoint over the randomized treatment period. For these summaries the nominal assessment time will be used, rather than the actual times.

#### 6.2.7.3 Severe exacerbations

Severe asthma exacerbations will be summarised descriptively as the frequency and percentage of subjects with at least 1 severe exacerbation, the number of severe exacerbations prior to discontinuation of the randomized treatment and the total number of severe exacerbations per treatment-year. Number of severe exacerbations per treatment-year will be calculated as described in section 5.1. The aforementioned descriptive statistics will be summarised for all severe exacerbations and will be further broken down into: severe exacerbations requiring systemic corticosteroid use; severe exacerbations requiring hospitalization; severe exacerbations requiring emergency room visit; severe exacerbations requiring urgent care visit.

An overall summary of severe asthma exacerbations during the treatment period will be summarized descriptively, presenting the frequency and percentage of subjects who had at least one severe exacerbation during the study (Yes/No) and the number of exacerbations per subject, described both as a categorical and as a continuous endpoint.

The cumulative total days of severe exacerbations will be summarized by treatment group. The total number of days of severe exacerbations per subject will be summarized as a continuous endpoint.

The signs and symptoms of asthma worsening are collected on the eCRF severe exacerbation module. These will be summarised categorically as the frequency each symptom is observed per severe exacerbation. The denominator for percentage calculations will be the number of exacerbations.

For all the aforementioned summaries of severe exacerbations, only the events with a start date equal or prior to the date of discontinuation of randomized treatment will be included.

#### 6.2.7.4 Deterioration of asthma

Annualized deterioration of asthma will be summarized in the same way as the annualized severe asthma exacerbation rate (Section 6.2.7.3).

#### 6.2.7.5 Peak FEV<sub>1</sub>

Change from baseline to Peak FEV<sub>1</sub> at Day 1 (Visit 2) and Day 7 (Visit 3) will be analyzed using the same method as for trough FEV<sub>1</sub>. The repeated measures model will include only the Day 1 and Day 7 timepoints. Baseline will be defined as the average of the pre-dose assessments collected on Day 1.

#### 6.2.7.6 Peak expiratory flow

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

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

Only the data prior to the date of randomized treatment discontinuation will be considered for analyses of PEF.

#### 6.2.7.7 Asthma Control Questionnaire-7 exploratory variables

The 3 factor categorization of ACQ-7 (Improvement; No change; Worsening) will be analysed using a logistic regression model adjusted for the same covariates as for the binary response of ACQ-7, see Section 6.2.5.2. The analysis will only include patients in the FAS who are uncontrolled at baseline (i.e. baseline ACQ-7  $\geq 1.5$ ).

The secondary analysis of the ACQ-7 binary response variable (section 6.2.5.2) will be repeated and exclude patients who have remote Week 12 visits. This will allow an assessment of variability of the secondary endpoint due to potential COVID-19 impacts and to quantify the impact of missing question 7 data due to COVID-19 on the overall response. Data that are excluded from the analysis due to patients having a remote assessment will be considered missing at random in the analysis, as opposed to being imputed as a non-responder.

#### 6.2.7.8 Asthma Control Questionnaire-5 variables

The responder variable for ACQ-5 at Week 12 will be analyzed using a logistic regression model in the same way as ACQ-7 (Section 6.2.5.2).

The treatment effect for change from baseline in ACQ-5 will be estimated using a repeated measures analysis in the same way as ACQ-7 (Section 6.2.5.2).

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

The responder analysis will be conducted in the same way as ACQ-7 (Section 6.2.5.2).

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

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

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

Only data collected prior to discontinuation of randomized treatment will contribute to AQLQ+12 and PAQLQ analyses described above.

#### **6.2.7.10 Ventolin therapy**

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

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

#### **6.2.7.11 Other eDiary variables**

Asthma daytime/ night-time symptoms and night-time awakenings due to asthma, asthma control days, asthma symptom score (total, daytime and night-time) and symptom free days will be compared with the mean value of available data during the run-in portion of the study. The data will be analyzed using analysis of covariance with treatment, ACQ-7 at randomization ( $\leq 1.5 / > 1.5$ ), and pre-study background therapy (ICS, Non-ICS) as factors, and age and baseline as continuous covariates. The summary measure for the comparison of

treatments will be the estimated mean difference, presented with the corresponding 95% confidence interval.

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

Change from baseline will also be summarized for each subject by treatment group using descriptive statistics.

