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

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Study Statistician [redacted]

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[redacted]

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
ACQ-5	Asthma Control Questionnaire-5
ACQ-7	Asthma Control Questionnaire-7
ACT	Asthma Control Test
AE	Adverse event
ALT	Alanine transaminase
AQLQ+12	Asthma Quality of Life Questionnaire for 12 years and older
AS MDI	Albuterol sulfate metered-dose inhaler
AST	Aspartate transaminase
BDA MDI	Budesonide/albuterol metered-dose inhaler

Abbreviation or special term	Explanation
BMI	Body mass index
C ACT	Childhood Asthma Control Test
CAR	Censoring at random
CM	Concomitant medications
DAE	Definition of adverse event leading to discontinuation of investigational product
ECG	Electrocardiogram
eCRF	Electronic case report form
eDiary	Electronic diary
EOS	End-of-study
FAS	Full analysis set
FEV_1	Forced expiratory volume in 1 second
GINA	Global Initiative for Asthma
HL	Hy's law
ICH	International Conference on Harmonization
ICS	Inhaled corticosteroid
IP	Investigational product
IPD	Important protocol deviation
LABA	Long-acting β2-agonist
LAMA	Long-acting muscarinic antagonists
LTRA	Leukotriene receptor antagonist
MDI	Metered-dose inhaler
MMRM	Mixed model repeated measures
OAE	Other significant adverse event
PAQLQ	Pediatric Asthma Quality of Life Questionnaire
PCD	Primary completion date
PDV	Premature discontinuation visit
PEF	Peak expiratory flow
PR	Pulse rate
prn	As needed
SABA	Short/rapid-acting β2-adrenoreceptor agonist
SAE	Serious adverse event
SCS	Systemic corticosteroids
SDTM	Study Data Tabulation Model
SV	Screening visit
TBL	Total bilirubin

Abbreviation or special term	Explanation
ULN	Upper limit of normal

AMENDMENT HISTORY

Date	Brief description of change
30JULY2021	Added the COVID-19 estimand. Added supportive analysis to the primary endpoint where the onset of a COVID-19 related adverse event or dose interruption are considered in the censoring rule. Added supportive statistics to describe the annualise dose of systemic corticosteroids. Added subgroup summaries of compliance with maintenance therapy. Detailed methodology for handling duplicate patients. Amended the list of AEs associated with local and systemic ICS effects which were deemed not appropriate following the physician review (section 4.5.2.5).

1. STUDY DETAILS

1.1 Study objectives

1.1.1 Primary objective

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

1.1.2 Secondary objective

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

1.1.3 Safety objective

Safety Objective:	Safety endpoints:
To evaluate the safety and tolerability of BDA MDI 80/180 µg and 160/180 µg administered prn in response to symptoms compared to AS MDI 180 µg	• *Adverse events (AE) /serious adverse events (SAE)* • *Vital signs* • *Clinical chemistry and hematology parameters* • *Electrocardiogram (ECG)*

1.1.4 Exploratory objective

Exploratory Objective:	Exploratory Endpoints:
To characterize the effect of BDA MDI 80/180 µg and 160/180 µg administered prn in response to symptoms compared to AS MDI 180 µg	• *ACQ-5 change from baseline and responder analysis at Week 12* • *Asthma Control Questionnaire-5 change from baseline and responder (3-factor) analysis at Week 12 and Week 24* • *AQLQ+12 / PAQLQ change from baseline and responder analysis at Week 12* • *Deteriorations of asthma (annualized rate and time to first deterioration)* • *Change from baseline in prebronchodilator forced expiratory volume in 1 second at Week 12 and Week 24* • *Morning and evening peak expiratory flow* • *Use of investigational product (reliever therapy)* • *Asthma daytime/night-time symptoms* • *Time to treatment discontinuation or change in maintenance therapy* • *Asthma Control Test (ACT) or Childhood Asthma Control Test (C ACT) change from baseline and responder analysis at Week 24* • *Percentage of 'as needed'- free days* • *Percentage of symptom-free days* • *Percentage of asthma control days* • *Inhaled corticosteroid exposure over the treatment period*

1.2 Study design

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

Subjects attending screening (Visit 1) will enter a 14- to 28-day screening and run-in period. The screening period may be extended to a maximum of 9 weeks for subjects who have a severe asthma exacerbation after Visit 1. Subjects may consent for the study in advance of Visit 1 and if required, request for medical records to support evidence of prior exacerbations

without triggering the 28-day screening period. Screened subjects will continue to take their regular asthma maintenance therapy throughout the study (from screening [Visit 1/1a, as applicable] through the treatment period). At Visit 1, eligible subjects will discontinue their usual prn inhaled product used for symptom relief and begin Sponsor-provided Ventolin to be used prn in response to symptoms or prior to exercise during the screening period only. Subjects will be asked to turn in their own inhaled reliever products to the investigational sites for storage until the individual subject last study visit. Eligible subjects will be randomized at Visit 2.

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

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

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

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

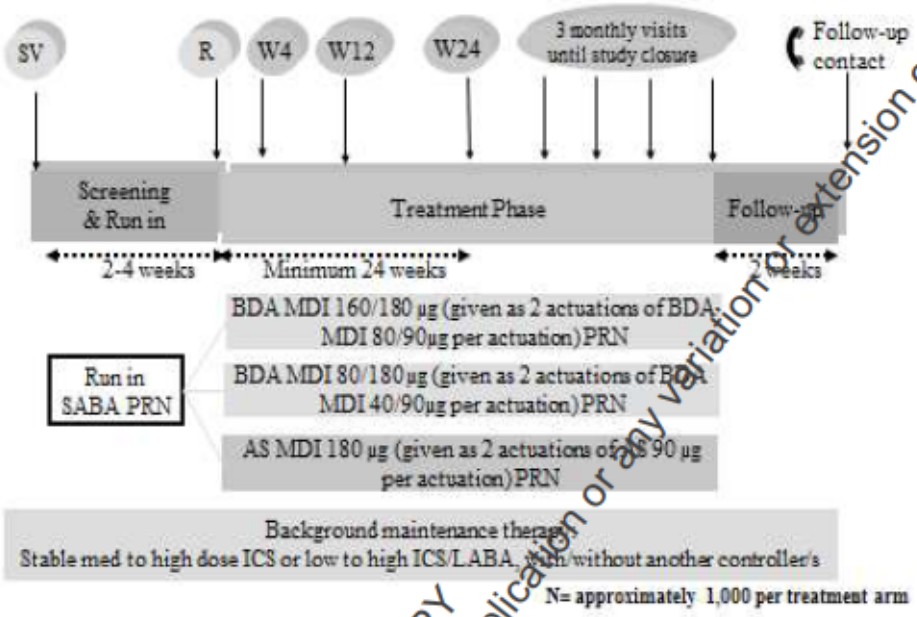
The study will consist of 3 periods:

- Screening period (14 to 28 days) except where a severe exacerbation event occurs during the screening period, and this may be extended to a maximum of 9 weeks. (Subjects may consent for the study in advance of Visit 1 and if required, request for medical records to support evidence of prior exacerbations without triggering the 28-day screening period.)

- Treatment period of at least 24 weeks. The study treatment period will continue (extension phase) until the required 570 first severe exacerbation events, as defined per protocol, have been reached and the last adult subject has completed 24 weeks of treatment, which will be defined as the primary completion date (PCD). Not all pediatric subjects will have 24 weeks of treatment at time of PCD.
  - In the event 570 events are captured **before** the last adult patient has had 24 weeks of treatment, all subjects on treatment for ≥24 weeks will have their end-of-study (EOS) visit at their next scheduled clinic visit. All subjects on treatment for < 24 weeks will continue until 24 weeks at which point they will complete their EOS visit
  - In the event 570 events will be captured **after** the last subject has had 24 weeks of treatment, each subject will return to complete the EOS visit at their next scheduled clinic visit
- Safety follow-up period: where a safety follow-up telephone contact will occur 2 weeks (±4 days) after the subject's EOS visit or premature discontinuation visit (PDV), whichever occurs first

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

Figure 1 Study design



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

Table 1 Study Assessments and Procedures

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

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

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

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

[b] Visit 1 will be split and used for repeated assessments, if needed (ie, Visit 1a will be needed for the repeat assessment of albuterol/salbutamol reversibility test and FEV$_1$, if applicable). Subjects may consent for the study in advance of Visit 1 and if required, request for medical records to support evidence of prior asthma exacerbations without triggering the 28-day screening period. Where a severe exacerbation event occurs during the screening period, this may be extended to a maximum of 9 weeks (to account for a course of systemic corticosteroids of up to 1 week duration followed by a 4-week washout period). In the event of an extension to the screening period due to a severe exacerbation event, the following will be repeated: safety laboratory assessments, ECG, vital signs, concomitant medications, and medical/surgical history.

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

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

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

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

[g] Demonstrate reversibility at Visit 1, with an increase in FEV$_1$ ≥12% (and ≥200 mL for subjects ≥18 years) relative to baseline after administration of Sponsor-provided Ventolin via central spirometry at either Visit 1 or Visit 1a (reversibility must be demonstrated at either Visit 1 or Visit 1a); Visit 1a must be used for re-testing, if needed; with only 1 reversibility re-test permitted in advance of randomization (Visit 2).

[h] A serum pregnancy test (β-hCG) will be performed at Visit 1, 6, and EOS/PDV; urine β-hCG test will be performed at all other clinic visits (for women of childbearing potential only). (In Argentina, women of childbearing potential will have additional pregnancy testing at monthly time points.)

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

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

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

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

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

1.3 Number of subjects

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

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

1.4 Primary outcome analysis

Primary outcome database lock (pDBL) will commence once all randomized adults (≥18 years) have attended their EOS visit at the PCD. The analyses of primary, secondary, exploratory and safety objectives will include all data up to the pDBL, which may include data for children and adolescents (4 to 17 years) who are still on-going in the trial and have not yet completed the 24-week treatment period.

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

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

All data collected will be available in the SDTM datasets.

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 to treatment and take any amount of IP. Subjects will be analyzed according to the treatment they were assigned 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 (see Section 2.2) and all data will be readily available in the SDTM and ADaM datasets.

All efficacy analyses will be conducted in the FAS.

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 BDA 160/180 vs AS MDI 180. Further details are provided in Section 5.

