**Bond Avillion 2 Development LP**

| **Clinical Study Protocol** | |
|---|---|
| Drug Substance | Budesonide/Albuterol (BDA) |
| Study Code | AV007 |
| Version | Version 3.0, Final |
| Date | 05 Jan 2024 |

# A Multicenter, 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)

**Sponsor:**
Bond Avillion 2 Development LP
Sarnia House, Le Truchot, St Peter Port
Guernsey, GY1 1GR

NCT05505734

# VERSION HISTORY

| |
|---|
| **Version 3.0, Final 05 Jan 2024** |
| Global Protocol Amendment 2 |
| **Version 2.0, Final 03 Mar 2023** |
| Global Protocol Amendment 1 |
| **Version Final 1.0, 03 Jun 2022** |
| Initial creation |

**Protocol Number:** AV007

**Amendment Number:** 2

**Study Investigational Medicinal Products (IMP):** PT027 (budesonide/albuterol 80/90 µg metered-dose inhaler) (BDA MDI); PT007 (albuterol 90 µg metered-dose inhaler) (AS MDI)

**Study Phase:** Phase IIIb

**Short Title:** A comparison of PT027 vs PT007 used as needed in participants with Asthma.

**Study Physician Name and Contact Information will be provided separately.**

**International Coordinating Investigator**

Craig LaForce, MD
North Carolina Clinical Research
2615 Lake Drive, Suite 301
Raleigh, NC 27607
United States

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# 1 PROTOCOL SUMMARY

## 1.1 Synopsis

**Protocol Title: A Multicenter, 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)**

**Short Title:**

A comparison of PT027 vs PT007 used as needed in participants with Asthma.

**Rationale:**

The purpose of this Phase IIIb study is to evaluate the efficacy and safety of budesonide/albuterol 160/180 µg metered-dose inhaler [MDI]; PT027; BDA MDI, used as needed in participants with asthma previously receiving short-acting $\beta_2$-agonists (SABA) alone or SABA as needed plus on a background of either low-dose inhaled corticosteroids (ICS) or a leukotriene receptor antagonist (LTRA). The rationale for BDA MDI to be used as a rescue therapy is based on the provision of rapid relief of asthma symptoms by albuterol while simultaneously treating underlying inflammation with budesonide. Use of BDA MDI will be driven by day-to-day symptom levels and will follow a patient's natural behavior to treat symptoms 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 will evaluate the efficacy of as-needed BDA MDI (used at a dose of budesonide/albuterol 160/180 µg) in reducing the risk of severe asthma exacerbations compared with AS MDI as needed (used at a dose of albuterol 180 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 will also investigate the effect of BDA MDI on the rate of severe asthma exacerbations, total annualized systemic corticosteroid (SCS) 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 will be fully decentralized for all participants, with no planned in-clinic visits, ie, all study visits will be conducted virtually. By employing a decentralized study delivery model, it is anticipated to reach a broader population of asthmatic patients who typically might not consider participating in clinical trials due to travel or time commitments.

## Objectives and Endpoints

| Objectives | Estimands* descriptions/Endpoints |
|---|---|
| Primary | |
| *To evaluate the efficacy of as-needed BDA MDI compared with as-needed AS MDI on the risk of severe asthma exacerbations, participants ≥12 years* | • *Treatment: Randomized Investigational Medicinal Product (IMP) alone or usual Maintenance therapy + randomized IMP*<br>• *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*<br>• *Endpoint: time to first severe asthma exacerbation*<br>• *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.*<br>• *Summary measure: Adjusted hazard ratio* |
| Secondary | |
| *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* | • *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*<br>• *Endpoint: time to first severe asthma exacerbation*<br>• *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*<br>• *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*<br>• *Endpoint: time to first severe asthma exacerbation*<br>• *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.*<br>• *Summary measure: Adjusted hazard ratio* |

| **Objectives** | **Estimands* descriptions/Endpoints** |
|---|---|
| *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*<br>• *Endpoint: time to first severe asthma exacerbation*<br>• *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*<br>• *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*<br>• *Endpoint: annualized rate of severe asthma exacerbations*<br>• *Summary measure: Adjusted rate ratio*<br>• 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*<br>• *Endpoint: annualized rate of severe asthma exacerbations*<br>• *Summary measure: Adjusted rate ratio*<br>• 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*<br>• *Endpoint: total amount (mg/year) per participant of systemic glucocorticoid exposure*<br>• *Summary measure: Difference in unadjusted treatment means*<br>• Treatment and strategy for IEs are the same as for the primary objective |
| | • *Endpoint: total days of systemic glucocorticoid exposure*<br>• *Summary measure: Difference in unadjusted treatment means* |