Overall eDiary compliance will be summarized descriptively by treatment group and a continuous endpoint. Additionally the subjects achieving <80% and ≥80% overall compliance will be summarised descriptively by treatment group.

Only eDiary data collected prior to discontinuation of randomized treatment will contribute to the above analyses.

## 6.2.8 Subgroup analysis

### 6.2.8.1 Efficacy subgroup analysis

The assessment of treatment effect will also be investigated for all primary and secondary endpoints in the stratification variables and other clinically important subgroups described in Table 8.

**Table 8 Subgroup Analysis**

<i><b>Group</b></i>	<i><b>Subgroup</b></i>
Sex	Male
	Female
Age group (years)	Children: ≥ 4 - < 12
	Adolescents: ≥ 12 - < 18
	Adults: ≥ 18 - < 65
	Elderly: ≥ 65
Pre-study background therapy	ICS
	Non-ICS
Baseline ACQ-7	≤ 1.5
	> 1.5
Smoking	Never
	Former
Region	USA
	Non-USA

For all subgroup analyses, if there are less than 30 subjects/events available within a subgroup and at least 5 subjects with data available per treatment group under comparison, or the model does not converge, then only descriptive (summary) statistics will be presented. Repeated measures analysis models will be tested under a compound symmetric covariance structure before resorting to descriptive-only summaries.

For repeated measures analysis; trough FEV<sub>1</sub>, FEV<sub>1</sub>AUC<sub>0-6 hours</sub> and ACQ-7 a similar model to the overall population will be carried out but adding factors for treatment-by-subgroup, subgroup-by-visit, and treatment-by-visit-by-subgroup. The 3-way interaction will be used to estimate the least squares mean of the treatment effect and its corresponding 95% CI by visit.

For time to onset (15% increase in FEV<sub>1</sub>) on Day 1 and duration of response, the summaries and analyses will be stratified by subgroup.

The dual-primary endpoint analyses of trough FEV<sub>1</sub> and FEV<sub>1</sub> AUC<sub>0-6 hours</sub> will be additionally repeated under the crossed subgroups of ACQ-7 at baseline and pre-study background therapy. Interim analysis

No interim efficacy analyses will be conducted in this study. Aside from the IDMC and unblinded statistician/programmer supporting activities related to safety monitoring as per the IDMC charter, the study is to be maintained blinded until all subjects have completed the treatment period and until after the database has been locked.

#### 6.2.8.2 Safety subgroup analysis

The following subgroup variables will be considered for safety analyses:

Group	Subgroup
Sex	Male
	Female
Age group (years)	Children: $\geq 4$ - $< 12$
	Adolescents: $\geq 12$ - $< 18$
	Adults: $\geq 18$ - $< 65$
	Elderly: $\geq 65$
Region	USA
	Non-USA

The following safety analyses will be repeated within the aforementioned subgroups:

- Number of patients (and incidence rate) with AEs during the randomized treatment period, by system organ class and preferred term.

- Number of patients (and incidence rate) with SAEs during the randomized treatment period, by system organ class and preferred term.

## 6.2.9 Supportive analysis

### 6.2.9.1 Tipping point analysis

Tipping point analysis under the missing not at random assumption (MNAR) will be conducted using multiple imputation. For subjects in the BDA MDI groups, and subjects in AS MDI and BD MDI when comparing to placebo MDI, this method will impute missing values post-study discontinuation for lack of asthma control assuming they were more likely to have a worse outcome than as implied under the missing at random assumption (MAR). The tipping point analysis will incrementally penalize the missing data under the missing not at random assumption until a non-statistically significant comparison is observed in the sequential testing strategy (Section 6.2.4).

#### The MNAR imputation step

The SAS procedure PROC MI will be used to impute missing data. The MNAR assumption will be applied by assigning a penalty (symbolically represented as  $\delta$ ) to the imputed values of the dual-primary endpoints of change from baseline in trough FEV<sub>1</sub> and FEV<sub>1</sub> AUC<sub>0-6 hours</sub>. A larger penalty applied ( $\delta > 0$ ) will correspond to smaller imputed values. A penalty of zero ( $\delta = 0$ ) corresponds to imputing results under a MAR assumption.

In the MNAR imputation step, only the post-study treatment discontinuation will be imputed under a MNAR assumption if the reason for discontinuation is due to a lack of asthma control. Missing data occurring prior to treatment discontinuation, and missing data post-treatment discontinuation which cannot be attributable to a lack of asthma control will be imputed under a MAR assumption. Please refer to section 6.1.2 for reasons for discontinuation due to lack of efficacy.