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

2.1.2 Safety analysis set

The safety analysis set is defined as all subjects receiving any amount of the IP. Subjects will be classified on the basis of treatment they actually received. If a subject receives more than 1 IP, he or she will be summarized according to the treatment the subject received the most. All safety summaries will be based on the safety analysis set. 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 (see Section 2.2) 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 Violations and deviations

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

A per-protocol analysis excluding subjects with significant protocol deviations is not planned. However, any subjects or site activity identified or suspected to be fraudulent (e.g. subjects are enrolled in this clinical study more than once or another interventional clinical study, subjects re-enrolling into the study or fabricated data) may 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 and were subsequently randomized into study 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.

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 summarized 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. Important protocol deviations will be identified by the sponsor prior to the primary database lock and unblinding of the study results. 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.

- Sex
- Ethnicity
- Race

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

- Children: ≥ 4 - < 12 years
- Adolescents: ≥ 12 - < 18 years
- Adults: ≥ 18 years

Region will be categorized into the 2-level factor used for randomization and will be collected on the electronic case report form (eCRF).

- Region 1: North America, Western Europe, and South Africa
- Region 2: Rest of world

Vital signs collected at screening will include height, weight and body mass index (BMI). Height will be further collected at additional visits for patients ≤ 18 years of age as per Table 1. BMI will be re-derived 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 calculated as [weight (kg)]*[height (m)]^2.

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. 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 date of randomization.

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

(Date of randomization (Visit 2) - Date of diagnosis of asthma +1)/365.25.

The day of most recent severe exacerbation will be calculated as

Date of randomization (Visit 2) – Date of most recent severe exacerbation prior to screening +1.

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

The number of severe exacerbations in the last 12 months (1, >1) will be collected on the eCRF.

4. PRIMARY AND SECONDARY VARIABLES

4.1 General Definitions

4.1.1 Definition of baseline

In general, the last measurement(s) prior to and including the date of randomization will serve as the baseline measurement for endpoints described below.

For eDiary variables recorded daily by the subject, baseline will be calculated as the average result over the last 10 days of the run-in period, prior to randomization. See section 4.1.6 for the derivation of daily scores from the eDiary.

Any alternative derivations will be described in the relevant section for the given endpoint.

4.1.2 Absolute change from baseline

Absolute change from baseline outcome variables is computed as

(post-randomization value – baseline value).

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

4.1.3 Reversibility

Reversibility percentage will be computed as

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

Pre- and post-bronchodilator FEV_1 measurements will be captured within the MasterScope.

4.1.4 Study day calculation

Study day will represent the number of days since randomization to study treatment of an observation and will be calculated as:

$$Pre-randomization\ study\ day = Date\ of\ assessment - Date\ of\ randomization$$

$$Post-randomization\ study\ day = Date\ of\ assessment - Date\ of\ randomization + 1$$

4.1.5 Visit windowing

The following visit windows will be applied to the scheduled study visits collected:

Visit	Target Day	Adjusted windows for analyses (days):
Baseline (Week 0)	1	1[1]
Week 4	29	22 – 36 (±1 week)
Week 8	57	50 – 64 (±1 week)
Week 12	85	71 – 99 (±2 weeks)
Week 24	169	148 – 190 (±3 weeks)

Visit	Target Day	Adjusted windows for analyses (days):
Week 36	253	232 – 274 (±3 weeks)
Week <36 + x>[2]	253 + 7x	± 3 weeks
End of Study	NA	NA – End of study will be defined as the last scheduled clinic visit prior to study termination.

[1] Baseline will be calculated as specified in section 4.1.1.

[2] Visits in the extension phase will be scheduled every 12 weeks after Week 36 until the PCD. The value x represents the number of weeks from week 36 to each visit in the extension phase (e.g. the first visit of the extension phase is Week 48; x = 12).

Scheduled assessments relating to a planned clinic visit 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 the earlier of the scheduled assessment will be used in analysis. Unscheduled visits will not be windowed to a scheduled assessment and will not be summarized descriptively in summaries grouped by visit. For the purposes of visit windowing, the PDV/EOS visit will be considered for visit windowing to scheduled assessments in the randomized treatment period and extension phase.

The eDiary variables collected daily will not be windowed to an analysis visit and analyses of these variables will be based on the mean value(s) across the treatment period (section 4.1.7).

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 ediary.

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, reliever therapy inhalation, symptom free days and asthma control days.

4.1.7 Treatment average

For ACQ-5 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 (Section 4.1.6) 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 result recorded in the evening and the result collected on the subsequent are non-missing.

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).
3. If completely missing then impute as date of treatment discontinuation.

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 randomization then impute as the randomization date;
   - 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 randomization;
    - End date of medication/ event (after partial date handling has been applied).

The treatment discontinuation/completion date will be as recorded on the discontinuation of investigational product eCRF page.

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

4.1.9 Severe asthma exacerbation definition

A severe asthma exacerbation is defined as a worsening of asthma resulting in at least one of the following criteria:

- A temporary bolus/burst of systemic corticosteroids (SCS) for at least 3 consecutive days to treat symptoms of asthma worsening; a single depo-injectable dose of corticosteroids will be considered equivalent to a 3-day bolus/burst of SCS

- An emergency room or urgent care visit (defined as evaluation and treatment for <24 hours in an emergency department or urgent care centre) due to asthma that required SCS (as per the above)

- An in-subject hospitalization (defined as admission to an in-subject facility and/or evaluation and treatment in a healthcare facility for ≥24 hours) due to asthma

All post-randomization severe asthma exacerbations identified by the investigator must be captured using the Severe Exacerbation form on the eCRF.

An adjudication committee will additionally review potential cases of severe exacerbations which have been identified. All adjudicated exacerbations and investigator identified exacerbations will be provided in the SDTM data.

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

4.1.10 Treatment exposure

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

Date of last dose of randomized study drug - Date of first dose of randomized study drug + 1.

The date of last dose of randomized study drug will be used in the above calculation regardless of a change in maintenance therapy due to a lack of asthma control.

4.2 Primary Efficacy Measure

4.2.1 Time to first severe asthma exacerbation

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

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

Under the efficacy estimand, subjects who do not experience a severe exacerbation prior to IP discontinuation or a change in maintenance therapy will be censored at the earliest occurrence of these intercurrent events.

Under the attributable estimand, subjects who are censored under the rules for the efficacy estimand will have their event times imputed. Imputation methods for the time to first severe exacerbation endpoint under the attributable estimand are detailed in Section 5.10.2.

Under the de facto estimand, all severe exacerbation events post-treatment discontinuation will be considered, regardless of any changes in maintenance therapy which might occur. Therefore, subjects not having a severe exacerbation event prior to study withdrawal will be censored at the date of study discontinuation.

Severe exacerbations will be recorded on the Severe Exacerbation eCRF page, one entry corresponds to one severe exacerbation, which includes the start time of the clinical event.

4.3 Secondary Efficacy Measures

4.3.1 Annualized severe asthma exacerbation rate

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

$$Annualized\ severe\ exacerbation\ rate = \frac{\sum Number\ of\ severe\ exacerbations\ during\ the\ follow-up}{\sum Follow-up} * 365.25$$

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

For subjects who do not discontinue IP or do not receive a change in maintenance therapy for lack of asthma control, follow-up is calculated as the duration (days) from date of

randomization, to the earliest occurrence of either IP discontinuation/completion or change in maintenance therapy:

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

The annualized severe asthma exacerbation rate will also be derived according to the de facto estimand, and consider all severe exacerbation events post-treatment discontinuation, until completion/withdrawal from the study, regardless of changes in maintenance therapy. Under the de facto estimand, the *follow-up* as described in the above calculation will be defined as the observation period from the date of randomization, up to the date of study completion, or withdrawal for each patient.

4.3.2 Derivation of total systemic corticosteroid exposure

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

Annualized total systemic corticosteroid dose = {Total systemic corticosteroid dose / (Date of treatment completion/discontinuation – Date of randomization + 1)} × 365.25

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

Total corticosteroid exposure will be calculated under the efficacy estimand and will consider steroid exposure prior to discontinuation of IP or a change in maintenance therapy. Additionally, this endpoint will be derived under the effectiveness estimand and will consider steroid exposure prior to the discontinuation of IP, regardless of changes in maintenance therapy, and the de facto estimand, which will consider steroid exposure, regardless of changes in maintenance therapy and up to withdrawal from the study.

Systemic corticosteroids to be considered for the total annualized dose of SCS will be identified with ATC code H02AB and being taken following a severe exacerbation, which is a specified field provided on the CM module.

The total dose for these steroids will be derived by multiplying the total daily dose by the duration the treatment was prescribed (in days).

Doses of SCS not collected in mg should be converted before being used in calculations.

SCS medication will be normalized to the equipotent dose of prednisone (mg) before being used in the calculation of total corticosteroid exposure. This will be facilitated through a scientific review of steroid medication reported on the CM module and the conversions will be provided to [redacted]. Additionally, the scientific review of SCS for asthma will ensure the daily dose for such medication is appropriately captured and that the units are of an acceptable format to allow conversions to equipotent doses of budesonide (i.e. ug or mg, not 'puff' or 'inhalation').

The cumulative duration of systemic corticosteroid use will be calculated as the overall number of days during the randomized treatment period for which patients were prescribed systemic corticosteroids.

4.3.3 Asthma Control Questionnaire-5 variables

All 5 symptom questions are assessed on a 7-point scale (0=good control; 6=poor control). The overall score is the mean of the 5 symptom items.

The ACQ-5 overall score will be calculated as the average of the non-missing 5 symptom questions. At least 4 out of the 5 symptom items are needed to provide an ACQ-5 overall score.

A responder status at Week 24 will be calculated as

- Responder: (Week 24 – baseline) $\leq$ -0.5
- Non-responder: (Week 24 – baseline) $>$ -0.5

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

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

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

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

There will be separate questionnaires for both adults and children. Both sets of questionnaires will be analyzed separately.

The AQLQ+12 includes 32 questions, on a 7-point scale (1-7), relating to 4 distinct domains, higher values indicate better health-related quality of life:

- Symptoms (12 questions; minimum 8 questions required for a valid score)
- Activity limitation (11 questions; minimum 7 questions required for a valid score)
- Emotional function (5 questions; minimum 3 questions required for a valid score)
- Exposure to environmental stimuli (4 questions; minimum 3 questions required for a valid score)

The PAQLQ includes 23 questions relating to 3 distinct domains, higher values indicate better health-related quality of life:

- Symptoms (10 questions; minimum 6 questions required for a valid score)
- Activity limitation (5 questions; minimum 3 required for a valid score)
- Emotional function (8 questions; minimum 5 required for a valid score)

For each of the domains, a domain score is calculated as the mean score of all its constituent questions. An overall score across the whole questionnaire is calculated as the mean score of all questions. In case of any missing answers, the overall score is calculated as a weighted mean of the domain scores, with the nominal fraction of items in each domain as weights. If one or more domains are missing, the overall score is also missing. (Note: when there are no missing answers, this method is equivalent to the average response of all 32 questions taken individually).