| Objectives | Estimands* descriptions/Endpoints |
|---|---|
| | • 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 exposure associated with asthma management, 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*<br>• *Endpoint: total amount (mg/year) per participant of systemic glucocorticoid exposure*<br>• *Summary measure: Difference in unadjusted treatment means*<br>• 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*<br>• *Endpoint: total days of systemic glucocorticoid exposure*<br>• *Summary measure: Difference in unadjusted treatment means*<br>• Treatment and strategy for IEs are the same as for the primary objective |
| Safety | |
| *Safety Objective: 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:*<br>• *Adverse Events (AEs)*<br>• *Serious Adverse Events (SAEs)* |

* See Section 9.4, Statistical Analyses, for additional details.
AE: Adverse events; AS: Albuterol Sulfate; BDA: Budesonide/albuterol; ICS: Inhaled corticosteroid; IE: Intercurrent event; IMP: Investigational Medicinal Product; LTRA: Leukotriene receptor agonist; MDI Metered-dose inhaler; SABA: short-acting β2-agonists; SAE: Serious adverse event.

For Tertiary/Exploratory objectives and estimand descriptions/endpoints, see Section 3 of the protocol.

## Overall Design

This is a Phase IIIb, US, multicenter, 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 up to 12 months. 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 for a SABA inhaler or ≥1 prescription for a SABA inhaler plus ≥1 prescription for a low-dose ICS inhaler or a LTRA in the 12 months prior to enrollment. 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.

In order to achieve 350 first severe asthma exacerbation events, approximately 1910 participants from 40 to 50 centers located in the US will be randomized 1:1 to receive one of the following two treatments, to be used as needed:

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

Participants will be stratified by pre-study asthma medication: SABA only, low-dose ICS + SABA, and LTRA + SABA and number of prior severe exacerbations (0, ≥1) in the 12 months prior to Screening visit.

The study will be double-blind with BDA and AS MDIs being identical in appearance. Participants will 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. Refer to Section 8.8 for further information on [redacted] sensor and app.

The study will employ a decentralized design with all planned participant assessment visits being conducted virtually ie, no in-clinic visits.

**Disclosure Statement**: This is a parallel-group treatment study with 2 arms that are participant and investigator blinded.

**Number of Participants:**

In order to achieve 350 first severe asthma exacerbations events, it is estimated that approximately 2122 participants will be enrolled/screened to ensure 1910 randomly assigned to study IMP, ie, approximately a 10% screen fail rate. If the observed first severe exacerbation 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. If the observed first exacerbation rate is lower than predicted, the number of

participants randomized may be increased to approximately 2500. Any assessment of accumulating data will be performed on pooled, blinded data. The timing and procedure for blinded sample size assessment will be documented in the statistical analysis plan (SAP).

**Note**: "Enrolled" means a participant, or their legally acceptable representative's, agreement to participate in a clinical study following completion of the electronic informed consent form (eICF) process. Potential participants who are screened for the purpose of determining eligibility for the study but are not randomly assigned/assigned in the study, are considered "screen failures", unless otherwise specified by the protocol.

**Investigational Medicinal Product (IMP) Groups and Duration:**

Participants who are not females of child-bearing potential and who meet all the inclusion criteria and none of the exclusion criteria at screening may be screened and randomized at the same visit or on separate visits. For females of child-bearing potential, following the initial screening assessment, a urine pregnancy test with high sensitivity is required. Female participants of child-bearing potential will only be randomized following confirmation of a negative urine pregnancy test. Therefore, the enrollment, screening assessments and randomization may occur on separate days within a 28-day period, if required.

Study-related supplies will be shipped directly to the participant. The randomization step will trigger a shipment of IMP and IMP sensors. As IMP is being sent direct to the participant's home, the Treatment Initiation visit (Visit 3) will occur once the participant is in receipt of the study medication (expected to be within 7 days following randomization). A total of 2 sensors will be sent to allow more than 1 inhaler to be used at the same time (eg, stored in different locations). Training on how to use the study inhaler and inhaler sensor attachment will be provided at the Treatment Initiation visit (Visit 3) with additional training materials available.

