Title: Statistical Analysis Plan for AV007: A Multicentre, Randomized, Double-blind, Parallel group, Event Driven, Decentralized, Phase IIIb Study Comparing PT027 with PT007 Administered As Needed in Participants 12 Years of Age and Older with Asthma (BATURA)

Compound Name/Number: PT027

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ABBREVIATIONS

AE	Adverse Event
ADaM	Analysis dataset model
AIRQ™	Asthma Impairment and Risk Questionnaire™
AS	Albuterol Sulfate
ATC	Anatomical Therapeutic Chemical
BDA	Budesonide / albuterol
CI	Confidence interval
CM	Concomitant medications
d.p.	Decimal place
DMC	Data monitoring committee
DRC	Data review committee
eCRF	Electronic case report form
eICF	Electronic Informed Consent form
ED-5D-5L	EuroQol 5 dimensions 5 levels

EOS	End of study
ER	Emergency room
FAS	Full analysis set
GW	General ward
HCRU	Healthcare resource utilization
IA	Interim analysis
ICE	Intercurrent Event
ICH	International Council for Harmonization
ICS	Inhaled corticosteroids
ICU	Intensive care unit
IDMC	Independent data monitoring committee
IMP	Investigational medicinal product
IPD	Important protocol deviations
IVRS	Interactive voice response system
IWRS	Interactive web response system
KM	Kaplan-Meier
LABA	Long-acting β^2-agonists
LTRA	Leukotriene receptor antagonist
MDI	Metered-dose inhaler
PCD	Primary completion date
PRO	Patient reported outcome
RTSM	Randomization and Trial Supply Management system
SABA	Short-acting β^2-agonist
SAE	Severe adverse event
SAP	Statistical analysis plan
SCS	Systemic corticosteroids
SDTM	Study data tabulation model

SoA	Schedule of Activities
VAS	Visual Analog Scale

TRADEMARK INFORMATION

SAS	SAS (Statistical Analysis Software) is a registered trademark of SAS Institute Inc.

REVISION HISTORY

Version	Date	Summary of revisions

1. INTRODUCTION

The purpose of this Phase IIIb study is to evaluate the efficacy and safety of PT027 (budesonide/albuterol [BDA] 80/90 µg metered dose inhaler [MDI]), used as needed in participants aged 12 years and older with asthma previously receiving short-acting β_2-agonists (SABA) alone or SABA on a background of either low-dose inhaled corticosteroids (ICS) or a leukotriene receptor antagonist (LTRA).

With BDA MDI, albuterol provides rapid relief of asthma symptoms while budesonide simultaneously treats underlying inflammation. Use of BDA MDI will be driven by day-to-day symptom levels and will follow a participant's natural behaviour to treat symptoms with when they arise and thus treatment for inflammation will be provided when needed most. Safety and efficacy of BDA MDI will be compared with albuterol (PT007; AS MDI) because albuterol is the standard of care rescue therapy in the United States (US).

The study evaluates the efficacy of as-needed BDA MDI (administered at a dose of budesonide/albuterol 160/180 µg, administered as 2 inhalations of BDA MDI 80/90 µg) in reducing the risk of severe asthma exacerbations, as measured by time to first severe asthma exacerbation, compared with AS MDI as needed (administered at a dose of albuterol 180 µg; administered as 2 inhalations of AS MDI 90 µg) either alone or on top of participants' usual low-dose ICS or LTRA maintenance therapy in approximately 1910 participants 12 years of age and older.

The study also investigates the effect of BDA MDI on the rate of severe asthma exacerbations, total annualized systemic corticosteroid use, asthma-related healthcare resource utilization, asthma control, and health-related quality-of-life. Safety will be assessed through the collection of adverse events (AEs) and serious adverse events (SAEs).

The study is fully decentralized for all participants, with no planned in-clinic visits, i.e., all study visits will be conducted virtually. By employing a decentralized study delivery model, it is anticipated to reach a broader population of asthmatic participants who typically might not consider participating

in clinical trials due to travel or time commitments. The MDI is also be fitted with a sensor to capture the frequency and timing of actuations of the study Investigational Medicinal Product (IMP).

This statistical analysis plan (SAP) provides details of the summaries and analyses to be performed to report the findings of the study. It should be read in conjunction with the Clinical Study Protocol.

2. STUDY OBJECTIVES AND ESTIMANDS

2.1 STUDY OBJECTIVES

2.1.1 PRIMARY OBJECTIVES

Primary Objective:	Primary Endpoint:
To evaluate the efficacy of as-needed BDA MDI compared with AS MDI on the risk of severe asthma exacerbations, participants ≥12 years	• Treatment: Randomized IMP alone or Maintenance therapy + randomized IMP • Population: Adult and adolescent participants (≥12 years) with asthma previously receiving SABA alone or SABA as needed on a background of low-dose ICS or a LTRA • Endpoint: Time to first severe asthma exacerbation • Intercurrent event (ICE) handling = Two ICEs are defined: 1) a step-up in maintenance therapy and 2) discontinuation of randomized treatment. A While on Treatment strategy will be implemented such that the estimator-level first severe asthma exacerbations that occur after an ICE will not be included and the data will be censored at the time at which the ICE occurred. • Summary measure: adjusted hazard ratio

2.1.2 SECONDARY OBJECTIVES

Secondary Objective:	Secondary Endpoint:
To evaluate the efficacy of BDA MDI as needed compared with AS MDI as needed on the risk of severe asthma exacerbations, participants ≥12 years	• Treatment: Randomized IMP alone or Maintenance therapy + randomized IMP, including subsequent therapies post IMP discontinuation. • Population: Adult and adolescent participants (≥12 years) with asthma previously receiving SABA alone or SABA as needed on a background of low-dose ICS or a LTRA • Endpoint: time to first severe asthma exacerbation • IE handling: A Treatment Policy strategy will be implemented in which all observed data while participants are in the study, regardless of IEs or whether they are on randomized study treatment, will be included in the estimation procedure • Summary measure: Adjusted hazard ratio
To evaluate the efficacy of BDA MDI as needed compared with AS MDI as needed on the risk of severe asthma exacerbations, participants ≥18 years	• Population: Adult participants (≥18 years) with asthma previously receiving SABA alone or SABA as needed on a background of low-dose ICS or a LTRA • Endpoint: time to first severe asthma exacerbation • Intercurrent event (IE) handling = Two IEs are defined: 1) a step-up in maintenance therapy and 2) discontinuation of randomized treatment. A While on Treatment strategy will be

	implemented such that the estimator-level first severe asthma exacerbations that occur after an IE will not be included and the data will be censored at the time at which the IE occurred. • Summary measure: Adjusted hazard ratio
To evaluate the efficacy of BDA MDI as needed compared with AS MDI as needed on the risk of severe asthma exacerbations, participants ≥18 years	• Population: Adult participants (≥18 years) with asthma previously receiving SABA alone or SABA as needed on a background of low-dose ICS or a LTRA • Endpoint: time to first severe asthma exacerbation • IE handling: A Treatment Policy strategy will be implemented in which all observed data while participants are in the study, regardless of IEs or whether they are on randomized study treatment, will be included in the estimation procedure • Summary measure: Adjusted hazard ratio
To evaluate the efficacy of BDA MDI as needed compared with AS MDI as needed on the rate of severe asthma exacerbations, participants ≥12 years	• Population: Adult and adolescent participants (≥12 years) with asthma previously receiving SABA alone or SABA as needed on a background of low-dose ICS or a LTRA • Endpoint: annualized rate of severe asthma exacerbations • Summary measure: Adjusted rate ratio Treatment and strategy for IEs are the same as for the primary objective
To evaluate the efficacy of BDA MDI as needed compared with AS MDI as needed on the rate of severe asthma exacerbations, participants ≥18 years	• Population: Adult participants (≥18 years) with asthma previously receiving SABA alone or SABA as needed on a background of low-dose ICS or a LTRA • Endpoint: annualized rate of severe asthma exacerbations • Summary measure: Adjusted rate ratio Treatment and strategy for IEs are the same as for the primary objective
To evaluate the effect of BDA MDI as needed compared with AS MDI as needed on systemic glucocorticoid exposure associated with asthma management, participants ≥12 years	• Population: Adult and adolescent participants (≥12 years) with asthma previously receiving SABA alone or SABA as needed on a background of low-dose ICS or a LTRA • Endpoint: total amount (mg/year) per participant of systemic glucocorticoid exposure • Summary measure: Difference in unadjusted treatment means Treatment and strategy for IEs are the same as for the primary objective
	• Endpoint: total days of systemic glucocorticoid exposure • Summary measure: Difference in unadjusted treatment means Treatment, population, and strategy for IEs are the same as for the primary objective
To evaluate the effect of BDA MDI as needed compared with AS MDI as needed on systemic glucocorticoid	• Population: Adult participants (≥18 years) with asthma previously receiving SABA alone or SABA as needed on a background of low-dose ICS or a LTRA • Endpoint: total amount (mg/year) per participant of systemic glucocorticoid exposure

exposure associated with asthma management, participants ≥18 years	• Summary measure: Difference in unadjusted treatment means Treatment and strategy for IEs are the same as for the primary objective
	• Population: Adult participants (≥18 years) with asthma previously receiving SABA alone or SABA as needed on a background of low-dose ICS or a LTRA • Endpoint: total days of systemic glucocorticoid exposure • Summary measure: Difference in unadjusted treatment means Treatment and strategy for IEs are the same as for the primary objective

2.1.3 EXPLORATORY OBJECTIVES

Tertiary/Exploratory Objectives:	**Tertiary/Exploratory Endpoints:**
To investigate healthcare resource use (HCRU) and days off work or school associated with BDA MDI as needed compared to AS MDI as needed	• Number of asthma related healthcare resource utilizations per participant year (including primary care, emergency room, hospital, ambulance, nurse, and other healthcare contacts) • Proportion of participants stepping up maintenance treatment • Proportion of participants stepping down/stopping maintenance treatment • Number of rescue medication actuations per day during the study period • Absenteeism, time off work/school due to asthma per participant year
To evaluate the effect of BDA MDI 160/180 µg taken as needed compared to AS MDI 180 µg on asthma control	• Change from baseline in AIRQ score at Week 16, Week 28, Week 40, and Week 52
To evaluate the effect of BDA MDI 160/180 µg taken as needed compared to AS MDI 180 µg on quality of life	• Change from baseline in EQ-5D-5L domain score at Week 4, Week 28, and Week 52

2.1.4 SAFETY OBJECTIVES

Safety Objective:	**Safety Endpoints:**
To evaluate the safety of BDA MDI as needed compared to AS MDI as needed in participants 12 years of age and older with asthma	Frequency and type of: • Adverse Events (AEs) • Serious Adverse Events (SAEs)

2.2 STUDY ESTIMANDS

The primary estimand for analysis is the estimand adopting a While on Treatment strategy in the full analysis set (≥12 years). The following attributes describe the estimand that will be used to define the treatment effect of interest:

- Treatment Condition = Randomized IMP or maintenance therapy + randomized IMP,
- Population = Participants 12 years of age and older with asthma who are taking SABA as needed alone or with a low-dose ICS or LTRA,
- ICE handling = Two ICEs are defined:
    - A step-up in maintenance therapy
    - All-cause discontinuation of study treatment

A While on Treatment strategy will be implemented such that effects of randomized treatment will be analysed using data collected during the period that participants were on treatment, before treatment discontinuation or a step-up in maintenance therapy. For time to event endpoints, patients will be censored at the time in which the ICE occurred. Annualized severe exacerbation rates and annualized systemic steroid exposure will be calculated from the data collected between randomized treatment initiation and the earliest occurrence of the ICE. For other secondary and exploratory endpoints, data collected following the ICE will be considered missing at random and excluded from the summaries and analyses under this estimand strategy.