A responder status at Week 24 will be calculated as subjects achieving a change from baseline of at least 0.5:

- Responder: (Week 24 – baseline) ≥ 0.5
- Non-responder: (Week 24 – baseline) < 0.5

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

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

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

4.4 Exploratory Efficacy Measures

4.4.1 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; 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
- 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[1]

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 lung function assessment (upon rising in the morning) and the evening lung function assessment.

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

If the above criteria are met for >=2 consecutive days, it will be considered as one deterioration of asthma until the criteria are no longer met or become unevaluable. Deteriorations of asthma will be considered as a single deterioration if there are fewer than 3 days between the two events.

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

[1]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.

Time to deterioration of asthma

Time to first deterioration of asthma will be calculated as

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

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

Annualized rate of asthma deteriorations

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

$$Annualized\ deterioration\ event\ rate = \frac{\sum Number\ of\ deteriorations\ during\ the\ follow-up}{\sum Follow-up} * 365.25$$

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

The *follow-up* time is calculated as described in Section 4.3.1.

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

Time to treatment discontinuation or change in maintenance therapy for lack of asthma control will be calculated as the time from randomization until the earliest of treatment discontinuation (for any reason) or change in maintenance therapy for lack of asthma control (i.e. a step-up in maintenance therapy):

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

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

4.4.3 Derivation of Asthma Control Test responder variable

The ACT is a 5-question health survey used to measure asthma control in subjects aged 12 and older. Each question is measured on a 5-point scale where 1 represents poor control of symptoms and 5 represents complete control.

The total ACT score will be calculated the sum of the 5 question scores (ranging from 0 to 25). All 5 question scores must be non-missing to calculate the total ACT score.

The responders at Week 24 are defined as subjects achieving an increase from baseline in ACT total score of at least 3:

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

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

The above analyses will be repeated in the children cohort (Ages 4 to 11 years) for the C ACT.

4.4.4 Derivation of other eDiary variables

Please see Appendix 1 for eDiary variables collected in this study.

Reliever therapy use

Number of day and night inhalations of reliever therapy will be collected on the eDiary. The total daily number of inhalations will be derived as the sum of the daytime and following night-time records, both the daytime and night-time score must be non-missing to calculate the total.

The daytime, night-time, and total daily reliever use will be grouped into 4-weekly averages across the 24-week randomized treatment period. The 4-weekly time intervals are defined as 28-day long periods starting from the date of randomization. The following Table 4 illustrates how the periods will be assigned using the study day of each record.

Table 2 4-Weekly Time Intervals for e-Diary data

Period	*Start Day*	*End Day*
Period 1	Day 1 (Date of randomization)	Day 29
Period 2	Day 30	Day 57 (Day 30 + 27)
Period 3	Day 58	Day 85 (Day 58 + 27)
Period 4	Day 86	Day 113 (Day 86 + 27)
Period 5	Day 114	Day 141 (Day 114 + 27)
Period 6	Day 142	Day 169 (Day 142 + 27)

Additionally, the daily average number of inhalations over the randomized treatment period will be calculated from the date of randomization to the date of discontinuation of randomized study drug or a change in maintenance therapy.

The daily average will be split by daytime, night-time, and total. The daily averages will only be based on days where complete diary information is available; on the date of randomization, there will be no morning result recorded in the eDiary, therefore this day will not contribute to the daily average. Similarly, on the date of randomized treatment discontinuation, no evening result will be available in the eDiary and therefore will not contribute to the daily average. As a result, the denominator for the calculation of daily average number of reliever therapy inhalations will not equal the duration of exposure to randomized study drug.

The reliever therapy use is collected in the eDiary in response to symptoms and for any use that the patient may take in prophylaxis to exercise. Summaries of daily average number of inhalations will be separated into 'prior to exercise' and 'symptom relief'.

A reliever therapy free day will be defined as a 'night' and a following 'day' with 0 puffs recorded in the eDiary. The number of reliever therapy free days will be derived as the percentage of evaluable days across the randomized treatment period, prior to discontinuation of randomized study drug or a change in maintenance therapy for lack of asthma control.

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 4.1.4 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 per Table 4.

Night-time awakenings

Night-time awakenings due to asthma symptoms will be recorded in the eDiary on a daily basis. The total number of night-time awakenings will be derived as the cumulative number of night-time awakenings over the randomized treatment period. This will be categorized into the 4-weekly time intervals as per Table 4 and also as an overall treatment average across the entire randomized treatment period, from the date of randomization up to and including treatment discontinuation, or a change in maintenance therapy. The percentage of night-time awakenings over the randomized treatment period will be represented as the total number of awakenings divided by the total number of days over the randomized treatment period for each patient.

Symptom-free days

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

- A day and night with no asthma symptoms (i.e., 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 randomization until discontinuation of IP or a change in maintenance therapy as per the efficacy estimand. As with the calculation of reliever therapy endpoints, symptom-free days will be categorized into the 4-weekly time intervals as per Table 4 and also as an overall treatment average across the entire randomized treatment period.

For the asthma symptom score component, it is important to consider the daytime and night-time score separately rather than as a daily total as described in section 4.1.6. 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, this can occur in the following instances:

Number of missing datapoints	Condition	Daily status
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.

'As needed'-free days

An 'as needed'-free day is defined as a day and night with no use of reliever medication (randomized treatment).

The percentage of 'as needed'- free days will be calculated as done for symptom-free days. As with the calculation of reliever therapy endpoints, 'as needed'-free days will be categorized into the 4-weekly time intervals as per Table 4 and also as an overall treatment average across the entire randomized treatment period.

Asthma control days

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

- A day and night with no asthma symptoms (i.e., asthma symptom score=0)
- A night with no awakenings due to asthma symptoms
- A day and night with no use of reliever medication.

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

As with the calculation of reliever therapy endpoints, 'asthma control days will be categorized into the 4-weekly time intervals as per Table 4 and also as an overall treatment average across the entire randomized treatment period.

Lung function

Prebronchodilator FEV_1 will be performed on a MasterScope provided for the study by the central reader at Visit 1 (screening), Visit 2, Visit 5 and Visit 6. Assessments at Visit 5 and 6 will only be used if collected between 6:00 and 11:00 AM and no more than ±1 hour from the spirometry assessment recorded at baseline. Baseline prebronchodilator FEV1 will be the most recent measurement prior to randomization, in most cases this should be the measurement collected at Visit 2.

Peak expiratory flow

Throughout the study, subjects will record the best of 3 Peak expiratory flow (PEF) measures on rising in the morning and before going to bed in the evening prior to taking any asthma therapy. Peak expiratory flow will be captured in the eDiary.

As with the calculation of reliever therapy endpoints, Peak expiratory flow will be categorized into the 4-weekly time intervals as per Table 4 and also as an overall treatment average across the entire randomized treatment period.

Overall eDiary compliance

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

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

Where the total expected compliance is:

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

as subjects are expected to fill in the eDiary once in the morning and once in the evening, each day. Note that the eDiary completion will not be considered in the morning of study day 1 and evening of the last day of participation in the study.

Additionally, subjects will be categorized into those achieving an overall eDiary compliance of at least 80%.

4.4.5 Derivation of Asthma Control Questionnaire – 5 exploratory variables

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

- Improvement: (Week 12 – baseline) ≤ -0.5
- No Change: -0.5 < (Week 12 – baseline) < 0.5
- Worsening: (Week 12 – baseline) ≥ 0.5

4.4.6 Derivation of inhaled corticosteroid exposure

Exposure to ICS will be derived using two components; reliever therapy use and background maintenance ICS received at baseline.

Corticosteroid exposure will be calculated under the effectiveness estimand and will consider steroid exposure prior to discontinuation of IP but will include data following changes in maintenance therapy.

Reliever therapy ICS

Reliever therapy ICS will be derived from the total daily number of puffs (puffs/day) of randomized treatment, as recorded in the e-Diary. Please refer to section 4.4.4 for total daily e-diary variables. The corresponding total daily dose (µg/day) of additional ICS will be derived using the following derivation:

- [# of puffs] × 80 µg for BDA MDI 160/180
- [# of puffs] × 40 µg for BDA MDI 80/180

[# of puffs] × 0 µg for AS MDI 180

Background maintenance therapy ICS

The following ATC codes will be used to identify maintenance and additional ICS treatments in the concomitant medications (CM) module:

- R03BA
- R03AK
- R01AD
- R03AL

All maintenance ICS flagged from the CM module will also require the following field values on the CM entry:

- The route of administration = "Respiratory (Inhalation)" and
- Therapy reason = "Asthma Maintenance"

The total daily ICS dose of maintenance therapy will be categorized into low, medium and high dose ICS as defined in Appendix 2. When calculating the total daily dose of maintenance therapy for this subgroup variable, only the most recently prescribed maintenance therapy taken during the run-in period, prior to randomization, will be considered in the derivation.

The ICS dosing categorizations provided in Appendix 2 is not exhaustive. As a result a medical review of maintenance therapy ICS will be carried out prior to database lock and unblinding to correctly assign dosing categories to each ICS taken as background maintenance therapy.

4.5 Safety variables

4.5.1 Vital signs

The following vital signs measurements will be conducted:

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

4.5.2 Adverse events (including serious adverse events)

4.5.2.1 Collection of AEs and SAEs

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

The following variables will be collected for each AE:

- AE (verbatim).

- The date when the AE started and stopped
- Maximum intensity
- Seriousness
- Investigator causality rating against the IP (yes or no)
- Action taken with regards to IP
- AE required treatment
- Outcome

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

- Date AE met criteria for serious AE
- Date investigator became aware of serious AE
- Reason why the AE is considered serious
- SAE onset date/AE met criteria for SAE
- SAE resolution date
- SAE outcome
- Maximum SAE intensity
- Treatment given for the SAE
- Date of hospitalization
- Date of discharge
- Probable cause of death.
- Date of death.
- Whether autopsy is performed.
- Causality assessment in relation to study procedure(s).
- Causality assessment to other medication.
- Description of AE.