Following treatment initiation, the treatment period for any individual will be for a maximum of 52 weeks but may be shortened to a minimum of 12 weeks, depending on when a participant is randomized into the study and when the required number of first severe asthma exacerbations events is reached (defined as the Primary Completion Date [PCD]). Subsequent visits will be performed after 4 weeks (Week 4) and then at 12-weekly intervals (Weeks 16, 28, 40 and 52) or until the PCD has been reached. Providing participants have received a minimum of 12 week's treatment, an end of study (EOS) treatment visit will scheduled within 4 weeks of the PCD. Between scheduled visits, participants will receive a message via a smartphone application ([redacted] app) bi-weekly to inquire as to whether they have needed to seek medical help as a result of their asthma worsening or any asthma-related unscheduled healthcare related contacts/visits.

**Data Monitoring Committee**

An independent, external Data Monitoring Committee (DMC) will be set up to review safety

data at three time points during the study. At a single time point (Interim Analysis), DMC will review the primary efficacy endpoint and the first secondary endpoint to determine stopping early for overwhelming efficacy, see Section 9.6. Further details of this planned review and the experts involved will be covered in a separate charter.

**Statistical Methods**

Primary Efficacy Analysis

The primary endpoint is time to first severe asthma exacerbation and is defined as the length in days from start of the IMP period until the first date when the event occurs, up to end of the study. The primary estimand will adopt a While on Treatment strategy in the Full analysis set (FAS), in which participants will be censored if they have not experienced a severe exacerbation event prior to an intercurrent event (IE).

The primary analysis will be based on a two-sided hypothesis testing approach. The statistical null hypothesis for the primary efficacy summary measure is that the adjusted hazard ratio for the primary treatment comparison is equal to 1 versus the alternative hypothesis that it is not equal to 1.

- The time to first severe asthma exacerbation from the start of the IMP period up to end of treatment will be analyzed using a Cox proportional hazards regression model. Treatment comparisons will be performed using a model including treatment, pre-study asthma therapy (SABA only, low-dose ICS + SABA, LTRA + SABA) and the number of prior severe exacerbations (0, ≥1) in the 12 months prior to Screening visit. The estimated adjusted hazard ratio for the primary treatment comparison will be displayed along with the associated Wald two-sided 95% confidence interval and p-value.

The key secondary endpoint will be the time to first severe exacerbation based on the estimand utilizing a Treatment Policy strategy.

Sample Size Estimate

In order 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, and LTRA +SABA and number of 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 secondary endpoint time to first severe asthma exacerbation targeting the estimand utilizing a Treatment Policy strategy.

The primary endpoint of time to first severe exacerbation targeting the estimand adopting a While on Treatment strategy assumes a 30% reduction in the risk of first severe exacerbation with BDA MDI versus AS MDI and is supported by results from the MANDALA study where the reduction in the rate of severe asthma exacerbations was 27% 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 90.8% power, with a 2-sided significance of 5%.

For the secondary endpoint of time to first severe asthma exacerbation targeting an estimand utilizing a 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 severe exacerbation with BDA MDI compared to AS MDI and a 1 year first severe exacerbation event rate of 21% in the AS MDI arm, 350 first severe exacerbation events are required to achieve 85% power, with a 2-sided significance of 5%.