Whilst the above list can directly link a randomized treatment discontinuation event as being due to a lack of efficacy, the list is not exhaustive. As a result, a sponsor review will be conducted on a case-by-case basis to identify any additional discontinuation events which can be attributed to a lack of asthma control. The final review of randomized treatment discontinuation reasons will be conducted prior to database lock and unblinding of the study.

Missing data that are attributable to a lack of asthma control in the following treatment groups will be imputed under the MNAR assumption:

- BDA MDI 160/180 ug QID (higher dose)
- BDA MDI 80/180 ug QID (lower dose)
- BD MDI 160 ug QID
- AS MDI 180 ug QID

Each treatment group will be imputed separately and will include the conditional variables as per the primary analysis: baseline FEV<sub>1</sub>, percentage reversibility to Ventolin, age, Pre-treatment with ICS and baseline ACQ-7 category.

The data will be imputed using the fully conditional specification model; the following piece of example code would create 50 multiple imputed datasets under the MNAR assumption:

```
proc mi data=<<input dataset>> seed=1213 nimpute=50 out=<<output dataset>>;
  * Impute each treatment group independently;
  by trtan;

  * Impute missing results at Baseline using baseline factors;
  fcs reg(y1 = bfev rev1 age ICS ACQ7BL /details);
  mnar adjust( y1 / shift=<<DELTA>>); ** Apply the penalty to imputed Baseline results;

  * Impute missing results at Week 4 using baseline factors;
  fcs reg(y2 = y1 bfev rev1 age ICS ACQ7BL /details);
  mnar adjust( y2 / shift=<<DELTA>>); ** Apply the penalty to imputed Week 4 results;

  * Impute missing results at Week 6 using baseline factors;
  fcs reg(y3 = y2 bfev rev1 age ICS ACQ7BL /details);
  mnar adjust( y3 / shift=<<DELTA>>); ** Apply the penalty to imputed Week 6 results;

  * Impute missing results at Week 8 using baseline factors;
  fcs reg(y4 = y3 bfev rev1 age ICS ACQ7BL /details);
  mnar adjust( y4 / shift=<<DELTA>>); ** Apply the penalty to imputed Week 8 results;

  * Impute missing results at Week 12 using baseline factors;
  fcs reg(y5 = y4 bfev rev1 age ICS ACQ7BL /details);
  mnar adjust( y5 / shift=<<DELTA>>); ** Apply the penalty to imputed Week 12 results;

  var y1 y2 y3 y4 y5 bfev rev1 age ICS ACQ7BL;
run;
```

Abbreviations: ACQ7BL = baseline ACQ-7 category; age = age group; bfev = baseline FEV<sub>1</sub>; delta = assigned penalty ( $\delta$ ); ICS = pre-treatment with ICS; rev1 = percentage reversibility to Ventolin.

The penalty assigned to the treatment groups listed above will be assumed equal per iteration of the tipping point analysis algorithm.

### The MAR imputation step

The MAR imputation step will create 50 multiple imputed datasets under the MAR assumption for the following treatment groups:

- Placebo MDI
- BD MDI 160 ug QID<sup>1</sup>
- AD MDI 180 ug QID<sup>1</sup>

<sup>1</sup> These will be additional to any imputed datasets produced in the MNAR imputation step.

Each treatment group will be imputed separately and will include the conditional variables from the primary analysis model. As we are imputing these data under the MAR assumption,  $\delta = 0$  is fixed.



## The analysis step

The analysis step will comprise analysing each of the imputed datasets, 1 to 50, in the sequence of the primary analysis. The following missing data assumptions which will be adopted at each stage can be seen in Table 9.

**Table 9 Missing Assumptions for Analysis**

Step in testing sequence	Treatment groups in comparison	Missing data assumption
<b>Change from baseline in FEV<sub>1</sub> AUC<sub>0-6 hours</sub> over 12 weeks</b>		
<b>1</b>	AS MDI 180 ug QID	MNAR
	Placebo QID	MAR
<b>2</b>	BDA MDI 160/180 ug QID	MNAR
	Placebo QID	MAR
<b>3</b>	BDA MDI 160/180 ug QID	MNAR
	BD MDI 160 ug QID	MAR
<b>Change from baseline in trough FEV<sub>1</sub> at week 12</b>		
<b>4</b>	BD MDI 160 ug QID	MNAR
	Placebo QID	MAR
<b>5</b>	BDA MDI 160/180 ug QID	MNAR
	Placebo QID	MAR
<b>6</b>	BDA MDI 160/180 ug QID	MNAR
	AS MDI 180 ug QID	MAR
<b>7</b>	BDA MDI 80/180 ug QID	MNAR
	Placebo QID	MAR
<b>8</b>	BDA MDI 80/180 ug QID	MNAR
	AS MDI 180 ug QID	MAR