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

Adverse events where "Action taken with regard to investigational product" is answered "Drug permanently discontinued" will be defined as DAEs and reported separately (in addition to being reported as general AEs).

4.5.2.3 Other significant adverse events (OAEs)

During the evaluation of the AE data, an Avillion medically qualified expert will review the list of AEs that were not reported as SAEs and DAEs. Based on the expert's judgement, significant adverse events of particular clinical importance may, after consultation with the Global Subject Safety Physician, be considered OAEs and reported as such in the Clinical Study Report.

OAEs will be reported in a separate table (in addition to being reported as general AEs).

Adverse events related to COVID-19 (confirmed or suspected cases) will also be identified via the assigned COVID-19 related preferred terms. Please refer to section 5.7.1 for further details.

4.5.2.4 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 randomization.

Adverse events will be considered as starting during the randomized treatment period if the onset date is on or after the date of randomization 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 recorded.

4.5.2.5 Definition of AEs associated with local and systemic ICS effects

Adverse events that are associated with **local** ICS effects will be identified using the following preferred terms:

- Oral candidiasis
- Oropharyngeal candidiasis
- Oral fungal infection
- Paradoxical bronchospasm
- Dysphonia

Adverse events that are associated with **systemic** ICS effects will be identified using the following preferred terms:

- Hypercorticism
- Adrenal suppression
- Reduction in bone mineral density (including fractures)
- Glaucoma
- Cataracts

Please note that these lists of preferred terms is not exhaustive and a comprehensive list of terms associated with local/systemic ICS effects will be confirmed at database lock and before unblinding of the clinical trial.

4.5.3 Laboratory Safety Variables

The laboratory variables described in Table 3 and morning serum cortisol will be collected during the study according to the schedule provided in Table 1.

Table 3 Laboratory Safety Variables

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

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

Hy's Law

Cases where a subject shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥ 3× upper limit of normal (ULN) combined with total bilirubin ≥ 2×ULN may need to be reported as SAEs.

To identify cases of potential Hy's law (HL) it is important to perform a comprehensive review of laboratory data for any subject who meets any of the following identification criteria in isolation or in combination:

ALT ≥3× Upper limit of the normal reference range

AST ≥3× Upper limit of the normal reference range

TBL ≥2× Upper limit of the normal reference range

Potential HL cases can occur at any time during the study. All timepoints, including unscheduled assessments, will be considered for meeting the criteria.

Laboratory results which are collected in the form of '< *x*' (i.e. below the lower limit of quantification) or '> *x*' (i.e. above the upper limit of quantification) will be imputed as *x* to be used in the descriptive summaries. However the original value recorded from the central laboratory will be retained to be presented in listings.

4.5.3.1 12-Lead ECG

A 12-lead ECG will be performed at the visits detailed in Table 1. The timing and number of ECGs may be adjusted in response to the emerging safety profile.

Twelve-lead ECGs will be obtained using a centralized laboratory. If an abnormal ECG finding at screening/baseline is considered to be clinically significant by the investigator, it should be reported as an AE. For all ECGs, details of rhythm, pulse rate (PR), RR, QRS, and QT intervals, an overall evaluation will be recorded.

4.6 Other variables

4.6.1 Concomitant medications

All prior and concomitant medication recorded during the study will be entered onto the CM module.

A medication which has started on the day of, or after randomization will be considered to be concomitant. Additionally, all medication starting prior to randomization and continuing after the first dose of randomized treatment will also be considered concomitant. All medication recorded which ends prior to the first dose of randomized treatment will be classified as a prior medication. Medication which occurs post-randomized treatment discontinuation will be defined as concomitant medication occurring during the follow-up period.

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.

4.6.2 Discontinuation of investigational product

Subjects may be withdrawn from the study at any time at their own request, upon request of the investigator, or by the Sponsor at any time or for any reason. The subject or his/her

parent/legal representative is free to discontinue treatment at any time, without prejudice to further treatment.

The date of IP discontinuation, along with the main reason for discontinuation of investigational product will be collected in the Discontinuation of Investigational Product CRF page. IP can be discontinued for the following reasons:

- Subject Decision
- Adverse event
- Severe non-compliance to protocol
- Condition under investigation worsened
- Lack of Therapeutic Response
- Development of study specific discontinuation criteria
    - ≥3 severe exacerbations within a 3-month period
    - ≥5 total severe exacerbation events
    - A single severe exacerbation event longer than 20 days in duration
    - Pregnancy
- Subject lost to follow-up
- Completed
- Other

4.6.3 Discontinuation/withdrawal from the study

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

Reasons for withdrawal will be recorded on the Disposition CRF (study completion) with the following reasons for discontinuation:

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

4.6.4 Compliance of study maintenance medication

Monitoring of compliance for maintenance medication will be done only through the eDiary question 'have you taken your regular maintenance therapy today as prescribed?' (Appendix 1). Responses will be 'Yes' or 'No', where 'Yes' is taken as compliant to dose and regimen and a 'No' equating to non-compliance (missed dose).

Overall compliance with maintenance therapy (%) will be calculated as

$$\frac{Number\ of\ days\ responded\ 'Yes'}{Total\ number\ of\ days\ in\ the\ observation\ period} \times 100\%$$

Compliance with study maintenance medication will be calculated under the efficacy and the effectiveness estimand. Therefore, the observation period given in the above equation will be equivalent to the time from randomization, to the earliest of IP discontinuation or a change in maintenance therapy under the efficacy estimand, and prior to IP discontinuation regardless of a change in maintenance therapy under the effectiveness estimand.

Per the above derivation, if there are missing compliance data in the eDiary for days during the observation period, this translates to a non-compliant (missed dose). If a patient has completely missing e-diary information during the given observation period, their estimated compliance will be 0%.

Additionally, subjects will be categorized into those achieving an overall compliance of at least 70%.

4.6.5 Derivation of GINA criteria subgroup variables

Patients will be categorized into the following background therapy subgroups, representative of GINA (2020) steps 3-5, with focus on ICS exposure categorization, according to prescribed maintenance therapy recorded at baseline:

- GINA Step 3: Low dose ICS-LABA (± LTRA, LAMA, or theophylline) or Medium dose ICS (± LTRA, LAMA, or theophylline)
- GINA Step 4: Medium dose ICS-LABA (± LTRA, LAMA, or theophylline) or High dose ICS (± LTRA, LAMA, or theophylline)
- GINA Step 5: High dose ICS-LABA (± LTRA, LAMA, or theophylline)

In order to define the above subgroups, patients will be categorized into low/medium/high dose using background maintenance ICS dosing categorisations (low/medium/high) according to section 4.4.6.

5. ANALYSIS METHODS

5.1 General principles

5.1.1 Estimands

Four estimands are of interest in this study.

The primary estimand of interest is the efficacy estimand, defined as the effect of the randomized treatment in all subjects assuming continuation of randomized treatment for the duration of the study, regardless of actual usage and assuming that maintenance therapy is not changed. This estimand could be considered as a while-on-treatment strategy or a hypothetical strategy as defined in the draft International Conference on Harmonization (ICH) E9 Addendum. All primary, secondary and exploratory endpoints will be analyzed under the efficacy estimand.

The second estimand of interest is the attributable estimand, defined as the effect of treatment in subjects attributable to the randomized treatment assuming that maintenance therapy is not changed. For this estimand, discontinuation of randomized treatment for tolerability or change in maintenance therapy for lack of asthma control is considered a negative outcome. This estimand is a mixture of composite and hypothetical strategies as defined in the draft ICH E9 addendum. The primary endpoint of time to first severe asthma exacerbation will be analyzed under the attributable estimand.

The third estimand of interest is the effectiveness estimand which is a combination of the hypothetical and treatment policy strategies as defined in the draft ICH E9 addendum. The

strategy is hypothetical in that the treatment effect will be estimated without collecting data post the intercurrent event of discontinuation from randomized treatment. However, the strategy is consistent with the treatment policy strategy in that the treatment effect is estimated irrespective of the occurrence of the intercurrent event of a change in the maintenance therapy. The summary of total corticosteroid exposure will be analyzed under the effectiveness estimand.

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

The fifth 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, assuming that maintenance therapy is not changed, and in the absence of COVID-19 impacts. The primary endpoint of time to first severe exacerbation 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.

5.1.2 Discontinuation of investigational product

The date of IP discontinuation and the main reason for discontinuation will be collected on the eCRF. The following reasons for discontinuation will be indicative of a lack of asthma control:

- Development of study specific discontinuation criteria *when the following criteria are specified in the verbatim field*
    - ≥3 severe exacerbations within a 3-month period
    - ≥5 total severe exacerbation events
    - A single severe exacerbation event longer than 20 days in duration
- Lack of therapeutic response
- Condition under investigation worsened
- Subject Decision *when the following criteria are specified in the verbatim field*:
    - Subject perceives the investigational product to be ineffective

- Subject perceives the logistics to be unacceptable

- Death

Whilst the above list can directly link an IP discontinuation event as being due to a lack of asthma control, 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 IP discontinuation reasons will be conducted prior to database lock and unblinding of the study.

5.1.3 Changes in maintenance therapy

All changes in maintenance therapy will be recorded on the eCRF, specifically under the concomitant medications page with the Therapy Reason = 'Asthma Maintenance' highlighted and identifiable by having start date on, or after the date of randomization.

A prescribed step-up in maintenance medication will be indicative of a change in maintenance therapy due to a lack of asthma control. Changes due to step up or or step down in maintenance treatment will be identifiable on the eCRF.

5.1.4 Type 1 error control

Only data collected up to the primary database lock (see section 1.4) will be included in primary, secondary, and exploratory efficacy analyses. There will be no efficacy analyses conducted on any data which may be collected after the primary database lock and up to the final database lock for patients aged 4 to 17 years.

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

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

Annualized severe exacerbation rate

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

Total annualized dose of systemic corticosteroid

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

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

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

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

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

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

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

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

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

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

5.1.5 Analysis methods

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

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 summaries of counts and percentages.

5.2 Subject Disposition

Subject disposition will be summarised for all subjects. The number of subjects who were enrolled (provided informed consent), 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 randomized treatment, randomized who did not receive randomized treatment (and reasons), completed, and discontinued the study (reasons). If the reason for premature discontinuation is "Development of study specific discontinuation criteria" then 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 region, country and centre. This table will be based on the Full analysis set.