To assess efficacy in the adult population, a secondary estimand defined is the While on Treatment strategy in the full analysis set (≥18 years). The treatment condition and ICE handling attributes are the same as defined in the primary estimand. The population attribute is defined as participants 18 years of age and older with asthma who are taking SABA as needed alone or with a low-dose ICS or LTRA.

A secondary estimand utilising a Treatment Policy estimation strategy in the full analysis set (≥12 years). All observed data while participants are in the study, regardless of whether they are on randomized treatment or have a step-up in maintenance therapy, will be included in the estimation procedure. The Treatment Policy strategy will be evaluated in the Full analysis set. Apart from the secondary endpoint of time to first severe exacerbation, all analyses produced under the Treatment Policy strategy will be considered supplemental. A similar secondary estimand is defined in the full analysis set (≥18 years). The population attribute is defined as participants 18 years of age and older with asthma who are taking SABA as needed alone or with a low-dose ICS or LTRA.

The attributable estimand is defined as the effect of treatment in participants attributable to the randomized treatment assuming that maintenance therapy is not increased. For this estimand, discontinuation from the study for tolerability or a step-up 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.

3. STUDY DESIGN

This is a Phase IIIb, US, multicentre, double-blind, randomized, parallel-group, event-driven, variable-length, decentralized study to evaluate the efficacy and safety of BDA MDI (used at a dose of budesonide/albuterol 160/180 µg) compared with AS MDI (used at a dose of albuterol 180 µg), both taken as needed, for at least 12 weeks and up to 52 weeks. Participants 12 years of age and older with asthma will be recruited with all visits conducted virtually.

Eligible participants must be using as-needed SABA alone, or as-needed SABA on a background of either low-dose ICS or a LTRA, for the treatment of asthma. Participants must have had either ≥2 prescriptions filled for a SABA inhaler or ≥1 prescription for a SABA inhaler plus ≥1 prescription filled for a low-dose ICS inhaler or a LTRA in the 12 months prior to enrolment. Participants continue their own maintenance treatment, if receiving. In addition, participants must have used a SABA on ≥2 days, for the relief of asthma symptoms, in the previous 2 weeks prior to Visit 2 and have an Asthma Impairment and Risk Questionnaire (AIRQ)^{TM} score ≥2 at Screening.

Participants from 40 to 50 centres located in the United States (US) will be randomized 1:1 to receive one of the following two treatments, to be used as needed:

- BDA MDI 160/180 µg (given as 2 inhalations of BDA 80/90 µg per actuation) up to a maximum of 12 inhalations per day
- AS MDI 180 µg (given as 2 inhalations of AS 90 µg per actuation) up to a maximum of 12 inhalations per day

Participants are stratified by pre-study asthma medication (3-factor): SABA only, low dose ICS + SABA or LTRA + SABA, and the number of documented prior severe exacerbations (0, >=1) in the 12 months prior to the screening visit.

The study is double-blind with BDA and AS MDI being identical in appearance. Participants also receive a [redacted] sensor attachment (referred to as an MDI sensor, or sensor) compatible with the study inhalers that will be used to capture each actuation of the inhaler throughout the study.

The schedule of assessments is presented in Appendix B.

4. SAMPLE SIZE CONSIDERATIONS

To achieve 350 first severe asthma exacerbation events, it is planned that 1910 participants (955 participants per arm) will be randomized. It is expected that most participants in the proposed US asthma population will be on SABA only. Randomization will be stratified by pre-study asthma therapy (SABA only; low-dose ICS + SABA or LTRA + SABA) and number of documented prior severe exacerbations (0, ≥1) in the 12 months prior to the Screening visit) to ensure treatment balance within each stratum. The target number of events required is estimated from the sample size determinations based on the analysis of the primary endpoint time to first severe asthma exacerbation.

The treatment effect is assumed to be a hazard ratio (HR) of 0.7 which is a 30% reduction in the risk of a first severe exacerbation (BDA MDI versus AS MDI) and is supported by results from the MANDALA study where the HR = 0.73 in participants ≥12 years old receiving BDA MDI 160/180 µg compared to AS MDI 180 µg. Assuming a 1-year first severe exacerbation event rate in the AS MDI arm of 21%, 345 events are needed to achieve 90% power, with a 2-sided significance of 5%.

For the secondary endpoint of time to first severe asthma exacerbation targeting the Treatment Policy strategy, it is assumed that 10% of participants in the study will discontinue IMP or step-up maintenance therapy resulting in a null treatment effect in this group of participants, such that the estimated overall hazard ratio is increased by 0.025. Therefore assuming, a 27.5% reduction in the

risk of a first event with BDA MDI compared to AS MDI and a 1 year first event rate of 21% in the AS MDI arm, 350 first events are required to achieve 85% power, with a 2-sided significance of 5%.

The estimated total number of participants to be randomized to treatment is 1910 to achieve the overall target number of 350 first severe asthma exacerbation events. However, if during the study the observed blinded overall first event rate is higher than expected then the required number of events may be met with less participants and recruitment will be stopped prior to reaching 1910 participants randomized. Similarly, if during the study the observed blinded overall rate is lower than predicted, the number of participants randomized may be increased up to approximately 2500 to ensure the required number of first severe asthma exacerbations are achieved. Any assessment of accumulating data will be performed on pooled, blinded data. Blinded event rate monitoring will be conducted during the study to ensure that the required number of events will be observed. Refer to section 11 for further details on blinded sample size reassessment.

5. ANALYSIS POPULATIONS

5.1 ALL PARTICIPANTS ENROLLED ANALYSIS SET

The all participants enrolled population will be defined as all participants who provide informed consent through the electronic informed consent form (eICF). This population will be used for descriptive summaries of disposition.

5.2 ALL PARTICIPANTS RANDOMIZED ANALYSIS SET

The all participants randomized population are all participants that are randomized regardless of amount of IMP taken. The population will be used for descriptive summaries of site and disposition.

5.3 FULL ANALYSIS SET

The full analysis set is defined as all participants who are randomized to treatment and receive any amount (i.e., at least 1 actuation) of IMP. Participants will be analyzed according to the treatment they were assigned at randomization, regardless of the actual treatment received.

The full analysis set includes all patients (aged ≥12 years). A subpopulation of the full analysis set, which only includes participants aged ≥18 years is also defined to facilitate secondary analysis in this age group. In the programmed outputs, the population will be clearly described in the titles and presented as:

- Full analysis set; >=12 years
- Full analysis set; >=18 years

5.4 SAFETY ANALYSIS SET

The safety analysis set is defined as all participants who are randomized to treatment and receive any amount (i.e., at least 1 actuation) of IMP. Participants will be analyzed according to the actual treatment received rather than randomized. If a participant receives more than 1 IMP then they will be summarized according to the treatment they received the most.

All safety summaries will be based on the safety analysis set.

6. PROTOCOL DEVIATIONS

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

A per-protocol analysis is not planned for this study.

All participants 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 participants failing any of the inclusion/exclusion criteria and will be based on the FAS.

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 participant's rights, safety, or well-being.

A prospective list of important protocol deviations will be identified by the Sponsor prior to the interim analysis and the collected listing of protocol deviations and their assignment of minor, major and important will be finalised prior to the unblinding of the study results. Another review by the Sponsor will be conducted to assign any new protocol deviations between the interim analysis and the final database lock.

Any participants stratified incorrectly will be identified as important protocol deviations. All participants 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.

Any additional protocol deviations will be defined both prior to the unblinding of data for the interim analysis and prior to the final database lock, in the protocol deviation specification.

7. GENERAL CONSIDERATIONS FOR DATA ANALYSES

7.1 TREATMENT PERIODS

The randomized treatment period for each participant is defined from treatment initiation (Visit 3) until the earliest occurrence of study completion, study withdrawal, discontinuation of randomized treatment, a step-up in maintenance therapy, or in the case of the participant being lost to follow-up, the date of last contact. For adverse events, the randomized treatment period will be defined from treatment initiation (Visit 3) until the earliest occurrence of study completion, withdrawal, date of last contact, or discontinuation of randomized treatment. This is regardless of a step-up in maintenance therapy.

The study period for each participant is defined from treatment initiation (Visit 3) until the earliest occurrence of study completion or withdrawal. This is regardless of any ICEs. The study period encompasses any time that the participant provides visit information, including information on severe exacerbations, adverse events, concomitant medications and hospitalizations.

Any severe exacerbations, adverse events, hospitalizations or systemic corticosteroids that start after randomization and before treatment initiation will not be included in the analyses over the treatment period, or study period.

7.2 TREATMENT INITIATION

The treatment initiation visit occurs once the participant is in receipt of the study medication (6 IMP inhalers are expected to be delivered to their home 3 to 5 days following randomization). Alongside study IMP, participants will also receive 2 [redacted] sensor attachments to capture each actuation of study inhaler use throughout the study, allowing more than 1 inhaler to be fully operational concurrently. Participants with asthma often have rescue inhalers stored in different places at once.

The start date of the IMP treatment period is defined as the day of first dose of IMP treatment, whereby at Visit 3, once the participant is in possession of study medication, all participants are required to take one inhalation of treatment as part of the training on how to use the study inhaler and inhaler sensor attachment. This is recorded in the eCRF Exposure page as the date of first actuation of IMP.

The exposure start date on the eCRF corresponds to the date of first dose of IMP. The eCRF exposure date of first dose of IMP is used as the official treatment initiation date. This date will be used to assign baseline results and the start of follow-up for severe exacerbation events, systemic corticosteroid exposure, concomitant medications, and treatment emergent adverse events.

In the event that the [redacted] app records a start date of IMP treatment inconsistent with the eCRF, this will be raised as a discrepancy by PHASTAR to [redacted] data management to be queried and resolved. Under this process, the eCRF exposure information will be used to define the first dose of randomized treatment in the statistical programming activities. Inconsistencies between the date of first dose of IMP and the date of first actuation per the [redacted] app may occur due to sensor malfunctions, errors in attaching the sensor device to the inhaler, issues with synchronization of the sensor with the user application, or other user general error or misuse of the device. Reasons for inconsistency between date of first dose (eCRF) and date of first actuation ([redacted] app) will be documented via data reconciliation orchestrated by the data management vendor.

7.3 STANDARD SUMMARY STATISTICS

For continuous endpoints we will summarise by the number of evaluable participants in the analysis (n); Mean; Standard Deviation; Median; Minimum; Maximum.

Summaries of categorical endpoints will include the absolute counts (n) and percentage, with the denominator used in the percentage calculation as the number of participants in the analysis set used for the descriptive summaries of counts and percentages, unless otherwise defined in section 9.

Percentages will be displayed with one decimal place (d.p.). If the number of participants in the analysis set is zero, then this will be displayed with no percentage. Unless otherwise stated in section 9, the Mean and Median will be displayed with 1 d.p., the Standard Deviation with 2 d.p. and the Minimum and Maximum will be displayed with the same d.p. as the data that the table is summarising.

Any summary statistics required in addition to the aforementioned will be detailed within section 9, for each relevant endpoint.

7.4 STRATA AND COVARIATES

Unless specified otherwise in the relevant subsection of 9.2, model-based analyses will be adjusted for covariates of pre-study asthma therapy (SABA alone; low-dose ICS with SABA or LTRA with SABA) and number of documented severe exacerbations in the 12 months prior to screening/randomization (0, ≥1) at a minimum.

7.5 EXAMINATION OF SUBGROUPS

7.5.1 EFFICACY SUBGROUPS

All primary and secondary endpoints will be further analyzed by subgroup variables as defined below in Table 1. In addition, the summary of demographics characteristics and asthma characteristics at study entry will be repeated by these subgroup categories.