An example of the SAS code which would be used for the analysis model for the imputed datasets can be seen from the following proc mixed code:

```
proc mixed data=<input dataset>;          *use the input dataset, including the
                                          correct combination of treatment groups and
                                          imputation methods as given in ;

  by imdata; * split analyses by imputed dataset;
  class avisit trtp ICS ACQ7BL;
  model chg= base avisit trtp avisit*trtp age ICS ACQ7BL /ddfm=kr;
  repeated avisit /subject=usubjid type=un;
  lsmeans trtp trtp*avisit/diff cl;
run;
```

Abbreviations: ACQ7BL = baseline ACQ-7 category; age = age group; avisit = visit; base = baseline; chg = change; ICS = pre-treatment with ICS; trtp =type of treatment; usubjid = unique subject id;



For each step, estimates and standard errors for the treatment differences will be output from the analysis model procedure for each of the 50 imputed datasets. The analysis results are combined to produce an aggregate p-value for each analysis step using Rubin's rules (Rubin, 1987). The SAS procedure PROC MIANALYZE will be used for this process, example code below is provided as a reference.

```
proc mianalyze data = <<treatment difference dataset>>;
  modeleffects estimate;
  stderr StdErr;
  ods output parameterestimates = <<output dataset>>;
run;
```

### Tipping point algorithm

The tipping point analysis will be conducted by iteratively performing the MAR imputation step, the MNAR imputation step and the analysis step.

The MAR imputation step will be conducted first and will impute all missing pre-treatment discontinuation data, and post-treatment discontinuation data under a MAR assumption ( $\delta = 0$ ).

Once the MAR step has been carried out, the post-treatment discontinuation data due to lack of asthma control for the treatment groups identified in Table 9 will be imputed under a MNAR assumption ( $\delta \geq 0$ ). Due to the complexity and number of comparisons between treatment groups for this study, the penalty will be assumed to be equal across the treatment groups which are imputed under the MNAR assumption.

Upon completion of the MAR and MNAR steps, the 50 multiple imputed datasets of complete data will be analysed individually and aggregated using Rubin's rule (Rubin, 1987) as outlined in the analysis step above.

The penalty in the MNAR step,  $\delta$ , will be initialised at 0 for the first iteration. If the null hypotheses are rejected for steps 1-8 of the primary analysis,  $\delta$  will be incremented by 0.1 and the algorithm will be repeated until a  $\delta$  equal to 2 times the difference between the change from baseline result of AS MDI 180 ug QID and Placebo QID is reached. The smallest penalty which fails to reject any of the null hypotheses specified in steps 1 to 8 of the primary analysis (Section 6.2.4) will denote the tipping point and the algorithm can be stopped when this occurs.

### 6.2.4.2 Attributable estimand

Analysis of the attributable estimand will be conducted in the FAS and will act as a supportive analysis to the dual-primary endpoint. Data that are missing due to treatment discontinuation will be imputed based on the 5th percentile of the reference group's distribution if the reason is reasonably attributable to tolerability or lack of efficacy (see Section 6.1.2). Imputing based

on the 5<sup>th</sup> percentile of the reference group will correspond to a smaller change from baseline imputed value for the dual-primary endpoints.

For this supportive analysis the attributable estimand will repeat steps 1-8 of the primary analysis (Section 6.2.4). Imputation of intermittent missing data will be under a MAR assumption using the multiple imputation implementation with no penalty ( $\delta = 0$ ), as per the tipping point analysis and creating 50 imputed datasets. Following this all post-treatment discontinuation data which are due to a lack of asthma control will be imputed based on the 5<sup>th</sup> percentile of the corresponding control group relevant to each analysis step 1 to 8. For this a single imputation method will be used within each of the 50 datasets. Similarly to the tipping point analysis step, the 50 imputed datasets will be analysed separately as per the primary analysis model and results will be combined using Rubin's rules (Rubin, 1987).

### 6.2.10 COVID-19 impacts

Denali is an on-going trial throughout the coronavirus disease 2019 (COVID-19) outbreak. It is important to be able to identify any potential intercurrent events due to COVID-19 and to be able to quantify their impact on the efficacy and safety profile of the study.