5.3 Demographic and Baseline Characteristics

Age (years), sex, race, ethnic group and region will be summarised by treatment group for the full analysis set. Percentages for demographics characteristics will be based on number of subjects with evaluable data. Baseline characteristics will be summarised by treatment for the full analysis set. These include subject characteristics (weight, height, BMI), previous disease-related treatments, medical and surgical histories, asthma history variables collected on the CRF, and the eDiary variables. The summary of demographic information will be repeated on the patients aged 4 to 11 years in the full analysis set.

FEV_1 (pre and post-bronchodilator at screening)- and reversibility will be summarized at screening and baseline by treatment. If pre-bronchodilator FEV_1 was not in the required range at Visit 1, patients may attend a retest at Visit 1a, in these instances, the pre-bronchodilator result at Visit 1a will be chosen in the summary of lung function at screening. Lung function reported at baseline will be repeated for patients aged 4 to 11 years in the full analysis set.

Baseline ACQ-5, and PEF recorded at baseline will be summarized descriptively by treatment group. Asthma duration (defined by Time in years since asthma diagnosis, and Time in years since asthma symptoms started) and the number of severe exacerbations in the previous 12 months will be summarized by randomized treatment group, for all subjects in the full analysis set.

Medical and surgical histories will be summarized by MedDRA preferred term within MedDRA system organ class.

Smoking status will be summarized categorically as the number of subjects who have never smoked 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 summarized as a continuous endpoint by randomized treatment group.

Additionally, asthma history variables collected on the eCRF will be summarized categorically, and time since diagnosis of asthma and time since severe exacerbation will be summarized as a continuous scale and present the median, minimum and maximum result by treatment group.

5.4 Treatment Exposure

Exposure to study medication will be summarized descriptively for the safety analysis set as the total duration (days) from the first dose to the last dose (inclusive) of randomized study drug.

Summary of exposure will also be displayed as the total daily number of puffs of IP. Please refer to Section 5.8.4 for further details.

5.5 Analysis of the primary variable

Only data collected up to the primary database lock (see section 1.4) will be included in primary efficacy analyses. There will be no efficacy analyses conducted on any data which may be collected after the primary database lock and up to the final database lock for patients aged 4 to 17 years.

The planned treatment comparisons for the primary analysis of time to first severe asthma exacerbation are:

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

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

Formally, the null and alternative hypotheses for comparisons are:

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

H_A: *Hazard ratio* (BDA MDI versus AS MDI) ≠ 1.

The primary variable, time to first severe asthma exacerbation, will be analyzed using a Cox proportional hazards regression model to compare treatment arms. The model will be adjusted for the randomization stratification factors (age group [≥ 4 to 11, ≥12 to 17, ≥18]); region (North America, Western Europe and South Africa [Region 1] and rest of world [Region 2]); and number of prior severe exacerbations (1, >1) in the 12 months prior to randomization. The summary measure to compare treatments is the estimated hazard ratio which will be presented with the corresponding 95% confidence interval and p-value.

Primarily, time to first severe exacerbation will be conducted under the efficacy estimand and will consider severe exacerbation events occurring prior to the discontinuation of IP or a change in maintenance therapy. 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. A sensitivity analysis will be conducted based on patients' actual strata to assess the impact of miss-stratification on the model results. The primary analysis of time to first severe exacerbation will consider events identified via an independent adjudication committee. A sensitivity analysis will be performed which excludes the adjudicated events from the endpoint derivation.

A supportive analysis will be performed in which patients will be censored at the earliest occurrence of: randomized treatment discontinuation, changes in maintenance therapy, the onset of a COVID-19 related treatment emergent adverse event or a treatment interruption due to COVID-19.

Additional supportive analyses under the de facto estimand, using analysis methods as per the efficacy estimand (above), but including data post-IP discontinuation or changes in maintenance therapy will be conducted.

Finally, these analyses will be repeated under the attributable estimand, in which censored results will have event times imputed under an informative censoring assumption. Further details are provided in Section 5.10.

The assumption of proportionality will be assessed. Proportional hazards will be tested firstly by examining plots of complementary log-log (event times) versus log (time) and, if these raise concerns, by fitting a time dependent covariate (adding a treatment-by-time or treatment-by-ln(time) interaction term) to assess the extent to which this represents random variation. If a lack of proportionality is evident the variation in treatment effect can be described by presenting piecewise hazard ratios. If lack of proportionality is found this may be a result of a treatment-by-covariate interactions, which will be investigated.

The number and percentage of subjects with at least one severe exacerbation post-randomization and prior to discontinuation of randomized treatment/ change in maintenance therapy due to lack of asthma control will be summarized by treatment group. Additionally,

the number of subjects who have been censored along with the reason for censoring (completed study prior to first exacerbation; discontinued treatment due to asthma; change in maintenance therapy due to poor asthma control; death; other). These descriptive summaries will be repeated under effectiveness estimand.

Reverse Kaplan-Meier plots for time to first severe exacerbation will be included and will be presented by randomized treatment.

5.6 Analysis of the secondary efficacy variables

For all secondary analyses the same treatment comparisons as for the primary analysis will be conducted (see Section 5.5). Please see section 5.1.4 for handling of the type-I error control for the secondary analyses.

Only data collected up to the primary database lock (see section 1.4) will be included in secondary efficacy analyses. There will be no efficacy analyses conducted on any data which may be collected after the primary database lock and up to the final database lock for patients aged 4 to 17 years.

5.6.1 Severe asthma exacerbation rate

Analysis of severe asthma exacerbation rate will target the efficacy estimand in the FAS population. Annualized severe asthma exacerbation rate will be analyzed using negative binomial regression to compare treatment groups. The response variable in the model will be the number of severe asthma exacerbations. The model will adjust for (age group [≥ 4 to 11, ≥12 to 17, ≥18]); region (North America, Western Europe and South Africa [Region 1] and rest of world [Region 2]); and number of prior severe exacerbations (1, >1) in the 12 months prior to randomization. Analyses of the annualized severe asthma exacerbation rate will be repeated under the de facto estimand, and will consider all severe exacerbations up to patient withdrawal from the trial.

The logarithm of the time at risk of experiencing a severe asthma exacerbation will be used as an offset variable in the model. Time during a severe asthma exacerbation or in the 7 days after an exacerbation will not be included in the calculation. From the negative binomial model, the annual severe asthma exacerbation rates will be estimated, and the summary measure for the comparison of treatments will be the estimated rate ratio which will be presented with the corresponding 95% confidence interval and p-value. The overdispersion parameter estimate will be included in the output.

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 IP discontinuation or a chance in maintenance therapy and the total number of severe exacerbations per treatment-year. Number of severe exacerbations per treatment-year will be

calculated as described in Section 4.3.1. 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/ 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); 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 will be summarised categorically as the frequency each symptom is observed per severe exacerbation prior to IP discontinuation or a change in maintenance therapy. The denominator for percentage calculations will be the number of exacerbations.

Time-event plots for severe exacerbations will be produced from the full analysis set and will be grouped by randomized treatment.

5.6.2 Asthma Control Questionnaire 5

Overall ACQ-5 Score

The overall ACQ-5 score and individual domains, including change from baseline, will be descriptively summarised by treatment and visit, prior to IP discontinuation or a change in maintenance therapy.

Analysis of change from baseline in ACQ-5 at Week 24 will target the efficacy estimand in the FAS population. The treatment effect for change from baseline in Overall ACQ-5 will be estimated using a mixed model repeated measures (MMRM) analysis. All scheduled assessments up to and including Week 24 that are within the visit windows (section 4.1.5) will be included in the model, with terms for treatment, visit, treatment* visit, and baseline ACQ-5. The model will also be adjusted for the randomization stratification factors (age group [≥ 4 to 11, ≥12 to 17, ≥18]); region (North America, Western Europe and South Africa [Region 1] and rest of world [Region 2]); and number of prior severe exacerbations (1, >1) in the 12 months prior to randomization. The variance-covariance matrix will be assumed to be unstructured. Kenward-Roger denominator degrees of freedom will be used (Kenward and Roger 1997). If the procedure does not converge, then a compound symmetric variance-covariance matrix will be used instead. This model will be used to give an overall assessment of the treatment effect as well as 95% confidence intervals and associated p-values.

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

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

Graphical plots of change from baseline ACQ-5 over time will also be presented using model estimates.

Responder Analysis

Responder status will be descriptively summarised by treatment and visit as the number (%) of responders and non-responders.

The responder variable described in Section 4.3.3 at Week 24 will be analysed using a logistic regression model to compare treatment groups. The model will be adjusted for baseline ACQ-5 and randomization stratification factors (age group [≥ 4 to 11, ≥12 to 17, ≥18]); region (North America, Western Europe and South Africa [Region 1] and rest of world [Region 2]); and number of prior severe exacerbations (1, >1) in the 12 months prior to randomization. From the logistic regression model, treatment effects will be estimated by odds ratios and their corresponding 95% confidence intervals and p-values.

The exploratory endpoint for responder analysis at Week 12 will be analysed in a similar way.

The number and percentage of responders will be summarised descriptively for all timepoints.

5.6.3 Asthma Quality of Life Questionnaire +12 and Pediatric Asthma Quality of Life Questionnaire

The denominator for the AQLQ+12 and PAQLQ summaries will be based on the number of subjects within the respective age group for whom each questionnaire is applicable; AQLQ+12 will include subjects aged 12 years and over whilst the PAQLQ will include ages 7 to 11 years old. Children aged 4 to 6 years old will not be included in the denominator for PAQLQ endpoint summaries and this information will be listed only.

The responder analysis will be conducted in the same way as ACQ-5 (Section 5.6.2). The exploratory endpoint for responder analysis at Week 12 will also be analysed in a similar way.

The domain scores as well as the overall scores are calculated from the unweighted arithmetic means of the individual question scores. The treatment effect for change from baseline in AQLQ+12 and PAQLQ overall scores up to Week 24 will be estimated in the same way as ACQ-5, using a MMRM analysis (Section 5.6.2). The PAQLQ will be analysed separately to the AQLQ+12.

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

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

Graphical plots of change from baseline AQLQ+12 and PAQLQ over time will also be presented using model estimates.

5.6.4 Total Systemic corticosteroid exposure

The total systemic corticosteroid exposure as total annualized dose of SCS will be presented descriptively by treatment. A comparison in total annualized SCS dose between BDA MDI 80/180 vs AS MDI 180 and BDA MDI 160/180 vs AS MDI 180 will be analysed using a Wilcoxon rank sum test and associated p-values will be presented along with the descriptive summary. The secondary analysis of total systemic corticosteroid exposure with be analysed under the efficacy estimand. The additional descriptive statistics of 75th, 80th and 90th percentiles will be presented in the summary of annualized SCS dose.