Table 1 ***Subgroups***

Group	Subgroup
Pre-study asthma therapy	SABA only
	Low dose ICS plus SABA or LTRA plus SABA
Number of documented prior severe exacerbations in the 12 months prior to screening/randomization	0
	≥1
Age group 1 (years)	≥12 - <18
	≥18 - <65
	≥65
Age group 2 (years)	<18
	≥18
Sex	Male
	Female
Race	White
	Black or African American
	Asian
	American Indian or Alaska Native
	Other[a]
Ethnicity	Hispanic or Latino

	Not Hispanic or Latino
Baseline AIRQ	Not well controlled (2≤AIRQ<5)
	Poorly controlled (5≤AIRQ≤10)

[a] The race category of Other will include participants who identified as >1 racial group per the eCRF categorisations. Patients who did not report a race will be excluded from subgroup analyses of race.

For all subgroup analyses, if there are less than 20 participants/events available, or the model does not converge, then only descriptive (summary) statistics will be presented.

For time to first severe exacerbation and severe exacerbation rate, similar models to the overall population will be carried out but adding treatment-by-subgroup interaction as factor into the model. The two-sided p-value for the Type-III effects of the treatment-by-subgroup interaction terms will be presented in the analysis tables. No formal adjustment to the significance level for testing of subgroups will be made, all subgroup analyses will be considered exploratory.

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. This will be repeated for the secondary endpoint analysis of time to first severe exacerbation under the Treatment Policy strategy.

7.5.2 SAFETY SUBGROUPS

Sex and age group will also be considered for the following safety analyses:

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

8. DATA HANDLING CONVENTIONS

8.1 STUDY ENDPOINTS

8.1.1 PRIMARY ENDPOINT

The primary endpoint is time to first severe asthma exacerbation and is defined as the length in days from treatment initiation (Visit 3) until the date of the first severe asthma exacerbation, up to the end of the study. The start date of the severe asthma exacerbation is the first day of systemic corticosteroid use, or date of hospitalization for a severe exacerbation. Severe exacerbation start and stop dates will be identified and collected on the eCRF by the Investigator.

An asthma exacerbation is defined as a deterioration of asthma which includes the worsening of asthma signs/symptoms and/or increased use of as needed reliever medication. The signs and symptoms associated with a worsening of asthma are outlined in more detail in section 8.2.1.1 of the CSP. Asthma symptoms present at the onset of a severe exacerbation will be documented by the Investigator on the eCRF.

An asthma exacerbation is considered severe if it results 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 an admission to an in-subject facility and/or evaluation and treatment in a healthcare facility for ≥24 hours) due to asthma
- Results in death

All post-randomization severe asthma exacerbations must be captured using the Asthma Exacerbation form in the electronic case report form. One entry corresponds to one severe exacerbation, which includes the start date and end date of the clinical event (last date of systemic corticosteroid use).

The duration of a severe exacerbation will be defined as the number of days from the date of prescribed treatment including systemic corticosteroids until the last day of prescribed treatment with a systemic corticosteroid.

Time to first severe asthma exacerbation will be calculated as the time (days) from the start of treatment initiation (Visit 3) until the start date of the first severe asthma exacerbation:

[Start date of first severe asthma exacerbation] – [Date of treatment initiation (Visit 3)] +1

The primary endpoint will be derived in accordance with the While on Treatment strategy. Participants will be censored if they experience an ICE prior to their first severe exacerbation event (see section 2.2 for details on ICEs). Participants that do not experience a severe asthma exacerbation event or an ICE will be censored at the date of withdrawal from the study or, in the case of lost to follow-up, the date of last contact.

If a participant has a severe asthma exacerbation after randomization and prior to receipt of IMP then the treatment initiation visit (Visit 3) will be delayed until the severe exacerbation is ended. The patient will be followed up and their first severe exacerbation event emerging post-Visit 3 will be used for analysis.

The time at risk up to the first severe exacerbation will be calculated as the time to first severe exacerbation (in days, as defined above), divided by 365.25 and multiplied by 100, to provide the time at risk per 100 patients years, per patient.

8.1.2 SECONDARY ENDPOINTS

8.1.2.1 TIME TO FIRST SEVERE EXACERBATION

The time to first severe asthma exacerbation will also be derived in accordance with the Treatment Policy strategy (see section 2.2), in which all data collected during the study period, following treatment initiation (Visit 3), will be included in the analyses, regardless of whether they have

prematurely discontinued randomized study treatment or had a step-up in maintenance therapy. A severe asthma exacerbation is defined as in the primary endpoint (section 8.1.1).

8.1.2.2 ANNUALIZED RATE OF SEVERE ASTHMA EXACERBATIONS

For the secondary analysis of annualized rate of severe asthma exacerbations, the While on Treatment strategy will be used. Under this estimand, severe asthma exacerbations that start during the treatment period, from treatment initiation (Visit 3) up to the end of treatment or a step-up in maintenance therapy, will be included in the analysis. Severe asthma exacerbations that start after an ICE will not be included in the analysis. Time during a severe asthma exacerbation and the 7 days after a severe exacerbation will not be included in the time at risk for a participant. As per the primary efficacy endpoint, exacerbations separated by less than or equal to 7 days will be treated as a continuation of the same exacerbation.

To produce summary statistics, the crude annualized severe asthma exacerbation rate will be calculated according to the following formula:

$$Annualized\ severe\ exacerbation\ rate = \frac{\Sigma\ Number\ of\ severe\ exacerbation\ during\ the\ treatment\ period}{Total\ time\ at\ risk\ (days)} * 365.25$$

where the summation is over all participants within a treatment arm.

The time at risk will primarily use the duration (days) from the date of the treatment initiation visit to the earliest occurrence of study completion/withdrawal, treatment discontinuation, or a step up in maintenance therapy.

[MIN(Date of study completion, IMP discontinuation, step-up in maintenance therapy)] – [date of treatment initiation (Visit 3)] – cumulative duration of severe exacerbation(s)] +1

The annualized severe asthma exacerbation rate will also be derived according to the Treatment Policy strategy. Under this estimand all severe asthma exacerbation events that start during the study period, defined from the treatment initiation visit up to study completion or withdrawal from study, regardless of treatment discontinuation or a step-up in maintenance therapy, will be included in the analyses. Therefore, there time at risk under the Treatment Policy strategy is calculated as:

[MIN(Date of study completion, study withdrawal)] – [date of treatment initiation (Visit 3)] – cumulative duration of severe exacerbation(s)] +1

The cumulative duration of severe exacerbations is calculated as the total number of days that a participant has been prescribed a course of SCS:

Cumulative duration of severe exacerbation(s) = Σ(adjusted stop date of severe exacerbation – date of start of severe exacerbation)

where the sum is over every severe exacerbation event a participant has.

If a participant experiences an ICE during a severe exacerbation, then, for analyses under the While on Treatment strategy, the exacerbation will be excluded from the cumulative duration of events

endpoint. Since in this scenario the severe exacerbation started prior to the ICE occurrence, the severe exacerbation will contribute to the total number of severe exacerbations (numerator) for the secondary endpoint of annualized exacerbation rate. However, the adjusted stop date of the severe exacerbation will be adjusted to the date of the ICE occurrence when calculating the time at risk.

8.1.2.3 TOTAL SYSTEMIC CORTICOSTEROID EXPOSURE

The secondary endpoint of total amount (mg/year) per participant of systemic glucocorticoid prescribed in response to severe asthma exacerbations will be expressed as the total annualized dose (mg/year) of SCS. ICEs will be handled such that only SCS doses related to severe exacerbation events that occurred during the treatment period and prior to a step-up in maintenance therapy will be included in the analysis (While on Treatment strategy).

Total SCS exposure will be reported as the total annualized dose (mg/year) and is calculated for each participant as the sum of the total dose of systemic corticosteroid per severe asthma exacerbation divided by the time (years) the participant was in the study, from the treatment initiation and up to study completion, treatment discontinuation, or a step-up in maintenance therapy. Specifically, the annualized total systemic corticosteroid dose will be calculated as follows:

$$Annualized\ total\ systemic\ corticosteroid\ dose = \frac{Total\ systemic\ corticosteroid\ dose}{Total\ time\ at\ risk} * 365.25$$

Where total time at risk is defined from treatment initiation until the earliest occurrence of study completion, treatment discontinuation, or a step up in maintenance therapy. If an ICE occurs during a severe exacerbation, the prescribed SCS up to the ICE will be included in the numerator of the equation above, inclusive of the onset day of the ICE.

Systemic corticosteroids to be considered for the total annualized dose of SCS will be identified with ATC codes of H02AB or H02BX, and being taken during a severe exacerbation, and is a specified field in the concomitant medications (CM) module. The list of ATC codes described in this analysis plan may not be exhaustive. As a result, a clinical review will be conducted on the CM blinded data, prior to database lock, to define an exhaustive list of ATC codes associated with systemic corticosteroids used to treat asthma exacerbations, for the study.

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 PHASTAR.

The total duration of systemic corticosteroid use will be calculated as the total number of days during the randomized treatment period for which participants were prescribed systemic corticosteroids. On-going systemic corticosteroids at participant discontinuation/completion of the study period will have systemic steroid end dates set to their last date of contact where concomitant medications were assessed.

As a supplemental endpoint, total SCS exposure will also be evaluated under a Treatment Policy strategy where all data collected from the treatment initiation visit up to the end of study, regardless of the occurrence of ICEs, will be included in the analyses.

8.1.3 EXPLORATORY ENDPOINTS

8.1.3.1 ASTHMA RELATED HEALTHCARE RESOURCE UTILIZATIONS

The number of asthma related HCRU per participant year will be described using the following categories collected in the eCRF:

- Any health-related event
- Number of hospital admissions or emergency department for more than 24 hours
- Hospitalizations (Number of days)
    - Hospital intensive care unit (ICU)
    - Hospitalization general ward (GW)
    - Hospitalization coronary care
- Emergency room visits
- Urgent care visits (defined as evaluation and treatment for <24 hours in an emergency department or urgent care centre) due to asthma that required systemic corticosteroids
- Number of ambulance transports
- Specialist visits
- Primary healthcare physician visits
- Other health care visits
- Home visits by:
    - A physician
    - A nurse
    - Other healthcare
- Telephone calls to:
    - A physician
    - A nurse
    - A specialist
    - Other physician/healthcare provider
- Number of following assessments:
    - Spirometry
    - Advanced pulmonary function tests
    - Plain chest X-ray
    - Computed tomography
- Oxygen initiated

HCRU will be asthma-related only. The summary measure to describe this data is the number of utilizations per participant year, calculated by:

$$Healthcare\ Resource\ Utilization\ rate = \frac{Number\ of\ utilizations\ of\ healthcare\ resource}{Total\ exposure\ time}$$

The total exposure time is the length of time in years from treatment initiation until study completion, discontinuation of IMP or a step up in maintenance therapy. The numerator and denominator will be the total across patients, within the respective treatment groups, in order to produce crude rates.

8.1.3.2 STEPPING UP MAINTENANCE TREATMENT

The proportion of participants stepping up maintenance treatment is calculated for each treatment arm as:

$$Proportion\ stepping\ up = \frac{Number\ of\ participants\ stepping\ up\ maintenance\ therapy}{Number\ of\ participants\ in\ treatment\ arm}$$

Proportion is calculated as number of participants since randomization that have increased the dosage of their maintenance therapy.

A step-up in maintenance therapy will be reviewed in accordance with the GINA guidelines. All maintenance therapy will be documented in the CM module with the *Therapy Reason* field selected as *Asthma Maintenance*. Patients with any maintenance therapy concomitant medication initiated following the treatment initiation visit will undergo a clinical review to categorise the maintenance therapy change as a step-up a step-down, or neither. Multiple changes in maintenance therapy during the treatment period will be classified relative to their pre-study maintenance therapy classification. The process of classifying changes in maintenance therapy will be finalised prior to the unblinding of efficacy data for interim and final analyses.