#### 6.2.10.1 Visits impacted due to COVID-19

Any missed visits due to COVID-19 will be summarized by the scheduled visit that was missed and treatment group and will present the number and percentage of patients in the full analysis set with a missed visit due to COVID-19. For each visit, the reason for missingness will be further split into the following categories as collected on the eCRF:

- Subject decision due to pandemic concerns
- Pandemic related logistic issues
- Other

Similarly, visits that have been delayed, or completed remotely will be summarized descriptively by treatment group.

A listing will be provided to show the patient level information for all visits that have been impacted by COVID-19.

#### 6.2.10.2 Premature discontinuation due to COVID-19

If a subject cannot continue with procedures and scheduled assessments due to COVID-19 post-randomization, they will be withdrawn from the trial and will be asked to complete the PDV. An additional field has been provided on the discontinuation of investigational product eCRF page to indicate whether or not the main reason for discontinuation is a result of COVID-19 complications.

All premature discontinuations due to COVID-19 will be summarized descriptively providing the number and percentage of patients in the full analysis set grouped by randomized treatment.

A separate listing of subjects who prematurely withdraw due to COVID-19 will be provided. The listing will detail the reason for withdrawal and relationship to COVID-19. The listing of premature withdrawals due to COVID-19 will be based on the full analysis set.

It is not expected that premature withdrawals will be related to randomized treatment. Therefore, the missing data subsequent to withdrawal will be considered as missing at random, in accordance with the efficacy estimand.

#### **6.2.10.3 Treatment interruptions due to COVID-19**

Treatment interruptions will be listed by patient and the length of each dose interruption that are due to complications imposed by COVID-19.

#### **6.2.10.4 Assessments not done due to COVID-19 Spirometry assessments**

Any subject that has not performed serial spirometry assessments at a post-randomization visit will be listed. The listing will provide the subject ID, the scheduled visit name and the corresponding reason for the missed assessment, detailing how COVID-19 impacted the missed assessment. The listing of missed spirometry data will be presented in the full analysis set.

Any missed spirometry data due to COVID-19 is not anticipated to be related to randomized treatment and as such, missed spirometry assessments will be considered missing at random, in accordance with the efficacy estimand.

#### **6.2.10.5 ACQ-7 data collected remotely due to COVID-19**

ACQ-7 data which is collected remotely will not include the question 7 result of FEV<sub>1</sub> %PN. As a result, a supportive analysis of the secondary analysis of responder status (section 6.2.5.2) will be repeated, but excluding the assessments collected remotely. This data will be assumed missing at random in the analysis.

#### **Scheduled safety assessments**

Any scheduled safety data, including clinical laboratory, pregnancy tests, ECG and vital signs that are missing due to COVID-19 will be listed for each subject. The listing will detail the safety procedure missed and its relationship to COVID-19. The listing of missed safety assessments will be presented in the safety analysis set.

#### 6.2.10.6 Adverse events and serious adverse events due to COVID-19

All subjects with a suspected or confirmed diagnosis of COVID-19 will be listed. The listing will present any AEs with either a suspected or confirmed relationship to COVID-19. The relationship between an AE and COVID-19 will be determined by the investigator and appropriately captured in the eCRF. The listings will provide an indication of whether the AE was serious or non-serious.

Listings of adverse events linked to COVID-19 will be based on the safety analysis set.

#### 6.2.10.7 Overall descriptive summary

A high-level descriptive summary will be provided and grouped by randomized treatment group and total number of subjects (across treatment groups). The following frequencies and percentages of subjects in the full analysis set will be presented:

1. Number of subjects affected by COVID-19 <sup>[a]</sup>
2. Number of patients with dose interruptions due to COVID-19
3. Number of premature withdrawals due to COVID-19
4. Number of patients with any missed visit due to COVID-19
5. Number of patients with a missing Week 12 visit due to COVID-19
6. Number of subjects with any spirometry not done due to COVID-19
7. Number of patients with Week 12 spirometry not done due to COVID-19
8. Number of patients with any ACQ-7 not done due to COVID-19
9. Number of patients with Week 12 ACQ-7 not done due to COVID-19
10. Number of patients with any ACQ-7 performed remotely due to COVID-19
11. Number of patients with Week 12 ACQ-7 performed remotely due to COVID-19
12. Number of subjects with clinical laboratory not done due to COVID-19
13. Number of subjects with pregnancy tests not done due to COVID-19
14. Number of subjects with ECG not done due to COVID-19
15. Number of subjects with vital signs not done due to COVID-19
16. Number of subjects with COVID-19 related AEs
17. Number of subjects with COVID-19 related SAEs

<sup>[a]</sup> Defined as the number of subjects who meet at least one of the listed criteria in points 2-9.