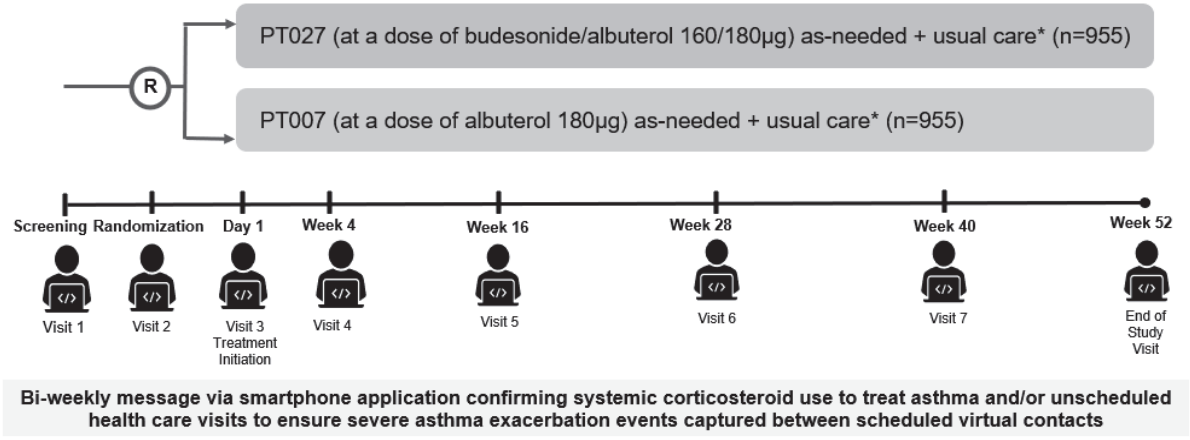
The estimated total number of participants to be randomized to treatment is 1910 to achieve the overall target number of 350 events. However, if during the study the observed first severe exacerbation rate is higher than expected then the required number of events may be met with less participants and recruitment will be stopped prior to reaching 1910 participants randomized. Similarly, if during the study the observed blinded first exacerbation rate is lower than predicted, the number of participants randomized may be increased to approximately 2500 to ensure the required number of first severe exacerbations is achieved. Any assessment of accumulating data will be performed on pooled, blinded data. The timing and procedure for blinded sample size assessment will be documented in the SAP.

An unblinded interim analysis for efficacy is planned once 50% of the events have been observed (172 events total), based on the primary analysis of the primary endpoint. Alpha spending will be governed through the O'Brien-Fleming approach, where 0.003 will be spent at the interim to assess significance. If efficacy cannot be established at the 50% of target number of event threshold, the study will continue until 350 total first events are observed or approximately 2500 participants have been randomized and completed treatment and assessed at alpha=0.049. If more than 172 events are available, the alpha will be adjusted accordingly (DeMets, 1994). The interim analysis, with unblinding firewalls, will be addressed in the Data Review Committee charter and administered by a separate unblinded analysis team.

If the study completes, ie, all participants are treated for one year, without reaching the required number of events then all planned analyses will be conducted with the number of events that have occurred as of completion of the study.

## 1.2 Schema

**Figure 1 Study Design**




**Note: All visits conducted remotely/virtually with no in-person clinic visits**

***Used alone for those entering the study receiving SABA as needed or on top of their usual maintenance therapy for those entering the study receiving low-dose ICS or LTRA**

Abbreviations: R = randomization; ICS: Inhaled corticosteroids; LTRA: Leukotriene receptor agonist; SABA: Short -acting $\beta_2$ agonist

## 1.3 Schedule of Activities

**Table 1 Schedule of Activities**

| Procedure | Screening[q] | Randomization[a] | IMP Delivery[b] (7 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[p] | 0 | | up to14 days after V2 | ±7 days | | | | | | | |
| **Clinical assessments** | | | | | | | | | | | | |
| Informed consent/assent | X | | | | | | | | | | | Section 5.1 |
| Inclusion/exclusion criteria[f] | X | X[f] | | | | | | | | | | Section 5.1 and Section 5.2 |
| Demography | X | | | | | | | | | | | |
| Medical and surgical history, including any smoking history | X | | | | | | | | | | | |
| Asthma history | X | | | | | | | | | | | |
| Urine pregnancy test[g] (WOCBP only) | | X | | | | | | | X | X | | |
| Randomization | | X | | | | | | | | | | |

| Procedure | Screening[q] | Randomization[a] | IMP Delivery[b] (7 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[p] | 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 | 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 | 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) | (X) | | | | |
| MDI demonstration/training | | | | X | | | | | | | | |
| IMP first dose[m] | | | | X | | | | | | | | |
| IMP treatment check[n] | | | | X | X | X | X | X | | | | Section 6.4 |