The following ATC codes will be used to identify maintenance therapy in the CM module:

- R03DC (LTRA)
- R03BA (ICS)

All maintenance therapy captured in the CM module will also require the following field values:

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

8.1.3.3 STEPPING DOWN/STOPPING MAINTENANCE TREATMENT

The proportion of participants stepping down/stopping maintenance treatment is calculated for each treatment arm as:

$$Proportion\ stepping\ down/stopping = \frac{Number\ of\ participants\ stepping\ down/stopping\ maintenance\ therapy}{Number\ of\ participants\ in\ treatment\ arm}$$

Proportion is calculated as number of participants since randomization that have decreased or stopped the dosage of their maintenance therapy.

Please see section 8.1.3.2 for details on the process of defining changes in maintenance therapy, post treatment initiation.

8.1.3.4 RESCUE MEDICATION ACTUATIONS

The frequency and timing of actuations of the study IMP will be automatically logged in the [redacted] app via the participant's smartphone cellular or wi-fi connection. An actuation is equal to 1 inhalation of IMP. Data is collected and transmitted via Bluetooth from the sensor attached to each MDI provided by [redacted]. The usage data generated will be visible to the investigator via [redacted] portal.

The total actuations as recorded in the [redacted] portal will be used to determine the mean number of rescue medication actuations per day per participant.

Rescue medication usage will be calculated as a mean daily actuations per participant over the treatment period, from the treatment initiation visit up to treatment discontinuation or a step-up in maintenance therapy. The total daily actuations will be derived from 00:00 to 23:59 within each calendar day, per participant.

Additionally, mean daily actuations will be calculated over 4-weekly (28 day) time intervals across the 52-week study period, if a patient prematurely discontinues or has a step-up in maintenance therapy during a 4-weekly interval, their mean daily actuations for that interval will be calculated using the days from the start of the 4-weekly interval and the start of the ICE, or withdrawal from the study.

The sensor data will only record the dates and times in which a puff of treatment was taken. Hence, any days during the interval of treatment initiation, up to randomized treatment discontinuation that are not present in the sensor data app will be considered as a day in which 0 inhalations were taken.

The mean daily number of actuations will be re-calculated with erroneous and/or nonsensical sensor data excluded as an additional endpoint. Identification of erroneous and/or nonsensical data will be performed on blinded data. A flag will be included in the [redacted] sensor data to indicate which actuations should be excluded from the supportive endpoint. Exclusion of identified actuation(s) assumes the actuation did not happen, rather than missing, on the date of recording.

To further assess the reliability of the sensor data, the mean daily actuations per participant will be calculated using the dose counter data, available in the drug accountability eCRF module. The mean daily actuations using this data will be calculated as follows:

$$\frac{[\#\text{ Dose counter value(s) at receipt of inhaler}] - [\#\text{ Dose counter value(s) at treatment discontinuation/completion}]}{[\text{Number of days in the treatment period}]}$$

The total number of doses shown on the counter(s) corresponds to the cumulative sum all inhalers the participant receives during the treatment period. The treatment period duration is defined as the time in days from the treatment initiation visit up to treatment discontinuation.

The percentage of days over the entire treatment period, in which participants dosed the following number of puffs between the times of 00:00 to 23:59 within any calendar day will be calculated for each participant:

- Exactly zero puffs
- ≥ 1 puff to ≤ 2 puffs
- ≥ 3 puff to ≤ 4 puffs
- ≥ 5 puff to ≤ 6 puffs
- ≥ 7 puff to ≤ 8 puffs
- ≥ 9 puff to ≤ 10 puffs
- ≥ 11 puff to ≤ 12 puffs
- ≥ 13 puffs

8.1.3.5 ABSENTEEISM

Absenteeism is the time a participant takes off from work or school over the study period per participant year. The participant will be asked about work and school productivity loss in term of:

- Work absence due to asthma (days)
- School absence due to asthma (days)

The summary measure to be included is Absenteeism per participant year and is calculated by:

$$Absenteeism = \frac{Total\ time\ off\ work\ or\ school}{Total\ exposure\ time\ (days)} \times 365.25$$

Per the While on Treatment strategy, total exposure time is the length of time from treatment initiation until the earliest of study completion, treatment discontinuation or a step up in maintenance therapy.

8.1.3.6 ASTHMA IMPAIRMENT AND RISK QUESTIONNAIRE (AIRQ)™

The Asthma Impairment and Risk Questionnaire (AIRQ)™ is a patient-reported outcome (PRO) tool intended to identify participants whose health may be at risk because of uncontrolled asthma. It has 10 questions that ask about respiratory symptoms, activity limitation, sleep, rescue medication use, social activities, exercise, difficulty controlling asthma, and exacerbations. All items have a yes/no response option and the tool is scored by summing the total number of "yes" responses. This sum score is used to assess level of asthma control where:

- 0-1 is well-controlled
- 2-4 is not well controlled
- 5-10 is very poorly controlled

Thus, a higher score indicates worse control status.

The AIRQ™ items have 2 different recall periods: the first seven impairment items are evaluated over the past 2 weeks and the last three risk items either over the past 3 months or the past year. This study will use the version with a recall period for the last three risk items over the past year at Screening, Randomization, Week 52 EOS visits and the version with last three risk items for the past

3 months recall for the remaining visits where it is collected. Since these two recall periods will overlap for different visits (i.e., the Week 52 EOS visit will recall the same period of time as assessed in a Week 40 visit) then these responses cannot be assumed independent and therefore only descriptive statistics will be presented for these data together.

The AIRQ™ will be administered within the [redacted] application and completed on the participant's smartphone by the participant as per the Schedule of Assessments (Appendix B). The AIRQ™ is estimated to take approximately 3 minutes to complete.

The total score will be defined as the sum of the 10 questions in which a participant answered *YES*. If an AIRQ™ response is missing for a participant, then this is assumed missing at random. If ≥1 individual answers in a questionnaire are missing, then the whole questionnaire is assumed missing. More information on missing values will be discussed in section 8.4. The total scores will be calculated in the PRO tool, PHASTAR will perform a programming check in the relevant ADaM dataset to validate the total score.

Baseline is defined as the most recent non-missing value recorded prior to the start of the IMP (treatment period). For all endpoints the start of the IMP (treatment) period is defined as Visit 3.

Absolute change from baseline outcome variables is computed as

(post-randomization value - baseline value).

Change from baseline will be calculated for every post-baseline visit, including the End of Study (EOS). 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.

8.1.3.7 EQ-5D-5L SCORE

The EQ-5D-5L is a 5 dimension, 5-level standardized instrument for use as a measure of health outcome from EuroQol. Applicable to a wide range of health conditions and treatment, it provides a simple descriptive profile and a single index value for health status. The EQ-5D-5L consists of 2 assessments, a descriptive system, and a Visual Analog Scale (VAS) which will not be used in analysis. The descriptive system comprises of the following 5 dimensions:

- mobility
- self-care
- usual activities
- pain/discomfort
- anxiety/depression

Each dimension has 5 severity levels:

- No problems
- Slight problems

- Moderate problems
- Severe problems
- Extreme problems

EQ-5D-5L index score can be calculated based upon participant' responses to the 5 dimensions and using an appropriate value set. A value set provides values (weights) for each health state description according to the preferences of the general population of a country/region. The SAS syntax for applying the EQ-5D-5L value set for the USA can be found in Appendix C.

The index score, after adjustment from the value set, will be used in analysis.

The EQ-5D-5L will be completed within the [redacted] application on the participant's smartphone by the participant as per the SoA (Appendix B).

Baseline is defined as the non-missing value recorded prior to treatment initiation. For all endpoints the start of the IMP (treatment) period is defined as Visit 3.

Absolute change from baseline outcome variables is computed as

(post-randomization value - baseline value).

Change from baseline will be calculated for every post-baseline visit, including the End of Study (EOS). 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. No imputation will be made for missing data.

8.1.4 SAFETY ENDPOINTS

8.1.4.1 ADVERSE EVENTS

AEs and SAEs will be collected from time of signature of informed consent/assent through to the study completion and EOS visit.

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 resolution date
- SAE outcome

- Maximum SAE intensity
- Treatment given for the SAE
- Date of hospitalization
- Date of discharge
- Primary and secondary 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

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

Other significant adverse events (OAEs) will be defined by an Avillion medically qualified expert as AEs that were not reported as SAEs or DAEs that have particular clinical importance. These will be considered OAEs after consultation with the Global Subject Safety Physician 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).

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. AEs that occur between randomization and treatment initiation will be listed.

Please refer to section 8.4.1 for the imputation rule to programmatically determine the classification of AEs when there are partial start and/or stop dates recorded.

Adverse events that are associated with local and systemic steroid effects will be identified using the pre-specified preferred terms provided in Appendix D. Please note that these lists of preferred terms are 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.

8.2 STATISTICAL HYPOTHESES

8.2.1 PRIMARY HYPOTHESIS

The primary objective of this study is to evaluate the efficacy of BDA MDI 160/180 µg administered as needed compared with AS MDI 180 µg administered as needed on the risk of a severe asthma exacerbation in participants receiving SABA alone or with a background of low-dose ICS or a LTRA over a variable length of 12–52-week treatment period. This is a superiority study to demonstrate the benefit of adding budesonide to albuterol in the fixed-dose combination BDA MDI used as needed compared to AS MDI. The primary efficacy endpoint is the time to first severe asthma exacerbation (While on Treatment strategy), from the treatment initiation visit to a step-up in

maintenance therapy or the end of treatment, as a measure of risk of experiencing a severe asthma exacerbation.

Formally the null and alternative hypotheses for the primary and secondary analyses of time to first severe exacerbation are:

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

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

The primary objective and all secondary objectives will be tested at α=0.05, two-sided.

8.2.2 SECONDARY HYPOTHESES

For the secondary endpoint of time to first severe asthma exacerbation, evaluating the Treatment Policy strategy, the null and alternative hypotheses are the same as in the primary analysis.

For the secondary endpoint of annualized severe asthma exacerbation rate, the null and alternative hypotheses are:

H_0: Annualized rate ratio (Annualized $rate_{BDA}$ / Annualized $rate_{AS}$) = 1,

H_A: Annualized rate ratio (Annualized $rate_{BDA}$ / Annualized $rate_{AS}$) ≠ 1.

The annualized severe exacerbation rate ratio will be analysed using a negative binomial model. Analysis will be repeated under the Treatment Policy strategy.

The secondary endpoints of total (amount, mg/year) systemic corticosteroid (SCS) exposure, and total (days) SCS exposure will be analysed using a Wilcoxon Rank Sum test Formally, the null and alternative hypotheses are:

H_0: D_{BDA}= D_{AS},

H_A: D_{BDA} ≠ D_{AS}.

Where D_T is the distribution of values in treatment group T.

8.3 MULTIPLE TESTING STRATEGY

A hierarchical testing strategy will be employed to control the two-sided Type I error rate for the primary and secondary endpoints, testing the endpoints in the following pre-specified order:

1) Time to first severe asthma exacerbation (While on Treatment strategy in the full analysis set; ≥12 years);
2) Time to first severe asthma exacerbation (Treatment Policy strategy in the full analysis set; ≥12 years);
3) Time to first severe asthma exacerbation (While on Treatment strategy in the full analysis set; ≥18 years);
4) Time to first severe asthma exacerbation (Treatment Policy strategy in the full analysis set; ≥18 years);

5) Annualized severe asthma exacerbation rate (While on Treatment strategy in the full analysis set; ≥12 years);
6) Annualized severe asthma exacerbation rate (While on Treatment strategy in the full analysis set; ≥18 years);
7) Total systemic glucocorticoid exposure (While on Treatment strategy in the full analysis set; ≥12 years); and
8) Total systemic glucocorticoid exposure (While on Treatment strategy in the full analysis set; ≥18 years).