To help describe the difference in total annualized dose of SCS between treatment groups, the predicted mean annualized dose of SCS will be estimated for each treatment group from a log-normal hurdle model adjusted for randomized treatment group. The log-normal hurdle model will be fit in SAS using PROC FMM with two model components: A constant distribution to describe the zero events and a log-normal distribution component to describe the patients with a non-zero annualized dose. Example code is provided below:

```
proc fmm data=adam.adexsph;
    where paramcd = 'SYSDOT1' and FASFL = 'Y';

    class trt01pn;
    model aval = trt01pn / dist=lognormal;
    model     +    / dist=constant;
    probmodel trt01pn / CL;
    output out=pred_y / allstats;
run;
```

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

Exploratory analyses will be repeated under the effectiveness and de facto estimands.

5.7 Analysis of safety variables

The safety analyses will include all data obtained up to the primary database lock (see section 1.4) before subjects discontinue randomized treatment and will use the safety analysis set.

All descriptive summaries and listings of patient exposure to randomized treatment, adverse events, vital signs, laboratory assessments and 12-Lead ECG will be produced to summarise the safety of data for patients aged 4 to 17 years that was collected following the primary database lock and up to the final database lock.

5.7.1 Adverse events

AEs 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:

- AEs in any category, which will include the number of subjects with: any AE; any AE that is related to IP; any AE with an outcome of death; any serious AE (SAE); and any AE leading to discontinuation of investigational product; any OAE.
- Number of patients with AEs during the randomized treatment period, by system organ class and preferred term.[1]
- Number of patients with most frequently occurring AEs (at least 2% subjects in any treatment group), by preferred term.
- Number of patients with AEs during the run-in period by system organ class and preferred term.
- Number of AEs and event rate during the randomized treatment period, by system organ class and preferred term.[2]
- Number of patients with AEs with an outcome of death, by system organ class and preferred term.
- Number of patients with AEs during the randomized treatment period by maximum reported intensity, system organ class and preferred term. [1]
- Number of patients with AEs during the randomized treatment period, by preferred term and relationship to IP, as assessed by the investigator. [1]
- Number of patients with AEs during the randomized treatment period by preferred term and outcome.

- Number of patients with SAE during the randomized treatment period, by system organ class and preferred term.[1]
- Number of SAEs during the randomized treatment period, by system organ class and preferred term.[2]
- Number of patients with AEs during the randomized treatment period leading to discontinuation of randomized treatment, by system organ class and preferred term.
- AEs during the randomized treatment period assessed by the sponsor to be significant, by system organ class and preferred term.
- Non-serious AEs (frequency >= 2%) by preferred term. [1]
- Number of patients with AEs during the follow-up period, by system organ class and preferred term.[3]

[1] 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.

[2] 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.

The number of patients with adverse events occurring post-randomized treatment discontinuation will be summarised separately.

For AEs leading to death, AEs leading to discontinuation of randomized treatment, and all SAEs will be listed by subject and treatment group, and will include the following key patient information: Sex; Age at study entry; AE term as reported by the investigator; AE preferred term; time from start of treatment to onset of AE (days); time from start of treatment to becoming serious (days); outcome; Action taken with randomized treatment; Causality to randomized treatment.

All AEs will also be listed for each subject and will include analysis phase (run-in; randomized treatment period; follow-up); age/sex/race; AE reported term and preferred term; start of AE relative to randomization and duration of event (days); maximum intensity; serious (Y/N); action taken with randomized treatment; causality with randomized treatment; outcome of AE.

A summary of number of patients with adverse events, by system organ class and preferred term will be produces and grouped within maintenance ICS dosing category

(low/medium/high). Please refer to section 5.8.9 for details on the derivation of total daily dose of maintenance ICS.

Additionally, the number (%) of patients with adverse events associated with local ICS (as defined in section 4.5.2.5) will be presented overall (at least 1 local ICS-related AE) and by preferred term for patients in the safety analysis set. Additionally, these AEs will be summarised within maintenance ICS dosing category (low/medium/high). A listing of ICS related AEs will be produced which will include the total daily number of puffs of randomized treatment (puffs/day) and background maintenance ICS dosing category (low/medium/high).

A similar output will be produced displaying the number (%) of patients with adverse events that are associated with systemic ICS effects (as defined in section 4.5.2.5).

Separate tabulations of patients with AEs of Pneumonia (non-COVID-19 related; COVID-19 related) will be presented by treatment group and daily maintenance ICS dose.

Separate tabulations of patients with AEs associated with COVID-19 will be presented by treatment group and daily maintenance ICS dose.

5.7.2 Vital signs

Absolute values and changes from baseline in vital signs variables (Section 4.5.1) will be descriptively summarised by visit and treatment group.

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

Height will be collected for patients ≤18 years of age at Visit 6 (Week 24) and the End of study or Premature discontinuation visit, where applicable. These additional assessments of height will be listed only.

5.7.3 Clinical chemistry and hematology

Absolute values and changes from baseline in clinical chemistry, haematology parameters and cortisol 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 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).

Subjects with cases meeting potential HL criteria (see Section 4.5.3) 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 HL (Section 4.5.3) will be added to the figure.

In all descriptive summaries by treatment group, laboratory results which are above the upper limit, or below the lower limit of quantification will be represented numerically as the corresponding limit it exceeds. The original standard result ('< x'; '> x') will be presented in the listings.

5.7.4 12-Lead ECG

The 12-Lead ECG variables described in Section 4.5.3.1 will be summarized descriptively by treatment group and visit.

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

5.7.5 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 and ATC classification (5th level) and generic term.

Summaries will be grouped by prior medication, concomitant medication occurring during the randomized treatment period and concomitant medication occurring during the follow-up period (i.e. post-randomized treatment discontinuation). Definitions are provided in Section 4.6.1. Maintenance medication will not contribute to these summaries and will be presented in a separate table.

5.8 Analysis of exploratory variables

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

Only data collected up to the primary database lock (see section 1.4) will be included in exploratory efficacy analyses. There will be no efficacy analyses conducted on any data which may be collected after the primary database lock and up to the final database lock for patients aged 4 to 17 years.

5.8.1 Deterioration of asthma

Annualized deterioration of asthma and time to first deterioration of asthma will be analysed in the same way as the time to first severe asthma exacerbation (Section 4.2.1) and annualized severe asthma exacerbation rate (Section 5.6.1).

Time-event plots for asthma deteriorations will be produced from the full analysis set and will be grouped by randomized treatment.

Reverse Kaplan-Meier plots for time to first deterioration of asthma will be included and will be presented by randomized treatment.

Plots of mean daily morning PEF, daily total reliever therapy use and daily total asthma symptom score, along with standard error bars, will be plotted over a 15 day interval either side of the onset of the patients' first deterioration of asthma event.

5.8.2 Pre-bronchodilator FEV_1

The treatment effect for change from baseline in FEV_1 (L) will be estimated using a MMRM analysis. FEV_1 data from all visits up to the earliest of Week 24 and prior to IP discontinuation or change in maintenance therapy will be included in the model, with terms for treatment, visit and treatment*visit with baseline FEV_1 included as a covariate. The model will be adjusted for the randomization stratification factors (age group [≥ 4 to 11, ≥12 to 17, ≥18]); region (North America, Western Europe and South Africa [Region 1] and rest of world [Region 2]); and number of prior severe exacerbations (1, >1) in the 12 months prior to randomization. Visit will be fitted as a categorical variable, and the variance-covariance matrix will be assumed to be unstructured. Kenward-Roger denominator degrees of freedom will be used (Kenward and Roger 1997). If the procedure does not converge then a compound symmetric variance covariance matrix will be used instead. This model will be used to give assessments of the treatment effect as well as 95% confidence intervals and associated p-values at Week 12 and Week 24.

A figure showing the change from baseline in pre-bronchodilator FEV_1 at each post-baseline visit up to Week 24 will be presented using the LS means and 95% confidence intervals from the MMRM model described above.

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

FEV_1 pre-bronchodilator will be summarised descriptively by treatment group and all scheduled visits.

5.8.3 Morning peak expiratory flow

The mean value of change from baseline in morning PEF data from randomization to IP discontinuation or a change in maintenance therapy will be analysed by analysis of covariance with treatment as a factor and, baseline morning PEF score as a continuous covariate. The model will also be adjusted for the randomization stratification factors (age group [≥ 4 to <12, ≥12 to 17, ≥18]); region (North America, Western Europe and South Africa [Region 1] and rest of world [Region 2]); and number of prior severe exacerbations (1, >1) in the 12 months prior to randomization. The summary measure for the comparison of treatments will be the estimated mean difference, presented with the corresponding 95% confidence interval and associated p-value.

Additionally, a 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.

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

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

5.8.4 Other eDiary variables

Evening PEF, asthma symptom score (daytime, night-time, total), night-time awakenings (%), symptom-free days (%), reliever therapy free days (%) and asthma control days (%) will be analysed in the same way as morning PEF.

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

5.8.4.1 Reliever therapy use

Reliever therapy use, displayed as total daily number of puffs of IP will be analysed in the same way as morning PEF.

Reliever therapy use will also be summarised descriptively to describe the additive steroid effect of BDA/MDI treatments. More detail on these data presentations are detailed in section 5.8.9.

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

Time to treatment discontinuation or change in maintenance therapy for lack of asthma control will be analysed as per the primary analysis described in Section 4.2.1.

5.8.6 Asthma Control Test

The ACT/C ACT will be summarized as per the secondary analysis of change from baseline and responder analysis in ACQ-5 in Section 5.6.2.

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

5.8.7 Asthma Control Questionnaire-5 exploratory variables

The 3 factor categorization of ACQ-5 (Improvement; No change; Worsening) will be analysed using a logistic regression model in the same manner as for the binary response of ACQ-5, see Section 4.4.5.

The changes from baseline ACQ-5, 2-factor clinically meaningful difference (response; non-response) and 3-factor categorization of ACQ-5 (Improvement; No change; Worsening) will be further analysed in all subjects who are, at most, partly controlled at baseline (i.e. baseline ACQ-5 $\geq$ 0.75).

The secondary analysis of ACQ-5 responder status (section 5.6.2) will be repeated and exclude patients where their Week 24 ACQ-5 result was collected remotely. This will be conducted to assess the impact of COVID-19 on the secondary analysis of ACQ-5.