| Procedure | Screening[q] | Randomization[a] | IMP Delivery[b] (7 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[p] | 0 | | up to14 days after V2 | ±7 days | | | | | | | |
| 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 7 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 EOS 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 before IMP is dispensed.*
[g] *Performed prior to randomization and at EOS or 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 had 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 or Early Study/ IMP Discontinuation visits. AIRQ version with a 3-month recall will be used at other visits as indicated above. AIRQ is performed at both screening/re-screen and randomization, however, where screening/re-screen 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 EOS or at early study/IMP discontinuation, participants will place all remaining used and unused IMP in the pre-paid packaging and return to Sponsor.*
*[p] The interval between screening and randomization may be up to 28 days. The screening period may be extended to collect documentation to confirm the asthma diagnosis only in the event that information has not been received within 28 days of consent. The screening period cannot be extended >56 days for any reason. See Section 5.1 for details.*
*[q] Participants who initially screen failed due to failure to receive confirmatory medical records within the original 28-day screening period, use of corticosteroids within 6 weeks of Screening Visit 1 or who were hospitalized for asthma within 3 months of Screening Visit 1 may re-screen once. Participants who re-screen must complete all Visit 1 procedures during re-screening and satisfy eligibility criteria before being permitted to randomize into the study. Participants who fail to satisfy eligibility criteria during re-screening cannot be re-screened for a second time.*

# 2 INTRODUCTION

Bond Avillion 2 Development LP (Sponsor) is studying BDA MDI (budesonide/albuterol) pressurized inhalation suspension product in patients with asthma, in partnership with AstraZeneca. BDA MDI was approved by the Food and Drug Administration on 10 Jan 2023 for the as-needed treatment or prevention of bronchoconstriction and to reduce the risk of exacerbations in patients with asthma 18 years of age and older (NDA 214070); AstraZeneca Pharmaceuticals LP is the New Drug Application (NDA) holder. Please refer to the current Investigator's Brochure (IB) for additional information on BDA MDI and the AS MDI (albuterol) pressurized inhalation suspension product.

## 2.1 Study Rationale

The aim of this study is to evaluate the efficacy and safety of BDA MDI, used as needed, in participants with asthma previously receiving SABA alone or SABA as needed plus on a background of either low-dose ICS or LTRA. The rationale for BDA MDI to be used as a rescue therapy is based on the provision of rapid relief of asthma symptoms by albuterol while simultaneously treating underlying inflammation with budesonide. Use of BDA MDI will be driven by day-to-day symptom levels and will follow a patient's natural behavior to treat symptoms when they arise and thus treatment for inflammation will be provided when needed most. Safety and efficacy of BDA MDI will be compared with AS MDI because albuterol is the standard of care rescue therapy in the US.

The study will evaluate the efficacy of as-needed BDA MDI (used at a dose of budesonide/albuterol 160/180 µg) in reducing the risk of severe asthma exacerbations (Section 8.2.1.3), compared with AS MDI as needed (used at a dose of albuterol 180 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 will also investigate the effect of BDA MDI on the rate of severe asthma exacerbations, total annualized SCS use, asthma-related healthcare resource utilization, asthma control and health-related quality-of-life. Safety will be assessed through the collection of AEs and SAEs. By employing a decentralized study delivery model, with all visits conducted virtually, it is anticipated to reach a broader population of asthmatic patients who typically might not consider participating in clinical trials due to travel or time commitments.

## 2.2 Background

Asthma is a common, chronic disease; it is estimated that globally over 300 million people are living with asthma (Dharmage, 2019). With an estimated prevalence of 7.8%, approximately 25 million individuals in the US were living with asthma in 2019 (CDC, 2022). Despite recent advances in our understanding, the frequency of emergency department visits due to asthma has remained relatively unchanged in the last 15 years and in 2018, there were more than 1.6 million emergency department visits due to asthma (CDC, 2022), indicating there

continues to be substantial unmet patient needs for improved treatment alternatives to reduce asthma exacerbations.

Asthma is an unpredictable and heterogeneous disease with a variable clinical course driven by airway inflammation, leading to bronchial hyperreactivity and corresponding symptoms (GINA, 2022). Patients tend to focus on immediate symptom relief leading to a reliance on rescue medication, such as albuterol, a short-acting β-agonist [SABA] (Partridge, 2006; Lugogo, 2019). Data from a US claims database from between 2010 and 2017 showed that in patients ≥12 years, 51% were receiving SABA only (IBM® Market Scan). SABAs induce smooth muscle airway relaxation and improve asthma symptoms short-term, but do not address underlying airway inflammation and exacerbation risk increases with increased SABA use (Lugogo, 2019). Preventing severe exacerbations is imperative as they pose a significant burden to patients and have potentially life-threatening consequences. Severe exacerbations require treatment with SCS; SCS address inflammation, but also increase risk of short- and long-term adverse reactions. Reliance on SABA is consistent across all asthma severities and age groups and regardless of maintenance therapy (Lugogo, 2020).