Testing will be conducted at the specified alpha for the final analyses. The hierarchical testing strategy will be applied whereby the full fraction of alpha will be passed down to endpoints tested per the pre-specified order. Inference for a test in the pre-specified hierarchy is dependent upon statistical significance having been achieved for the previous tests in the hierarchy. Once statistical significance is not achieved further inferential testing will not be performed. Further discussion about alpha spending and interim analyses will be in section 10.

8.4 PREMATURE WITHDRAWAL AND MISSING DATA

If the sponsor, investigator, study monitor, IDMC, or regulatory officials discover conditions arising during the study that indicate that the participant'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 centre's participation may be terminated. Ongoing participants will be discontinued from the study and assigned to receive treatment as per local standard of care.

Participants who withdraw will not be replaced on the study. A participant may withdraw from the study at any time at their own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioural, compliance or administrative reasons.

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

- Participant decision
- Adverse event
- Severe non-compliance to protocol
- Condition under investigation worsened
- Lack of therapeutic response
- Lost to Follow-up
- Completed
- Physician decision
- Study terminated by sponsor
- Site terminated by sponsor
- Death
- Withdrawal by parent/guardian
- Pregnancy
- Other

For all analyses under the While on Treatment strategy and Treatment Policy strategy, all missing data will be considered non-informatively missing and therefore missing at random. For the sensitivity analysis of the primary endpoint and for the analyses conducted under the attributable estimand, a subset of missing data will be considered missing not at random. Please see section 9.4 for the handling of missing data under these specific analyses and estimands.

If a participant chooses to prematurely discontinue randomized treatment, then they will be assigned to receive treatment as per local standard of care. The participant may choose to remain on the study and complete any subsequent visits up to the end of the study, including providing instances of severe asthma exacerbation, SCS exposure, hospitalizations, absences from work or school, and completing study questionnaires up to their EOS visit.

If a participant chooses to prematurely discontinue randomized treatment and subsequently withdraw from the study completely, then an Early Study IMP Discontinuation visit should be conducted. The schedule of assessments (Appendix B) should be referred to for data to be collected at the time of study withdrawal and follow-up and for any further evaluations that need to be completed. If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent. Further information on premature withdrawal from the study is outlined in section 7 of the CSP.

All missing AIRQ™ and EQ-5D-5L responses will be assumed to be missing at random and excluded from analysis. No imputation will be made for any missing data in either questionnaire.

8.4.1 DATE IMPUTATION RULES

In the instance that the eCRF records partial dates for a severe exacerbation, SCS prescription, concomitant medication or adverse event then a conservative imputation rule is applied.

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

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 the treatment initiation date then impute as the treatment initiation 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 treatment initiation;

   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 listings produced. The intention for date imputation is to facilitate a programmatical decision making process to classify on-treatment observations.

8.4.2 SENSITIVITY ANALYSES

Sensitivity analyses in which censored results will have event times imputed under an informative censoring assumption will be performed. Sensitivity analysis will only be performed on missing data from the primary endpoint of time to severe exacerbation and must meet missing data assumptions.

In these analyses, the following primary reasons for discontinuation, as collected on the eCRF will correspond to missing not at random data:

- Participant decision, with a specific reason of:
  - Participant perceives the investigational product to be ineffective
- Adverse event, indicated as treatment related
- Condition under investigation worsened
- Lack of therapeutic response
- Investigator decision
- Death

Further details on the imputation procedure will be presented in section 9.4.

8.5 STUDY POPULATION

Participants must be ≥12 years of age, at the time of signing the eICF.

Participants must be actively using SABA alone or SABA on a background of either low dose ICS or LTRA, and have self-reported use of a SABA in response to symptoms on ≥2 occasions in the previous 2 weeks prior to enrolment. Participants must also have an AIRQ™ score of ≥2 at Screening.

See sections 5.1 and 5.2 of the CSP for further details on inclusion and exclusion criteria, respectively, for this study.

8.5.1 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Sex, ethnicity, and race will be collected at screening. Age (years) collected at screening will be summarised as a continuous variable. Additionally, age group strata will be summarised under the following groupings:

Age group 1

- Adolescents: ≥12 - <18 years
- Adults: ≥18 - <65 years
- Elderly: ≥65 years

Age group 2

- Adolescents: <18 years
- Adults: ≥18 years

Medical (including surgical), asthma (including exacerbations) and smoking history are 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 asthma exacerbation, relative to randomization, 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 8.4.1.

The number of severe exacerbations (0, ≥1) in the last 12 months prior to randomization will be collected on the eCRF.

8.5.2 CONCOMITANT MEDICATIONS

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

A medication which has a start date on the day of, or after the treatment initiation visit will be concomitant. Additionally, all medication starting prior to treatment initiation and continuing after treatment initiation will also be considered concomitant. All medication recorded for which the stop date is prior to treatment initiation will be classified as a prior medication.

If a concomitant medication is recorded with missing or 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 8.4.1 will be considered. The raw dates will be used in listings.

Prohibited medication will be identified following a clinical review of WHO drug dictionary terms prior to unblinding.

8.5.3 TREATMENT COMPLIANCE

As the study medication is being taken as needed, no assessment of compliance will be made. However, the Investigator / authorized delegate will check overall inhaler usage at each contact with the participant to ensure that the participant has a sufficient number of inhalers. The number of MDIs sent to the participant, as well as the number of inhalers returned by the participant to the central depot at the end of the trial will be captured in the RTSM as well as documented and stored at the Investigator Site.

Adherence to asthma maintenance medications for those currently receiving will not be assessed.

8.6 ASSESSMENT TIME WINDOWS

For endpoints with repeated measures values collected at premature discontinuation visits should be assigned to the next available visit. The schedule of assessments (presented in Appendix B) has further detail on the visit window intervals.

Enrolment, screening assessments and randomization may occur on the same day or on separate days within a 28-day period.

IMP delivery is expected to take 3-5 days, but Day 1, or Visit 3, can be up to 14 days after randomization (Visit 2).

Visit windowing for analysis will consider the midpoint between two scheduled assessments. If two visits occur in the same window, then the closest to the target will be used for analysis. If the two visits are equidistant from the target day, then we choose the earliest occurrence. Please see table below for the visit windows. The early termination visit will be considered in the visit windowing rules. In a situation where two scheduled visits (as labelled in the eCRF), including the early termination visit, occur in the same window as the early termination visit, then the visit closest to the target day will be used in analysis.

Unscheduled visits will not be used in the visit windowing algorithm.

Table 2 Visit Windows

Visit number / Visit label	Target day (window)
Visit 3 / Day 1	Day 1
Visit 4 / Week 4	Day 28 (day 2 - 70)
Visit 5 / Week 16	Day 112 (day 71 – 154)
Visit 6 / Week 28	Day 196 (day 155 – 238)
Visit 7 / Week 40	Day 280 (day 239 – 322)
Visit 8 / Week 52	Day 364 (day 323+)

Week 52 will be the End of Study (EOS) visit for participants who complete the full treatment period. If a participant prematurely discontinues from the study, then the early study IMP discontinuation visit will be conducted as soon as possible.

8.6.1 METHODS FOR HANDLING OUT-OF-WINDOW OBSERVATIONS

Telephone/televisit contact to be performed if confirmation received from the participant through the bi-weekly messages within the [redacted] app that there was any systemic corticosteroid use and/or unscheduled asthma related healthcare visits. This data will not be summarised and will be mapped to SDTM datasets only. Unscheduled visits and unmapped visits that are not assigned a visit number will be listed.

Participants who prematurely withdraw from the study will undergo an early study IMP/discontinuation visit. Participants who do not withdraw consent for follow-up will be encouraged to continue with all study assessments as scheduled until withdrawal from study or completing at 12 months. When reaching the Primary Completion Date (i.e., when 350 events have been reached), participants who have had at least 12 weeks of treatment but not completed the entire 52 weeks treatment period, will have their end of study visit scheduled within 4 weeks. The end of study and IMP/discontinuation visits will be mapped to a scheduled visit according to the rules defined above (section 8.6).

9. STATISTICAL ANALYSES AND METHODOLOGY

9.1 STUDY POPULATION

9.1.1 DISPOSITION OF SUBJECTS

Subject disposition will be summarised for all enrolled participants. The number of participants who were enrolled (provided informed consent) will be summarised. The number and percentage of participants randomized and not randomized (and reasons) will be presented, with percentages calculated from the total number of participants enrolled. The number and percentage of participants who were: randomized and received randomized treatment, randomized and did not receive randomized treatment (and reasons), completed (broken down by *on-treatment* and *off-treatment* completion), discontinued IMP (reasons) and discontinued the study (reasons) will also be presented with percentages calculated from the total number of participants randomized.

A separate table will present the number and percentage of participants randomized to each treatment group, by site. This table will be based on the full analysis set (≥12 years) and repeated on the full analysis set (≥18 years).

The number and percentage of participants included in the full analysis set (≥12 years), full analysis set (≥18 years) and in the safety analysis set, along with the corresponding number of participants excluded from each analysis set will be summarised by treatment group and overall. Additionally, listings of enrolled patients who were excluded from the randomized full- and safety analysis sets will be listed separately, the listing will provide the treatment group (if applicable) basic demographic information (age, sex, race) and the reason for exclusion. Those who have not met eligibility criteria for randomization will also be listed.

9.1.2 PROTOCOL DEVIATIONS

Important deviations will be summarized by the number and percentage of participants meeting the pre-defined protocol deviation coded term. These will be identified by the sponsor prior to the primary completion date and unblinding of the study results. All protocol deviations, major and minor, will be listed, along with a flag to indicate whether the deviation was considered important. Listings of protocol deviations will additionally include the date of the deviation occurrence, the protocol deviation verbatim term and the coded term.

9.1.3 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Age (years), sex, race and ethnic group will be summarised by treatment group and overall for the full analysis set (≥12 years). Percentages for demographics characteristics will be based on number of participants with non-missing data. Baseline characteristics will be summarised by treatment group and overall for the full analysis set (≥12 years). These include previous disease-related treatments, medical and surgical histories, and asthma history variables collected on the CRF.

Asthma history will be summarised descriptively for participants in the full analysis set (≥12 years). The time in years since asthma diagnosis and the time in days since the participant's last severe exacerbation will be presented by descriptive statistics of median, 25th percentile, 75th percentile, minimum and maximum. The number of severe exacerbations in the previous 12 months will be summarized by treatment group and overall as a discrete outcome, presenting the number (%) of participants with 0 exacerbations, 1 exacerbation, 2 exacerbations, and >2 exacerbations, and further broken down for SEEs that resulted in emergency room treatment or hospitalization. Associated conditions, triggers or allergies will also be summarised by treatment group and overall. Additional asthma history information will be listed for each participant in the full analysis set (≥12 years).

A separate table will present the number and percentage of participants randomized to each treatment group, by stratification factor allocated at randomization. This table will be based on the full analysis set (≥12 years).

Medical and surgical histories will be summarized by treatment group by MedDRA preferred term within MedDRA system organ class for participants in the full analysis set (≥12 years).

Smoking status will be summarized categorically as the number of participants who currently smoke, have never smoked or are former smokers and grouped by randomized treatment group. Nicotine pack years of cigarette usage and duration of e-cigarette use (years) will be summarized as a continuous endpoint by randomized treatment group. Smoking status summaries will be based on the full analysis set (≥12 years).