5.8.8 Asthma Control Questionnaire-5 exploratory variables

The secondary analysis of AQLQ+12 responder status (section 5.6.3) will be repeated and exclude patients where their Week 24 AQLQ+12 result was collected remotely. This will be conducted to assess the impact of COVID-19 on the secondary analysis of AQLQ+12.

5.8.9 Total additional inhaled corticosteroid exposure

Descriptive summaries of the total daily number of puffs of IP will be presented for all patients in the full analysis set and per the effectiveness estimand will include rescue medication inhalations occurring from the date of randomization and up to treatment discontinuation, regardless of any changes in maintenance therapy. These descriptive summaries will be further broken down into the ICS maintenance dosing categories (low/medium/high, as described in section 4.4.6) across all background medication. The continuous summaries of total number of daily puffs will additionally report the 25th, 75th and 90th percentiles per treatment group, along with the standard descriptive statistics.

Tables of mean total daily ICS split by maintenance ICS subgroups will be repeated, but showing the budesonide dose (µg) contribution of the BDA MDI applied to the respective total number of puffs.

Additionally, descriptive summaries of total daily dose within background ICS dosing category (low/medium/high) will be repeated for the following individual background medication drug name categories:

- Budesonide
- Fluticasone propionate
- Beclometasone
- Fluticasone furoate
- Mometasone

Drug name categories will include all maintenance treatment of the ICS regardless of inhaler type or whether administered as a monotherapy or a combination therapy.

Summary statistics displaying high use of reliever medication (>=4, >=8 and >=12 inhalations on one day) will be produced. The summary will be further grouped by subjects meeting the above threshold on at least one occasion; on at least 7 consecutive days; and on at least 14 consecutive days.

Total daily number of puffs of IP will be further summarized by the frequency of patients meeting the following mean total daily categories over the randomized treatment period:

- ≥ 0 to < 2 puffs per day
- ≥ 2 to < 4 puffs per day
- ≥ 4 to < 6 puffs per day
- ≥ 6 to < 8 puffs per day
- ≥ 8 to < 10 puffs per day
- ≥ 10 to < 12 puffs per day

5.9 Subgroup analysis

5.9.1 Efficacy subgroup analyses

All primary and secondary endpoints, and exploratory endpoints of time to first deterioration of asthma, symptom-free days, reliever therapy free days and asthma control days over the randomized treatment period will be further analysed by subgroup variables as defined in Table 4.

Additionally, compliance with baseline maintenance therapy descriptive summaries will be repeated under the subgroup categories defined in Table 4.

Table 4 Subgroups

Group	Subgroup
Sex	Male
	Female
Age group (years)*	Children: ≥4 - <12
	Adolescents: ≥12 - <18
	Adults: ≥18 - < 65
	Elderly: ≥ 65
Severe exacerbations 12 in the last months prior to randomization	1
	>1
Smoking	Never
	Former
Region 1	North America, Western Europe and South Africa
	Rest of World
Region 2	USA
	Non-USA
Maintenance therapy at baseline (GINA 2020)	Low dose ICS-LABA (± LTRA, LAMA, or theophylline) or Medium dose ICS (± LTRA, LAMA, or theophylline)
	Medium dose ICS-LABA (± LTRA, LAMA, or theophylline) or High dose ICS (± LTRA, LAMA, or theophylline)
	High dose ICS-LABA (± LTRA, LAMA, or theophylline)
Baseline FEV_1	< 60% PN
	≥ 60% PN

* Children and adolescents (>=4 to <18 years) may have not completed the 24-week follow-up visit by primary database lock. The subgroup analysis tables programmed will include all patient data collected up to the pDBL, regardless how much exposure time a patient as accrued. To assess the potential impact low exposure time in these specific ages, analyses in these subgroups will be repeated but only include patients with:

- At least 24 Weeks on treatment (or prematurely discontinued prior to Week 24)
- At least 12 Weeks on treatment (or prematurely discontinued prior to Week 12)

For all subgroup analyses, if there are less than 20 subjects/events available, or the model does not converge, then just descriptive (summary) statistics will be presented. Repeated measures analysis models will be tested under a compound symmetric covariance structure before resorting to descriptive summaries only.

For time to first severe exacerbation, severe exacerbation rate, ACQ-5, AQLQ+12 responder analysis, time to first deterioration of asthma, symptom-free days, reliever therapy free days and asthma control days similar models to the overall population will be carried out but adding treatment-by-subgroup interaction as factor into the model. The p-value ($\alpha = 0.05$) for the Type-III effects of the treatment-by-subgroup interaction terms will be presented in the analysis tables.

For repeated measures analysis; ACQ-5 and AQLQ+12, a similar model to the overall population will be carried out but adding 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.

Forest plots for the primary endpoint of time to first severe exacerbation will be provided, presenting the overall and subgroup categories treatment effects and their associated 95% CI will be generated.

5.9.2 Safety subgroup analyses

The following subgroup variables will be considered for safety analyses:

Group	Subgroup
Sex	Male
	Female
Age group (years)	Children: ≥4 - <12
	Adolescents: ≥12 - <18
	Adults: ≥18 - < 65
	Elderly: ≥ 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.

5.10 Supportive analysis

5.10.1 Tipping point analysis

Multiple imputation tipping point analysis under an informative censoring assumption (Censored not at random; CNAR) will be conducted for the primary endpoint of time to first severe exacerbation using the full analysis set. For subjects in the BDA MDI treatment groups, this method will impute unobserved event times post early IP discontinuation/ change in maintenance therapy for lack of asthma control, assuming they were more likely to have a severe asthma exacerbation event than was implied under the censoring at random (CAR) assumption. For subjects in the AS MDI treatment group, event times will be imputed using multiple imputation but will assume non-informative CAR.

Reasons for early IP discontinuation and changes in maintenance therapy will be collected in the eCRF and are detailed in Section 5.1.2 and Section 5.1.3, respectively, along with criteria which will be used to determine whether these intercurrent events are due to a lack of asthma control or otherwise.

Appling informative censoring assumption

Consider the Cox proportional hazards model for observed events of severe exacerbations:

$$h(t \mid \mathbf{Z}_i) = h_0 e^{\boldsymbol{\beta} \mathbf{Z}_i} \quad (1)$$

for subject i and covariates as specified for the primary analysis $\mathbf{Z}_i$, h_0 is the baseline hazard function for the Cox model and $\boldsymbol{\beta}$ are the parameter estimates from the regression model.

For a subject censored at time C_i, we can impute the event time based on the hazard function

$$h(t \mid t_i > C_i, \mathbf{Z}_i) = h_0 e^{\boldsymbol{\beta} \mathbf{Z}_i + \delta_i}. \quad (2)$$

Where a penalty δ will be applied and corresponds to the increased log-hazard of a severe exacerbation. For subjects in the AS MDI, $\delta = 0$ will be applied and this will correspond to imputing under a CAR assumption. For subjects in the BDA MDI groups, $\delta > 0$ will be assigned if they have discontinued IP and/or had a change in maintenance therapy due to a lack of asthma control. Otherwise $\delta = 0$ will be applied as with the AS MDI treatment group. This will correspond to an increased hazard and consequentially a reduced time to event to what would be assumed under a CAR assumption (Jackson et al 2014).

The tipping point analysis will initialize with a $\delta = 0$ for imputing the event time for all subjects who are censored. For subjects in the BDA MDI treatment groups who discontinue the study and/or maintenance therapy due to a lack of asthma control, the penalty will be subsequently incremented with a step of 0.1 until either null hypothesis is not rejected or $\delta = 10$ is reached. An applied penalty of $\delta = 10$ would correspond to imputing event times immediately after the observed censoring date.

The multiple imputation process will be conducted using bootstrapped samples with replacement within each treatment group to create 100 bootstrap samples, one for each imputed dataset.

To impute an event time for a subject who has been censored at time C_i, the following hazard function will be used to propose A_i, a time-to-event from censoring; where C_i is the origin of follow up. The following hazard function can be used:

$$h_{A_i}(t) = \hat{h}_0(t + C_i)e^{\hat{\beta}\mathbf{z}_i + \delta_i} \quad (3)$$

Where $\hat{h}_0(t)$ and $\hat{\beta}$ are the estimated baseline hazard function and parameter estimates from the Cox regression model for a single bootstrap sample.

Bender et al (2005) propose a method to simulate event times from the hazard function given in (3) which requires the cumulative baseline hazard function. For the event time A_i, the cumulative baseline hazard function is

$$H_{A_i}(t) = \hat{H}_0(t + C_i) - \hat{H}_0(C_i) \quad (4)$$

Where $\hat{H}_0(t)$ denotes the cumulative baseline hazard function from the cox regression model of a single bootstrap sample. The following formula proposed by Bender et al (2005) can be used to propose an event time:

$$A_i = H_{A_i}^{-1}[-\log(U_i)\, e^{-\hat{\beta}\mathbf{z}_i - \delta_i}] \quad (5)$$

Where $H_{A_i}^{-1}$ denotes the inverse of the cumulative baseline hazard function for A_i and $U_i \sim Unif(0,1)$. The inverse cumulative hazard $H_{A_i}^{-1}$ can be calculated as

$$H_{A_i}^{-1}(y) = \min[t: H_{A_i}(t) \geq y] \quad (6)$$

Once we have A_i, the overall event time can be calculated as $C_i + A_i$.

If a random number U_i is generated such that $H_{A_i}(t) < -\log(U_i)\, e^{-\hat{\beta}\mathbf{z}_i - \delta_i}$; the event time to be would be greater than the last event observed in the study, and in such cases we will impute the subject as being censored at the end of the follow-up period.

Each fully imputed dataset will be individually analysed using a cox proportional hazards model as specified in the primary analysis. The estimates of the treatment effect, confidence intervals and p-values will be combined using Rubin's rules (Rubin, 1987). As the time to event data are not normally distributed, results will be combined on the log-scale and will be back-transformed for reporting in displays.

5.10.2 Attributable estimand

Analysis of the attributable estimand will be conducted for the primary endpoint time to first severe exacerbation using data obtained before subjects discontinue randomized treatment and/or before a change in maintenance therapy and will use the FAS. However, the data that is censored due to randomized treatment discontinuation and/or a change in maintenance therapy will have their event time imputed on the basis of the percentile of the AS MDI prn distribution if the reason is reasonably attributable to tolerability or lack of control. For all other subjects who do not experience a severe exacerbation during the treatment period, event times will be imputed using multiple imputation but will assume non-informative CAR.