Asthma exacerbations typically follow exposure to environmental triggers (Lambrecht, 2012; Lambrecht, 2015; Yawn, 2008). Increases in airway inflammation contribute to worsening of asthma symptoms, prompting patients to use their rescue medication. Inhaled corticosteroids (ICS), such as budesonide, treat inflammation and there is evidence of a 'window of opportunity' during periods of worsening symptoms in which the timely administration of ICS can prevent symptoms developing into an exacerbation (Tattersfield, 1999; Balter, 2008; Larsson, 2020; Thomas, 2015).

The clinical efficacy of concomitant anti-inflammatory ICS and rapid-acting bronchodilators has been demonstrated in patients with moderate to severe asthma using ICS-formoterol as rescue on top of ICS-long-acting beta-2-agonist (LABA) maintenance. This combination reduced the relative risk of severe exacerbations by more than 30% compared with patients using ICS-LABA as maintenance and SABA as rescue (Kuna, 2007; O'Byrne, 2005; Rabe, 2006; Bousquet, 2007). Data also show that in mild asthma, patients taking the fixed-dose combination of budesonide-formoterol as needed have greater protection from severe exacerbations versus those taking as-needed SABA alone, with no increase in adverse effects (Bateman, 2018; O'Byrne, 2018, Beasley, 2019).

These results are reflected in the 2022 Global Initiative for Asthma (GINA) report, where as-needed ICS-formoterol is the preferred (Track 1) rescue therapy at all treatment steps in patients 12 years of age and older, and also as an alternative option for patients aged 6 to11 years (GINA, 2022). The recently updated US National Asthma Education and Prevention Program (NAEPP) Expert Panel Report-4 (EPR-4; 2020) also recommends the use of concomitant ICS plus SABA as needed for patients 12 years and older with mild persistent

asthma.

BDA MDI is a fixed-dose combination product containing an ICS (budesonide) and a SABA (albuterol), two established asthma medications with well-known safety and efficacy profiles, in a novel Co-suspension Delivery Technology™ formulation. BDA MDI is being developed to provide a rescue alternative for the control of acute symptoms and to provide prevention against worsening of asthma symptoms and severe asthma exacerbations requiring systemic steroids or hospitalization in patients with asthma aged 4 years and older. BDA MDI is planned to be used as needed alone or on top of any regularly scheduled maintenance asthma therapy. BDA MDI would be the first fixed-dose rescue medication containing both albuterol and an ICS in the US, addressing the need to further reduce the risk of severe asthma exacerbations.

Results from the recently completed Phase III MANDALA study demonstrated a significant reduction in the risk of severe asthma exacerbations with BDA MDI compared with albuterol, both used as needed, in participants with moderate to severe asthma on a background of ICS containing maintenance therapy without an increase in ICS related AEs (Papi, 2022).

The current study will further evaluate the effect of BDA MDI on the reduction of exacerbation risk in participants with asthma using either no maintenance therapy or receiving either low-dose ICS or LTRA.

A detailed description of the chemistry, pharmacology, efficacy, and safety of BDA MDI is provided in the IB.

## 2.3 Benefit/Risk Assessment

More detailed information about the known and expected benefits and potential risks of BDA MDI may be found in the IB.

### 2.3.1 Risk Assessment

**Table 2 Risk Assessment**

| Risk Category | Potential risk of clinical significance | Summary of data/rationale for risk | Mitigation strategy |
|---|---|---|---|
| **Study IMP(s) BDA MDI** | • Increased local or systemic corticosteroid side-effects | • Participants using >12 inhalations daily may potentially be at an increased risk of local or systemic corticosteroids side effects including adrenal suppression and, in adolescent participants, growth retardation | • Participants instructed to take no more than 12 inhalations in a 24-hour period<br>• Investigators to assess overall inhaler usage to check for excessive use |
| **Study procedures** | • Fully decentralized study delivery model with no in-person contact with study participants | • Difficulty ensuring the participant has understood how to use the study inhaler and sensor attachment correctly | • Participants will be required to demonstrate correct inhaler technique during the telemedicine Treatment Initiation visit (Visit 3) and be required to watch a training video which demonstrates best practice |
| | | • Lack of engagement due to virtual visits<br>• Loss of data due to connection issues | • Initiatives to enhance the participant experience |
| | • Exclusion of participants due to the reliance on technology | • Digital exclusion for participants either due to age, socio-economic factors, or a dislike of technology | • Use of the participant's own smartphone.<br>• Ensuring the technology is simple to use<br>• Dedicated technical support desk |

BDA: Budesonide/albuterol; MDI: Metered-dose inhaler

### 2.3.2 Benefit Assessment

For participants randomized to BDA MDI, the combination of budesonide and albuterol may provide benefits to participants in terms of potential reduction in the risk of asthma exacerbation and improvement in the control of asthma symptoms beyond what is typically seen with albuterol alone. For those participants randomized to receive AS MDI, the benefit of the treatment is unchanged.