The number and percentage of participants in the full analysis set (≥12 years) who take allowed concomitant medications, and those who take prohibited medications during the study, will be presented by treatment group and ATC classification and generic term. A review of the CM data will be conducted by the clinical team to identify an exhaustive list of concomitant medication ATC terms, and doses (where applicable) according to the clinical study protocol, prior to database lock and unblinding of study results at each milestone of interim and final analysis.

Summaries will be grouped by prior medication, concomitant medication occurring during the randomized treatment period. Concomitant medication will be presented under both the While on Treatment strategy Maintenance medication will not contribute to these summaries and will be presented in a separate table. Concomitant medication prescribed following an ICE (step-up in maintenance therapy or premature discontinuation of randomized treatment) will be summarized separately.

Exposure to study medication will be summarised descriptively for the safety analysis set as the total duration (days) from the first dose at treatment initiation, up to treatment discontinuation. Summary of exposure will also be displayed as the total daily number of actuations of the IMP. Please refer to section 9.2.3.2 for further details.

Demographics and baseline characteristics will also be summarized by the pre-specified subgroups, as described in Section 7.5.1.

9.2 EFFICACY ANALYSES

All efficacy analyses will be conducted in the full analysis set (≥12 years).

9.2.1 PRIMARY EFFICACY ANALYSIS

The primary efficacy analysis is the time to first severe asthma exacerbation based on the While on Treatment strategy, as defined in section 8.1.1.

The time to first severe asthma exacerbation from the treatment initiation visit up to the end of the treatment period will be analysed fitting a Cox proportional hazards regression model including terms for treatment, pre-study asthma therapy (SABA only, SABA + low-dose ICS or LTRA) and the number of severe exacerbations (0, ≥1) in the 12 months prior to randomisation (Visit 2). The summary measure to compare treatments is the estimated hazard ratio which will be presented with the associated Wald two-sided 95% confidence interval and two-sided p-value. In addition, the number and percentage of participants with a severe exacerbation event will be presented. Ties in the data will be handled using the Breslow method.

The assumption of proportionality will be assessed. Proportionality will be tested firstly by examining plots of complementary log-log (event times) versus log (time). If these raise concerns, a time dependent covariate would be fitted (adding a treatment-by-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 HR calculated over distinct time-periods as supportive estimates. Time-event plots for first severe exacerbations will be produced from the full analysis set (≥12 years) and will be grouped by randomized treatment.

Kaplan-Meier (KM) plots of time to first severe asthma exacerbation will be presented by treatment group with final KM estimate presented.

Severe asthma exacerbations will be summarised descriptively as the frequency and percentage of participants with at least 1 severe exacerbation, the number of severe exacerbations prior to IMP discontinuation or a step up 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 8.1.2.2.

The number of participants who have been censored along with the reason for censoring (completed study prior to first severe exacerbation; discontinued treatment due to asthma; change in maintenance therapy; death; other).

The descriptive statistics for first severe exacerbations 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. This summary will be repeated for all severe exacerbations.

Sensitivity analyses in which censored results will have event times imputed under an informative censoring assumption will be performed. Please refer to section 9.4.1.1 for the detail on imputing event times. A Cox proportional hazards regression model will be performed including treatment, pre-study asthma therapy and the number of documented severe exacerbations in the 12 months prior to randomization as stratification factors. The estimated adjusted hazard ratio for the treatment comparison will be displayed along with the associated Wald two-sided 95% confidence interval (CI) and two-sided p-value.

A forest plot will be produced to show the changing hazard ratio and two-sided 95% CIs for different values of delta assigned in the tipping point analysis. These delta values presented in the forest plot are as follows:

1. Integer delta from 0 to 10
2. In the event that the tipping point occurs between two integer values of delta, the range of this unit of delta will be presented in 0.1 increments

Finally, the Cox regression and forest plots 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 section 9.4.1.1.

As a supportive descriptive measure, the cumulative (across-participant sum) time at risk per 100 participant years up to first severe exacerbation will be summarized by treatment group under the While on Treatment strategy, Treatment Policy strategy and Attributable estimand. Refer to section 9.2.1 for a description of this endpoint calculation.

9.2.2 SECONDARY EFFICACY ANALYSIS

Unless specified otherwise in the relevant subsection, secondary analyses described below will be based on the full analysis set (≥12 years) population and repeated on the full analysis set ≥18 years population, in accordance with the multiple testing strategy (section 8.3).

9.2.2.1 TIME TO FIRST SEVERE EXACERBATION, TREATMENT POLICY STRATEGY

The secondary efficacy analysis of time to first severe exacerbation under the Treatment Policy strategy (≥12 years) will be analysed using a Cox proportional hazards model as defined for the

primary analysis. The descriptive summaries of severe exacerbations defined under section 9.2.1 will be repeated under the Treatment Policy strategy; severe exacerbations occurring from treatment initiation and up to study completion/withdrawal.

These secondary analyses will be repeated on the full analysis set (≥18 years).

9.2.2.2 TIME TO FIRST SEVERE EXACERBATION, WHILE ON TREATMENT ESTIMAND (≥18 YEARS)

The primary analysis under the While on Treatment strategy includes all participants in the full analysis set (≥12 years). The analyses described in section 9.2.1 will be repeated on the full analysis set ≥18 years population.

9.2.2.3 ANNUALIZED SEVERE EXACERBATION RATE

The annualized severe asthma exacerbation rate will be analyzed using a generalized linear model, assuming the number of exacerbations has a negative binomial probability distribution and that its mean is related to covariate variables with a 'log link' function. The logarithm of time at risk (years) will be used as an offset variable. The model will include covariates for treatment, pre-study asthma therapy (SABA only, SABA + low-dose ICS or LTRA) and the number of prior severe exacerbations (0, ≥1) in the 12 months prior to screening/enrolment (Visit 1/2). From the negative binomial model, the annual severe asthma exacerbation rates will be estimated for each treatment group, and the summary measure for the comparison of treatments will be the estimated annualised rate ratio which will be presented with the corresponding two-sided 95% confidence interval and corresponding 2-sided p-value. In addition, the model-adjusted annualised severe asthma exacerbation rate and the overdispersion parameter estimated from the negative binomial model will be presented.

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

The analysis of annualized exacerbation rate assessed under the While on Treatment strategy will be considered a secondary analysis and included in the type-I error controlled testing strategy. The annualized rate of severe exacerbations will also be evaluated under a Treatment Policy strategy, where all data collected from treatment initiation up to the end of study participation, regardless of ICE occurrence, will be used. The analysis of annualized exacerbation rate assessed under the Treatment Policy strategy will be considered a supplemental analysis.

These secondary analyses will be repeated on the full analysis set (≥18 years).

9.2.2.4 TOTAL SYSTEMIC CORTICOSTEROID EXPOSURE

Annualized dose of systemic corticosteroid exposure prescribed in response to severe exacerbations will be summarized as a continuous measure descriptively for patients in the full analysis set (≥12 years). For this endpoint, additional descriptive statistics will include the treatment difference in

arithmetic means, percentage reduction in the treatment arithmetic means, 2.5th, 5th, 75th, 80th, 95th and 97.5th percentiles will be presented in the summary of annualized SCS dose.

A comparison in total annualized SCS dose between BDA MDI 160/180 versus AS MDI 180 will be analyzed using a Wilcoxon rank sum test, comparing the distribution of exposure. The p-value from the Wilcoxon rank sum test will be presented alongside the percentage difference in arithmetic means, and the difference in predicted means (mg) estimated from a log-normal hurdle model adjusted for randomized treatment. Additionally, the total SCS exposure will be summarised descriptively as the total number of days with SCS treatment due to asthma for all participants.

The analysis of total systemic corticosteroid exposure assessed under the While on Treatment strategy is a secondary analysis and included in the type-I error controlled testing strategy. SCS exposure analyses will be repeated under the Treatment Policy strategy and will be considered a supplemental analysis.

Exposure will also be summarised for each treatment group and overall under the following categories: average duration (days) of course of SCS prescribed per exacerbation; average daily dose of SCS prescribed for a severe exacerbation; total number of courses prescribed per participant per year; total SCS (mg); total duration (days) of SCS use.

These secondary analyses will be repeated on the full analysis set (≥18 years).

9.2.3 EXPLORATORY EFFICACY ANALYSIS

Unless stated otherwise in the relevant endpoint section, exploratory efficacy analyses will be conducted in the full analysis set (≥12 years).

9.2.3.1 CHANGE IN MAINTENANCE THERAPY

The time to a step up in maintenance therapy will be summarized descriptively along with the time to a step down or stop in maintenance therapy. The proportion of participants changing their maintenance therapy will be summarized for each treatment group. Step up and step-down analyses will be under the While on Treatment strategy (≥12 years).

9.2.3.2 RESCUE MEDICATION ACTUATIONS

Rescue medication actuations (number of as-needed inhalations per day) will be summarised descriptively by randomized treatment group as a continuous endpoint. Reliever use will be summarized under the While on Treatment strategy (≥12 years), which includes reliever use from treatment initiation and up to randomized treatment discontinuation or a step-up in maintenance therapy.

Summaries of rescue medication will be repeated based on the supportive endpoints which 1) exclude erroneous and/or nonsensical data; 2) where mean daily dose is calculated from the dose counter data. Refer to section 9.2.3.2 for a description of these supportive endpoints.

The percentage of days in which participants dosed exactly zero, ≥1 to ≤ 2 puffs, ≥3 to ≤ 4 puffs, …, ≥11 to ≤ 12 puffs and ≥ 13 puffs will be summarized as a continuous measure by randomized treatment group. A supportive bar chart plotting the mean percentage of days under the pre-

specified categories of puffs will also be produced and grouped by randomized treatment. Percentage days of reliever use will be summarized under the While on Treatment strategy (≥12 years).

9.2.3.3 THE EXPLORATORY ANALYSES OF RESCUE MEDICATION USE WILL BE REPEATED ON THE FULL ANALYSIS SET (≥18 YEARS).HEALTHCARE RESOURCE UTILIZATION

Descriptive statistics will be presented for each health care resource item described in section 8.1.3.1, by treatment group. Summary measures to be included are total number of each HRU event (visits) and/or days of events, number and percentage of participants experiencing at least one HRU event, and the total number of each HRU event or days of event divided by participant treatment years (annualized event rate). Healthcare resource utilization will be summarized under the While on Treatment strategy (≥12 years) and include HCRU from treatment initiation up to randomized treatment discontinuation or a step-up in maintenance therapy.

9.2.3.4 WORK AND SCHOOL ABSENCE

Descriptive statistics will be presented for work and school absence, by treatment group. Summary measures to be included are total number of days, number and percentage of participants experiencing at least one absence day, and mean number of days absent per participant per year. Work and school absence will be summarized under the While on Treatment strategy (≥12 years) and include absence data from treatment initiation up to randomized treatment discontinuation or a step-up in maintenance therapy.

9.2.3.5 AIRQ™

Analysis of change from baseline in AIRQ™ at Week 52 will target the While on Treatment strategy (≥12 years). The overall AIRQ™ score and the change from baseline, will be descriptively summarised by treatment and visit. Boxplots of change from baseline AIRQ™ over time will be presented. Boxplots will also be produced to show the absolute values at baseline and each visit.

Baseline will be defined as the most recent score prior to treatment initiation. Only Week 16, Week 28, Week 40, and Week 52 will be assessed alongside the baseline assessment.

An ANCOVA model for the change in AIRQ™ scores at each visit from baseline will be analysed with stratification factors of randomized treatment group, pre-study asthma therapy [SABA only, SABA + low-dose ICS or LTRA] and the number of prior severe exacerbations [0, ≥1] in the 12 months prior to screening/randomisation. Least squared means by randomized treatment group and differences in least squared means between each treatment group along with corresponding 95% confidence intervals and two-sided p-values will be estimated.