Imputation methods specified in Section 5.10.1 will be implemented, using the 5th percentile of the AS MDI treatment group time to first severe exacerbation instead of a delta-adjustment. i.e., when imputing the BDA MDI or AS MDI treatment groups under the informative censoring assumption, we will impute the time from censoring as $A_i = H_{A_i}^{-1}[0.05e^{-\hat{\beta}z_i}]$. The multiple imputed datasets will be analysed with a Cox proportional hazards model as in the primary analysis and results will be aggregated using Rubin's rules (Rubin, 1987). As the time to event data are not normally distributed, results will be combined on the log-scale and will be back-transformed for reporting in displays.

5.10.3 Effectiveness estimand

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

Under this estimand, subjects not having any severe asthma exacerbation will be censored at the date of their latest contact prior to IP discontinuation, regardless of a change in maintenance therapy.

5.10.4 De facto estimand

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

The primary analysis of time to first severe exacerbation and secondary efficacy analyses of severe exacerbation rate will be repeated under the de facto estimand and will include all

observed data post-randomized treatment discontinuation, up until study completion/withdrawal. Additionally, all observed data will be utilized regardless of any changes in maintenance therapy which may occur post-randomization.

Please see section 4.2.1 for the calculation of time to first severe exacerbation and section 4.3.1 for the derivation of the annualized severe exacerbation rate under the de facto estimand.

5.11 COVID-19 pandemic impacts

Mandala 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.

5.11.1 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.

5.11.2 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.

5.11.3 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.

5.11.4 ACQ-5 and AQLQ+12 data collected remotely due to COVID-19

ACQ-5 and AQLQ+12 may be collected remotely due to reasons related to COVID-19. Although these questionnaires are patient reported outcomes of asthma control and quality of life, it is unknown to what extent the secondary analyses of responder status might be affected due to the change in format of the assessments. As a result, the responder analyses will be repeated, but exclude patients whose Week 24 ACQ-5/AQLQ+12 was performed remotely, please refer to section 5.8.7 and 5.8.8 for details.

5.11.5 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.

5.11.5.1 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.

A summary of COVID-19 related adverse events will be reported by preferred term and background therapy dosing categorization (low/medium/high). Please refer to section 5.7.1 for further details.

5.11.5.2 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 [a]
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 any ACQ-5 not done due to COVID-19
6. Number of patients with Week 24 ACQ-5 not done due to COVID-19
7. Number of patients with any ACQ-5 performed remotely due to COVID-19
8. Number of patients with Week 24 ACQ-5 performed remotely due to COVID-19
9. Number of patients with any AQLQ+12 not done due to COVID-19
10. Number of patients with Week 24 AQLQ+12 not done due to COVID-19
11. Number of patients with any AQLQ+12 performed remotely due to COVID-19
12. Number of patients with Week 24 AQLQ+12 performed remotely due to COVID-19
13. Number of subjects with clinical laboratory not done due to COVID-19
14. Number of subjects with pregnancy tests not done due to COVID-19
15. Number of subjects with ECG not done due to COVID-19
16. Number of subjects with vital signs not done due to COVID-19
17. Number of subjects with COVID-19 related AEs
18. Number of subjects with COVID-19 related SAEs

[a] Defined as the number of subjects who meet at least one of the listed criteria in points 2-18.

6. 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.	Exclude all data associated with randomized duplicate patients from the full analysis set. All patients who have been confirmed as duplicates will be included in the safety analysis set.

All confirmed duplicate patients identified in the trial will be recorded as a protocol deviation and will be listed accordingly.

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

7. CHANGES OF ANALYSIS FROM PROTOCOL

The following table provides a brief summary of changes of analysis from the protocol Version 1.0 (finalised 17th December 2018).

7.1 Type-I error control for secondary endpoints

In order to make claims on the key secondary endpoints for the study, a multiple testing strategy has been implemented on the secondary analyses, controlling the type-I error rate. Please see section 5.1.4 for more details.

7.2 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/IWRS. As a sensitivity analysis, the primary endpoints will be analysed using the actual strata of patients.

7.3 Total corticosteroid exposure

The total systemic corticosteroid exposure will be calculated as the total annualized dose. Additionally, systemic corticosteroid exposure will be presented as a total annualized dose of systemic steroids for asthma. Total inhaled corticosteroid exposure and total systemic corticosteroid exposure will be analysed separately due to the differing magnitudes of the doses taken in the two regimens. Please see section 4.3.2 for further details.

The systemic steroid component will be considered the key secondary endpoint and inhaled ICS will be an exploratory measure. The contribution of maintenance ICS to this endpoint will be estimated using the total daily dose recorded in the CM module.

In order to assess the difference between treatments in systemic steroid exposure, an inferential analysis will be conducted. Please refer to section 5.6.4 for further details.

Total inhaled corticosteroid exposure will be summarised descriptively as the total daily number of puffs of randomized treatment. To assess the additive effects of randomized ICS, the total daily number of puffs will be grouped by overall and by low/medium/high dose background maintenance therapy ICS categories. Please refer to 4.4.6 for the background ICS categorisation derivations and 5.8.9 for further details on descriptive summaries of ICS exposure.

7.4 Exploratory analysis of ACQ-5 Changes from baseline

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

- Improvement: (Week 12 – baseline) ≤ -0.5
- No Change: -0.5 < (Week 12 – baseline) < 0.5
- Worsening: (Week 12 – baseline) ≥ 0.5

The endpoint will be analysed using an ordinal logistic regression as per the ACQ-5 secondary endpoint of clinically meaningful difference.

7.5 eDiary variables grouped into 4-weekly time intervals

The daily eDiary variables for reliever therapy use, nighttime awakenings, symptom-free days, 'as needed'-free days, asthma control days and PEF will be grouped into 4-weekly time intervals over the 24-week treatment period (section 4.4). Additional repeated measures analyses of these endpoints have been specified as exploratory analyses (section 5.8).

7.6 Deterioration of asthma

Plots of average daily PEF, reliever therapy use, and asthma symptom score will be produces around the +/- 15 days of the onset of the first deterioration of asthma event.

7.7 Additional subgroup analyses

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

A subgroup focusing on USA vs non-USA patients has been specified as an additional subgroup to the stratification factors used in randomization (North America, Western Europe and South Africa; Rest of World).

The subgroups analyses of background ICS have been defined based on GINA criteria have been specified. See section 4.6.5 for details on this derivation.

Subgroup analyses for adverse events have been specified (see section 5.9.2).

7.8 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 5.11 for full details.

8. REFERENCES

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APPENDIX 1

LIST OF E-DIARY QUESTIONS

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

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

Question	Answers
Please record your asthma symptoms during the night (or during sleep):	Single Select: 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 sleep 3 = You were unable to sleep because of your asthma
Did your asthma cause you to wake up last night (or during sleep)?	Single Select: 0 = No 1 = Yes
How many puffs of rescue/reliever medication (study medication) did you take to relieve your asthma symptoms since filling your eDiary last evening?	Range: 0 .. 99 puff(s)
If any puffs of rescue/reliever medication (study medication) were taken before exercise, please indicate the number of puffs.	Range: 0 .. 99 puff(s)
Please record your daytime asthma symptoms:	Single Select: 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
Have you taken your regular maintenance therapy today as prescribed?	Single Select: 0 = No 1 = Yes
How many puffs of rescue/reliever medication (study medication) did you take to relieve your asthma symptoms since filling your eDiary this morning?	Range: 0 .. 99 puff(s)
If any puffs of rescue/reliever medication (study medication) were taken before exercise, please indicate the number of puffs.	Range: 0 .. 99 puff(s)
Have you received any new asthma related therapy in the last week?	Single Select: 0 = No 1 = Yes
Have you been hospitalized or seen in the emergency room/urgent care in the last week?	Single Select: 0 = No 1 = Yes

Question	Answers
On average, during the past week, how often were you woken by your asthma during the night?	Single Select: 0 = Never 1 = Hardly ever 2 = A few times 3 = Several times 4 = Many times 5 = A great many times 6 = Unable to sleep because of asthma
On average, during the past week, how bad were your asthma symptoms when you woke up in the morning?	Single Select: 0 = No symptoms 1 = Very mild symptoms 2 = Mild symptoms 3 = Moderate symptoms 4 = Quite severe symptoms 5 = Severe symptoms 6 = Very severe symptoms
In general, during the past week, how limited were you in your activities because of your asthma?	Single Select: 0 = Not limited at all 1 = Very slightly limited 2 = Slightly limited 3 = Moderately limited 4 = Very limited 5 = Extremely limited 6 = Totally limited
In general, during the past week, how much shortness of breath did you experience because of your asthma?	Single Select: 0 = None 1 = A very little 2 = A little 3 = A moderate amount 4 = Quite a lot 5 = A great deal 6 = A very great deal
In general, during the past week, how much of the time did you wheeze?	Single Select: 0 = Not at all 1 = Hardly any of the time 2 = A little of the time 3 = A moderate amount of the time 4 = A lot of the time 5 = Most of the time 6 = All the time
On average, during the past week, how many puffs/inhalations of short-acting bronchodilator (eg. Ventolin/Bricanyl) have you used each day?	Single Select: 0 = None 1 = 1 - 2 puffs/inhalations most days 2 = 3 - 4 puffs/inhalations most days 3 = 5 - 8 puffs/inhalations most days 4 = 9 - 12 puffs/inhalations most days 5 = 13 - 16 puffs/inhalations most days 6 = More than 16 puffs/inhalations most days
Based on the subject's spirometry reading, which of the following best describes this subject's FEV1 % predicted?	Single Select: 0 = >95% predicted 1 = 95 - 90% 2 = 89 - 80% 3 = 79 - 70% 4 = 69 - 60% 5 = 59 - 50% 6 = <50% predicted

APPENDIX 2

GLOBAL INITIATIVE FOR ASTHMA (GINA, 2018)

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

The below defines the minimally acceptable documentation for inclusion 4 criteria:

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

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

Low, Medium, and High Doses of Inhaled Corticosteroids

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

Budesonide (nebules)	250-500	>500-1000	>1000
Ciclesonide	80	>80-160	>160
Fluticasone furoate (DPI)	NA	NA	NA
Fluticasone propionate (DPI)	100-200	>200-400	>400
Fluticasone propionate (HFA)	100-200	>200-500	>500
Mometasone furoate	110	≥220-<440	≥440
Triamcinolone acetonide	400-800	>800-1200	>1200

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

[a] Beclometasone dipropionate CFC is included for comparison with other literature.

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

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

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

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

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