### 2.3.3 Overall Benefit: Risk Conclusion

Taking into account the measures to minimize risk to participants in this study, the potential risks identified in association with BDA MDI are justified by the anticipated benefits that may be afforded to participants with asthma.

# 3 OBJECTIVES AND ENDPOINTS

**Table 3 Objectives and Endpoints**

| Objectives | Estimand* description/Endpoints |
|---|---|
| Primary | |
| *To evaluate the efficacy of as-needed BDA MDI compared with as-needed AS MDI on the risk of severe asthma exacerbations, participants ≥12 years* | • *Treatment: Randomized IMP alone or usual Maintenance therapy + randomized IMP*<br>• *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*<br>• *Endpoint: time to first severe asthma exacerbation*<br>• *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.*<br>• *Summary measure: Adjusted hazard ratio* |
| Secondary | |
| *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* | • *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*<br>• *Endpoint: time to first severe asthma exacerbation*<br>• *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.*<br>• *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*<br>• *Endpoint: time to first severe asthma exacerbation*<br>• *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.*<br>• *Summary measure: Adjusted hazard ratio* |

| **Objectives** | **Estimand* description/Endpoints** |
|---|---|
| *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*<br>• *Endpoint: time to first severe asthma exacerbation*<br>• *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*<br>• *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*<br>• *Endpoint: annualized rate of severe asthma exacerbations*<br>• *Summary measure: Adjusted rate ratio*<br>• 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*<br>• *Endpoint: annualized rate of severe asthma exacerbations*<br>• *Summary measure: Adjusted rate ratio*<br>• 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*<br>• *Endpoint: total amount (mg/year) per participant of systemic glucocorticoid exposure*<br>• *Summary measure: Difference in unadjusted treatment means*<br>• Treatment and strategy for IEs are the same as for the primary objective |
| | • *Endpoint: total days of systemic glucocorticoid exposure*<br>• *Summary measure: Difference in unadjusted treatment means* |

| Objectives | Estimand* description/Endpoints |
|---|---|
| | • 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 ≥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*<br>• *Endpoint: total amount (mg/year) per participant of systemic glucocorticoid exposure*<br>• *Summary measure: Difference in unadjusted treatment means*<br>• 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*<br>• *Endpoint: total days of systemic glucocorticoid exposure*<br>• *Summary measure: Difference in unadjusted treatment means*<br>• Treatment and strategy for IEs are the same as for the primary objective |
| Safety | |
| *Safety Objective: 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:*<br>• *Adverse Events (AEs)*<br>• *Serious Adverse Events (SAEs)* |
| Tertiary/Exploratory | |
| *To investigate healthcare resource use (HCRU) and days off work or school associated with BDA MDI as needed compared with AS MDI as needed* | • *Number of asthma-related healthcare resource utilizations per patient year (including primary care, emergency room, hospital, ambulance, nurse and other healthcare contacts)*<br>• *Proportion of participants stepping up maintenance treatment*<br>• *Proportion of participants stepping down/stopping maintenance treatment*<br>• *Number of rescue medication actuations per day during the study period*<br>• *Absenteeism, number of days off work/school due to asthma per patient year* |
| *To evaluate the effect of BDA MDI as needed compared with AS MDI as needed on asthma control* | • *Change from baseline in AIRQ score at Week 16, Week 28, Week 40 and. Week 52* |

| Objectives | Estimand* description/Endpoints |
|---|---|
| *To evaluate the effect of BDA MDI as needed compared with AS MDI as needed on quality of life* | • *Change from baseline in EQ-5D-5L domain score, at Week 4, Week 28 and Week 52* |

* See Section 9.4, Statistical Analyses, for additional details.