Additionally, a figure showing the least squares means estimates over time from the ANCOVA analyses, along with 95% confidence intervals will be presented. The least squares means will not be joined together for this visualisation.

AIRQ descriptive summaries and analyses will be repeated under the Treatment Policy strategy (≥12 years), which will include all collected AIRQ total scores regardless of step-up in maintenance therapy or premature treatment discontinuation.

9.2.3.6 EQ-5D-5L

Summary statistics by treatment will be provided for absolute and change from baseline values by treatment and visit and will target the While on Treatment strategy (≥12 years). Boxplots will be produced to show the absolute values at baseline and each visit, and the change from baseline over time.

Baseline will be defined as the most recent score prior to treatment initiation.

The treatment effect for change from baseline in EQ-5D-5L index value will be estimated using a repeated measures model analysis. All scheduled visits up to and including Week 52 where EQ-5D-5L is completed will be included in the model, with terms for treatment, visit, treatment*visit, and baseline EQ-5D-5L. The model will also be adjusted for the randomization stratification factors (pre-study asthma therapy [SABA only, SABA + low-dose ICS or LTRA] and the number of prior severe exacerbations [0, ≥1] in the 12 months prior to screening/randomisation). 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 2-sided p-values.

Only index values provided at weeks 4, 28 and 52 will be used in EQ-5D-5L analysis alongside the baseline response.

9.3 SAFETY ANALYSES

9.3.1 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 participants 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 participants with adverse events and incidence rate during the randomized treatment period
- Number of participants with most frequently occurring AEs (at least 2% participants in any treatment group), by preferred term
- Number of AEs and event rate during the randomized treatment period, by system organ class and preferred term
- Number of participants with AEs with an outcome of death, by system organ class and preferred term
- Number of participants with AEs during the randomized treatment period by maximum reported intensity, system organ class and preferred term
- Number of participants with AEs during the randomized treatment period, by preferred term and relationship to IP, as assessed by the investigator

- Number of participants with AEs during the randomized treatment period by preferred term and outcome
- Number of participants with SAE during the randomized treatment period, by system organ class and preferred term
- Number of SAEs during the randomized treatment period, by system organ class and preferred term
- Number of participants 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%) during the randomized treatment period by preferred term
- Number of participants with AEs during the study period by system organ class and preferred term
- Number of AEs during the study period by system organ class and preferred term

Treatment emergent adverse events summarized during the randomized treatment period are identified as any AE where the onset date is on or after the date of treatment initiation, up until the participant discontinues randomized treatment, regardless of a step-up in maintenance therapy.

AEs occurring during the randomized treatment period will include the incidence rate. The incidence rate is defined as the number of participants who have experienced the event per 100 participant treatment years. 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 participants in the treatment group per 100 participant treatment years. The number of participants with adverse events occurring post-randomized treatment discontinuation will be summarised separately.

In the overall summary table of AEs in any category, and the summary of most frequent AEs (≥2% total incidence) by preferred term, risk differences between treatment groups will be presented along with associated 95% CIs. Agresti-Caffo CIs will be computed for risk differences, which can accommodate zero events in one of the two treatment groups.

AEs that start after randomization and before the treatment initiation visit will be listed. These AEs will not be included in the descriptive summary tables.

All AEs will also be listed for each participant and will include 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 the number of participants with adverse events, by system organ class and preferred term will be produced and grouped within background maintenance therapy (SABA, SABA + low-dose ICS, SABA + LTRA).

Additionally, the number (%) of participants with adverse events associated with local ICS (as defined in section 8.1.4.1) will be presented overall (at least 1 local ICS-related AE) and by preferred

term for participants in the safety analysis set. Additionally, these AEs will be summarised within pre-study asthma therapy category (SABA, SABA + low-dose ICS, SABA + LTRA).

A similar output will be produced displaying the number (%) of participants with adverse events that are associated with systemic ICS effects (as defined in section 8.1.4.1). The number of participants with pneumonia during the randomized treatment period will also be summarised by pre-study asthma therapy.

For AEs leading to death, AEs leading to discontinuation of randomized treatment, and all SAEs will be listed by participant and treatment group, and will include the following key participant 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.

9.4 SUPPLEMENTARY AND SENSITIVITY ANALYSES

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. For subjects in the BDA MDI treatment group, this method will impute unobserved event times post early IP discontinuation for lack of asthma control/ step-up in maintenance therapy, 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. The tipping point analysis will be conducted on the While on Treatment strategy and the Treatment Policy strategy. For a breakdown of treatment discontinuation criteria which are indicative of a lack of asthma control/informative censoring, please refer to section 8.4.

All supplemental and sensitivity analyses will be conducted on the full analysis set (≥12 years) and repeated using the full analysis set ≥18 years population.

9.4.1.1 APPLYING THE INFORMATIVE CENSORING ASSUMPTION

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

$$h(t|\boldsymbol{Z_i}) = h_0 e^{\boldsymbol{\beta Z_i}} \quad [1]$$

for participant i and covariates as specified for the primary analysis $\boldsymbol{Z_i}$, h_0 is the baseline hazard function for the Cox model and $\boldsymbol{\beta}$ are the parameter estimates from the regression model. For a participant censored at time C_i, we can impute the event time based on the hazard function

$$h(t|t_i > C_i, \boldsymbol{Z_i}) = h_0 e^{\boldsymbol{\beta Z_i} + \delta_i} \quad [2]$$

Where a penalty δ will be applied and corresponds to the increased log-hazard of a severe exacerbation. For participants in the AS MDI treatment group, $\delta = 0$ will be applied and this will correspond to imputing under a CAR assumption. For participants in the BDA MDI group, $\delta > 0$ will be assigned if they have discontinued IMP and/or had a step up 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 participants who are censored. For participants in the BDA MDI treatment group who discontinue the study and/or step-up maintenance therapy, 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:

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

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 even 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:

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

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

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

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 $H_{A_i}(\mathrm{t}) < -\log\,(U_i)\; e^{-\hat{\boldsymbol{\beta}}\mathbf{Z}_i - \delta_i}$; the event time to would be greater than the last event observed in the study, and in such cases the participant will be imputed as being censored at the end of the study at 52 weeks.

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-value (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.

9.4.1.2 ATTRIBUTABLE ESTIMAND

The supplementary analysis of the attributable estimand will be conducted for the primary endpoint time to first severe exacerbation using data obtained before participants discontinue randomized treatment and/or before a step-up in maintenance therapy and will use the FAS. However, the data that is censored due to study withdrawal will have the event time imputed on the basis of the percentile of the AS MDI as needed distribution if the reason is reasonably attributable to tolerability or lack of control. For all other participants 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 9.4.1.1 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.

10. INTERIM ANALYSIS

An unblinded interim analysis for efficacy is planned once 50% of the target number of first severe exacerbation events according to the While on Treatment strategy in the full analysis set (≥12 years) have been observed (172 first severe exacerbation events total, prior to treatment discontinuation or a step-up in maintenance therapy). Alpha spending will be governed through the O'Brien-Fleming approach, where 0.003 will be spent at the interim to assess statistical significance of the primary endpoint, and the first secondary endpoint of time to first severe exacerbation under the Treatment Policy strategy in the full analysis set (≥12 years).

No minimum exposure time is required and all patients in the full analysis set (≥12 years) will be analyzed. Patients who are on-going at the time of the interim analysis, who have not had a severe exacerbation event or ICE will be censored at the date of the interim data cut.

Formally, the stopping criteria for overwhelming efficacy are:

1. Reject the null hypothesis for the primary endpoint, time to first severe asthma exacerbation under the While on Treatment strategy in the full analysis set (≥12 years) at 2-sided alpha = 0.003

AND

2. Reject the null hypothesis for the secondary endpoint, time to first severe asthma exacerbation under the Treatment Policy strategy in the full analysis set (≥12 years) at 2-sided alpha = 0.003

Members of the data monitoring committee will review the primary and secondary analysis of time to first severe exacerbation at the interim and recommend to the Sponsor if the trial can be stopped due to overwhelming efficacy.

No evaluation of superiority will be conducted on the remaining secondary endpoints detailed in Section 8.3 at the interim analysis.

In the event that the DMC recommends stopping the study due to overwhelming efficacy per the above stopping criteria, the sponsor, once informed, will inform site personnel and participants that the study is closing due to overwhelming efficacy. If the study is still enrolling, enrolment will be immediately closed. All participants who have not completed 12 weeks of treatment will continue in the study and complete their EOS visit once they completed 12 weeks of treatment. All participants ongoing in the study who have completed 12 weeks of treatment will return for their EOS visit at their next scheduled visit or within 4 weeks of notification, whichever comes first.

Type-I error control for remaining secondary endpoints

In the event of stopping the clinical trial following a recommendation due to overwhelming efficacy from the DMC, the remaining untested secondary endpoints detailed in Section 8.3 will be analysed following database lock and formal unblinding of the study once all participants have completed their EOS visits following a minimum of 12 weeks on treatment. These remaining secondary endpoints will be evaluated at an alpha= 0.05 (2-sided).

If the DMC recommends that the trial continues until the earliest occurrence of 350 first severe exacerbation events, or all patients have been randomized and followed up for 12 months, then the remaining secondary endpoints will be tested at the same alpha threshold used for the primary endpoint of time to first severe exacerbation at the final analysis, i.e. alpha=0.049 (2-sided).

If the final number of first severe exacerbations is above or below the expected pre-specified total, then the generalized Haybittle-Peto method will be used to correct the alpha to ensure the overall type-I error is controlled at 5% for the final analysis.

11. BLINDED SAMPLE SIZE REASSESSMENT

A reassessment of the sample size will be expected to ensure that the required number of events will be observed once all participants have completed the study or discontinued or had a step up in maintenance therapy, with the aim of preserving 90% power.

A BSSR will be performed, the timing of which will be dictated by there being a sufficient number of severe asthma exacerbation events and exposure time on study to provide good precision and a meaningful event rate prediction.

A blinded estimate of the annualized first severe exacerbation rate will be calculated on the accrued data at the point triggering the formal sample size review.

If the observed blinded first exacerbation rate is lower than predicted, the number of randomized participants may be increased to a maximum of 2,500.

Due to the nature of the criteria triggering the blinded sample size reassessment, care must be taken when evaluating the estimated annualised first severe exacerbation rate. Seasonal trends and total cumulative exposure might impact the under- or over-estimation of the annualized event rate. As such, supportive data presentations of cumulative exposure and enrolment will be considered when making decisions on changes to the number of participants required to meet the expected 350 first severe exacerbation events.

Any changes to the number of patients randomized following the sample size reassessment will be documented in a protocol amendment.

12. CHANGES FROM THE PROTOCOL-SPECIFIED ANALYSIS

1) The multiple testing strategy has been updated to include repeats of the primary and secondary analyses in an ≥18 years sub-population of the full analysis set. Note: as of SAP V1.0, this is a change from the protocol-specified analyses. However, a protocol amendment is planned to detail this change. For clarity, the following text has been added to the SAP with respect to this change:
    a. Clarified the additional objectives and endpoints in section 2.1
    b. The description of the sub population full analysis set (≥18 years) has been defined in section 5.3
    c. Repeats of all primary and secondary analyses are to be performed on this sub-population of the full analysis set (≥18 years). Clarification on which age group will be used for all analyses on the full analysis set has been added to the relevant sub-section within section 9
    d. The multiple testing strategy has been updated to include the repeat primary and secondary analyses on the full analysis set (≥18 years) in section 8.3.