## 7. HANDLING OF DUPLICATE PATIENTS

In the event of identifying confirmed duplicate patients, the same patient may be included under more than one patient identifier code (patient ID) in the raw data. The following types of duplicate patient data will need to be accordingly handled in analyses of safety and efficacy:

Type of duplicate patient	Action
Randomized once with one or more patient IDs which were screen failed.	Use data from the randomized patient ID for analyses of safety and efficacy.
Randomized more than once, either within the same trial or concurrently across multiple PT027 trials.	<p>Exclude all data associated with randomized duplicate patients from the full analysis set.</p> <p>All patients who have been confirmed as duplicates will be included in the safety analysis set.</p>

All confirmed duplicate patients identified in the trial will be raised as protocol deviations and will be listed.

All patient data collected on confirmed duplicates will be present in the raw data and retained in the SDTM and ADaM datasets.

## 8. CHANGES OF ANALYSIS FROM PROTOCOL

The following table provides a brief summary of changes of analysis from the protocol Version 1.0 (finalised [REDACTED] [REDACTED])

### 8.1 Baseline derivation

The protocol text specifies that the baseline derivation will be based as the most recent, non-missing measurement prior to first dose of randomised study treatment, typically this should be the result recorded at Visit 2. If missing the result is taken from the screening period. However, due to patients not being sufficiently run-in at the screening visit, the results collected at this point will not be suitable values for baseline. As such for this trial, baseline will be defined as the pre-dose value collected on Visit 2 (randomisation visit).

### 8.2 Changes to the primary analyses

Analysis of the dual-primary endpoints of trough FEV<sub>1</sub> and FEV<sub>1</sub> AUC0-6 hours has been changed to be conducted where all treatment comparisons exclude children (aged 4-11 years) and then repeated with children included. The analyses excluding children will be considered primary.

The justification for this change is due to a small proportion of pediatric patients to be enrolled, and the expectation that early drop out will occur at a higher percentage in this age group than compared to the adolescent/adult population.

### 8.3 Stratification factors recorded at randomisation

The stratification factors used to assign patients to a randomized treatment group will be adjusted for in the inferential models of this study. Clarifying text has been added to the SAP to state that in any cases of miss-stratification, patients will be analysed according to their assigned stratum in IVRS/IVRS. As a sensitivity analysis, the primary endpoints will be analysed using the actual strata of patients.

### 8.4 Time to onset and duration of response FEV<sub>1</sub> endpoints

The endpoints for time to onset and duration of response (defined as a 15% increase from baseline) on Day 1 will be calculated using all spirometry efforts spirometry data, as opposed to the best effort data which is used in the other primary and secondary analyses of spirometry data. The justification for this change is to allow for a more precise approximation for the time in which the event is observed to have started.

### 8.5 Exploratory analysis of ACQ-5 and ACQ-7 Changes from baseline

ACQ-5 and ACQ-7 changes from baseline will be assessed as the following 3-level factor:

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

The endpoint will be analysed using an ordinal logistic regression. Please see section 6.2.8.7 for further details.

## 8.6 Additional subgroup analyses

Exploratory analyses stratified by age have been specified to additionally represent the elderly age population ( $\geq 65$  years).

A subgroup focusing on USA vs non-USA patients has been specified as an additional subgroup.

Subgroup analyses for adverse events have been specified (see section 6.2.8.2).

## 8.1 COVID-19 impacts

Additional analyses have been specified to quantify the impact of the Coronavirus outbreak 2019 (COVID-19) on the trial data. Please refer to section 6.2.10 for full details.

## 9. REFERENCES

1. Juniper, EF., Guyatt, GH., Willan, A. and Griffith, LE. Determining a minimal important change in a disease-specific quality of life questionnaire. J Clin Epidemiol. 1994;47(1):81-87.
2. Juniper, EF., Svensson, K., Mörk, AC. and Ståhl, E. Measurement properties and interpretation of three shortened versions of the asthma control questionnaire. Respir Med. 2005;99(5):553-558.
3. Rubin, DB. Multiple Imputation for Nonresponse in Surveys. Wiley, New York, 1987

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# DENALI Statistical Analysis Plan V3.0

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Final Audit Report

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