13. REFERENCES

1. Jackson D., White I. R., Seaman S., Evans H., Baisley K., and Carpenter J. (2014), Relaxing the independent censoring assumption in the Cox proportional hazards model using multiple imputation, *Statist. Med.,* 27, 4681–4694. DOI: 10.1002/sim.6274

2. Rubin DB. Multiple Imputation for Nonresponse in Surveys. Wiley: New York, 1987

3. Bender, R., Augustin, T. and Blettner, M. (2005), Generating survival times to simulate Cox proportional hazards models. Statist. Med., 24: 1713-1723. doi:10.1002/sim.2059

14. APPENDIX A

14.1 LIST OF TABLES, LISTINGS AND FIGURES

The list of tables, listings of figures are provided in a separate supporting mock shells document.

15. APPENDIX B

15.1 SCHEDULE OF ASSESSMENTS

Procedure	Screening	Randomization [a]	IMP Delivery[b] (3-5 days)	IMP (treatment) period						End of Study (EOS)[c]	Early Study IMP/ Discontinuation [d]	Unscheduled [e]	Details in CSP Section or Appendix
Days/Weeks	-28 to 0	0		Day 1	W4	W16	W28	W40		W52			
Virtual Visit number	V1	V2		V3 Treatment Initiation	V4	V5	V6	V7		V8			
Visit interval	-28 to 0	0		up to14 days after V2	±7 days								
Clinical assessments													
Informed consent/assent	X												Section 5.1
Inclusion/exclusion criteria[f]	X												Section 5.1 and Section 5.2
Demography	X												
Medical and surgical history	X												
Asthma history	X												
Urine pregnancy test[g] (WOCBP only)		X								X	X		
Randomization		X											

Procedure	Screening	Randomization [a]	IMP Delivery[b] (3-5 days)	IMP (treatment) period						End of Study (EOS)[c]	Early Study IMP/ Discontinuation [d]	Unscheduled [e]	Details in CSP Section or Appendix
Days/Weeks	-28 to 0	0		Day 1	W4	W16	W28	W40		W52			
Virtual Visit number	V1	V2		V3 Treatment Initiation	V4	V5	V6	V7		V8			
Visit interval	-28 to 0	0		up to14 days after V2	±7 days								
Efficacy assessments													
Severe asthma exacerbations[h]		X		X	X	X	X	X		X	X	X	Section 8.2.1
Healthcare resource utilization		X			X	X	X	X		X	X	X	Section 8.9
Notification to participant's smartphone to assess changes in asthma management over previous two weeks period[i]				↕									
AIRQ[j]		X				X	X	X		X	X	X	Section 8.2.2.1
EQ-5D-5L		X			X		X			X	X	X	Section 8.2.2.2
Safety assessments													
AEs and SAEs[k]	X	X	□═══						═══□		X	X	Section 8.4
Prior and Concomitant medication	X	X	□═══						═══□		X	X	
Study IMP													
IMP dispatched[l]		X		(X)	(X)	(X)							
MDI demonstration/training				X									
IMP first dose[m]				X									
IMP treatment check[n]				X	X	X	X	X					Section 6.4
IMP Return[o]										X	X		

Abbreviations: AE: Adverse event; AIRQ=Asthma Impairment and Risk Questionnaire; CSP: Clinical study protocol; EOS=End of Study; EQ-5D-5L=EuroQol-5 Dimension 5 Level; IMP=investigational medicinal product; MDI; Metered-dose inhaler SAE=Serious adverse event; SoA: Schedule of Activities; V; Visit; WOCBP=Females of Child-bearing Potential

[a] *Enrollment, screening assessments and randomization may occur on the same day or on separate days within a 28-day period.*

[b] *After randomization, the IMP will be shipped to the participant (expected to be within 3-5 days)*

[c] *When reaching the Primary Completion Date (ie, when 350 events have been reached), participants who have had at least 12 week's treatment but not completed the entire 52 weeks treatment period, will have their end of study visit scheduled within 4 weeks.*

[d] *Participants who prematurely withdraw from the study will undergo an early study IMP/discontinuation visit. Participants who do not withdraw consent for follow-up will perform the assessments at the scheduled visit intervals or just at the EOS visit depending on the participant's preference (see Section 7.1). The bi-weekly notifications upon withdrawal will be received via [redacted] app depending on the participant's preference (see Section 7.1)*

[e] *Telephone/televisit contact to be performed if confirmation received from the participants through the bi-weekly messages within the [redacted] app that they had sought medical help as a result of their asthma worsening or had any asthma-related unscheduled healthcare contacts/visits. If the participant withdraws from study IMP but remains in the study, they may choose whether to continue to receive the bi-weekly messages from the [redacted] app. Visits performed in clinic are acceptable.*

[f] *Recheck eligibility status before randomization and/or 1st dose of study IMP*

[g] *Performed prior to randomization and at EOS/Early Study IMP Discontinuation. WOCBP must provide a negative test before randomization*

[h] *Specific inquiry and documentation available for assessment of severe asthma exacerbations. Participants are to be reminded not to take any albuterol product except for the IMP. Information about absence from school/work in connection to the asthma will be collected*

[i] *Bi-Weekly, participants will receive a notification via [redacted] app to inquire as to whether they have potentially had needed to seek medical help as a result of their asthma worsening or any asthma-related unscheduled healthcare related contacts/ visits.*

[j] *AIRQ version with 12-month recall period will be used at Screening, Randomization and EOS visits. AIRQ version with a 3-month recall will be used at all other visits. AIRQ is performed at both screening and randomization, however, where screening and randomization is performed on the same day, the AIRQ questionnaire will only be completed once.*

[k] *AEs & SAEs collected from time of eConsent.*

[l] *IMP will be dispatched at randomization (V2) and will only be dispatched between V3and V8 if required*

[m] *Participants will be trained on the correct MDI technique and management of the device and sensors in accordance with the IFU before administering the first dose at V3. The first dose will be taken during the telemedicine visit to enable site personnel to assess MDI inhalation technique and ensure the sensor is attached appropriately as part of participant training.*

[n] *At each visit site staff to check if participants have sufficient supplies and any concerns with equipment use (including inhalers and the digital sensor attachments)*

[o] *Pre-paid packaging for the return of all IMP will be provided to participants. At the end of study/at early discontinuation, participants will place all remaining used and unused IMP in the pre-paid packaging and return to Sponsor.*

16. APPENDIX C

16.1 USA VALUE SET

```
Computing EQ-5D-5L index values with SAS using the United States (US) Pickard value set
Version 1.2 (Updated 31/01/2022)

The variables for the 5 dimensions of the EQ-5D-5L descriptive system should be named
'mobility', 'selfcare', 'activity', 'pain', and 'anxiety'.
If they are given different names the syntax code below will not work properly. The 5
variables should contain the values for the different dimensions
in the EQ-5D health profile (i.e. 1, 2, 3, 4 or 5). The variable 'EQindex' contains the
values of the
EQ-5D-5L index values on the basis of the US set of weights.

You can copy and paste the syntax below directly into a SAS syntax window.

*****************************************************************
*SAS syntax code for the computation of index*
*values with the US TTO value set*
*****************************************************************

data WORK.CAT;
set WORK.CAT;


if mobility eq 1 then disut_mo=0;
else if mobility eq 2 then disut_mo=0.096;
else if mobility eq 3 then disut_mo=0.122;
else if mobility eq 4 then disut_mo=0.237;
else if mobility eq 5 then disut_mo=0.322;

if selfcare eq 1 then disut_sc=0;
else if selfcare eq 2 then disut_sc=0.089;
else if selfcare eq 3 then disut_sc=0.107;
else if selfcare eq 4 then disut_sc=0.220;
else if selfcare eq 5 then disut_sc=0.261;

if activity eq 1 then disut_ua=0;
else if activity eq 2 then disut_ua=0.068;
else if activity eq 3 then disut_ua=0.101;
else if activity eq 4 then disut_ua=0.255;
else if activity eq 5 then disut_ua=0.255;

if pain  eq 1 then disut_pd=0;
else if pain  eq 2 then disut_pd=0.060;
else if pain  eq 3 then disut_pd=0.098;
else if pain  eq 4 then disut_pd=0.318;
else if pain  eq 5 then disut_pd=0.414;

if anxiety eq 1 then disut_ad=0;
else if anxiety eq 2 then disut_ad=0.057;
else if anxiety eq 3 then disut_ad=0.123;
else if anxiety eq 4 then disut_ad=0.299;
else if anxiety eq 5 then disut_ad=0.321;

disut_total=disut_mo+disut_sc+disut_ua+disut_pd+disut_ad;
EQindex=1-disut_total;
run;
```

https://euroqol.org/wp-content/uploads/2020/12/US_valueset_SAS.txt

17. APPENDIX D

17.1 LIST OF PREFERRED TERMS INCLUDED FOR ASSESSMENT OF LOCAL AND SYSTEMIC STEROID CLASS EFFECTS, POTENTIALLY ASSOCIATED WITH INHALED CORTICOSTEROIDS

Location	Medical Concept	MedDRA (Version 24) Preferred Term
Local steroid effects	Candidiasis	Candida infection
		Oral candidiasis
		Oropharyngeal candidiasis
		Oesophageal candidiasis
		Oral fungal infection
		Infection
	Voice effects	Aphonia
		Dysphonia
	Bronchospasm	Paradoxical bronchospasm
Systemic steroid effects	Adrenal suppression	Addison´s disease
		Adrenal insufficiency
		Adrenal suppression
		Adrenocortical insufficiency acute
		Blood cortisol decreased
		Cortisol free urine decreased
		Secondary adrenocortical insufficiency
		Urine cortisol/creatinine ratio decreased
	Cortisol level impact	Hypercorticism
Systemic steroid effects	Diabetes control	Diabetes mellitus
		Diabetes mellitus inadequate control
		Diabetic metabolic decompensation
		Type 2 diabetes mellitus
		Hyperglycaemia
		Blood glucose increased
		Glucose tolerance impaired
Systemic steroid effects	Fractures	Ankle fracture
		Compression fracture
		Femoral neck fracture
		Femur fracture
		Fibula fracture

Location	Medical Concept	MedDRA (Version 24) Preferred Term
		Foot fracture
		Fracture
		Hand fracture
		Hip fracture
		Osteoporotic fracture
		Radius fracture
		Rib fracture
		Scapula fracture
		Spinal compression fracture
		Spinal fracture
		Stress fracture
		Tibia fracture
		Ulna fracture
		Wrist fracture
		Cervical vertebral fracture
		Lumbar vertebral fracture
		Thoracic vertebral fracture
		Upper limb fracture
		Lower limb fracture
Systemic steroid effects	Growth retardation	Growth retardation
		Body height below normal
		Body height decreased
Systemic steroid effects	Metabolic bone effects	Osteoporosis
		Osteoporosis postmenopausal
		Osteopaenia
		Bone density decreased
		Osteocalcin decreased
Systemic steroid effects	Ocular effects	Cataract
		Cataract cortical
		Cataract diabetic
		Cataract nuclear
		Cataract subcapsular
		Glaucoma
		Intraocular pressure increased

Location	Medical Concept	MedDRA (Version 24) Preferred Term
		Lenticular opacities
		Ocular hypertension
		Glaucomatous optic disc atrophy
		Intraocular pressure test abnormal
Systemic steroid effects	Psychiatric effects	Depressed mood
		Adjustment disorder with depressed mood
		Depressive symptom
		Depression
		Mixed anxiety and depressive disorder
		Dysphoria
		Euphoric mood
		Insomnia
		Initial insomnia
		Psychotic disorder
		Restlessness
Systemic steroid effects	Skin effects	Contusion
		Ecchymosis
		Increased tendency to bruise
		Petechiae
		Purpura
		Skin atrophy
Systemic steroid effects	Taste effects	Dysgeusia