AE: Adverse events; AIRQ: Asthma Impairment and Risk Questionnaire; AS: Albuterol Sulfate: BDA: Budesonide/albuterol; EQ-5D-5L: EuroQol-5 Dimension 5 Level; HCRU: Healthcare resource use; ICS: Inhaled corticosteroid; IE: Intercurrent event; IMP; Investigational Medicinal Product; LTRA: Leukotriene receptor agonist; MDI; Metered-dose inhaler; SABA: short-acting $\beta_2$-agonist; SAE: Serious adverse event.

# 4 STUDY DESIGN

## 4.1 Overall Design

This is a phase IIIb, US, multicenter, randomized, double-blind, parallel-group, event-driven, variable-length, decentralized study comparing the efficacy and safety of BDA MDI (used at a dose of budesonide/albuterol 160/180 µg) with AS MDI (used at a dose of albuterol 180 µg), both administered as needed for up to 12 months. 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 ≥2 prescriptions for either a SABA inhaler or ≥1 prescription for a SABA inhaler plus ≥1 prescription for an ICS inhaler or a LTRA in the 12 months prior to enrollment. 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 plus an AIRQ score of ≥2 at Screening.

In order to achieve 350 first severe asthma exacerbation events, approximately 2122 participants from around 40 to 50 centers located in the US will be screened to ensure 1910 participants randomized 1:1 to receive one of the following two treatment to be used as needed:

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

Participants will be stratified by pre-study asthma medication (SABA only, low-dose ICS + SABA and LTRA + SABA) and number of prior severe exacerbations (0, ≥1) in the 12 months prior to Screening visit.

Participants who are not females of child-bearing potential and who meet all the inclusion criteria and none of the exclusion criteria at screening may be screened and randomized (Visit 1 & Visit 2) at the same visit or on separate visits. For females of child-bearing potential, following the initial screening assessment, a urine pregnancy test, with high sensitivity is required. Female participants of child-bearing potential will only be eligible for randomization following confirmation that the urine pregnancy test is negative. The interval between screening and randomization may be up to 28 days. The screening period may be extended to collect documentation to confirm the asthma diagnosis only in the event that information has not been received within 28 days of consent. The screening period cannot be extended > 56 days for any reason. See Section 5.1 and Schedule of Activities (SoA) (Table 1)

for details.

The maximum daily dose of BDA or AS MDIs should not exceed 12 inhalations (6 doses) during one calendar day. Asthma maintenance medication (low-dose ICS or LTRA) will be continued throughout the study for participants enrolled on these medications.

All visits will be conducted virtually with study-related supplies shipped directly to the participant. The randomization step will trigger a shipment of the investigational medicinal product (IMP). As the IMP is being sent direct to the participant's home, the Treatment Initiation Visit (Visit 3) will occur once the participant is in receipt of the study medication (expected to be within 7 days following randomization). Participants will also receive a [redacted] sensor attachment (referred to as an MDI sensor, or sensor [see Section 8.8]) compatible with the study inhalers that will be used to capture each actuation of study inhaler use throughout the study. A total of 2 sensors will be sent to allow more than 1 inhaler to be used concurrently (eg, kept in different locations for convenience). Training on how to use the study inhaler and inhaler sensor will be provided at the Treatment Initiation visit (Visit 3) with additional training materials available.

Following treatment initiation, the treatment period for any individual will be for a maximum of 52 weeks and a minimum of 12 weeks depending on when a participant is randomized (Visit 2) into the study and when the required number of severe asthma exacerbations events is reached (defined as the Primary Completion Date [PCD]). Subsequent visits will be performed after 4 weeks (Week 4) and then at 12-weekly intervals (Weeks 16, 28, 40 and 52) or until the PCD has been reached. Providing participants have received a minimum 12 weeks treatment, the last EOS treatment visit will then be scheduled within 4 weeks of the PCD.

Between scheduled visits, participants will receive a message via a smartphone app ([redacted]) bi-weekly to inquire as to whether they have needed to seek medical help as a result of their asthma worsening or any asthma-related unscheduled healthcare related contacts/visits.

If the participant replies yes, then the Investigator/site staff will receive a notification to contact the participant to collect further information.

During any scheduled or unscheduled contact, the Investigator or site staff will review and query the participant regarding:

- AEs and SAEs
- Any documentation available suggesting or supporting of a severe asthma exacerbation including:
    - Any medical review (primary care/emergency room/hospitalization)

- Any SCS use
- Any changes in asthma medication
- The details of any asthma signs/symptoms experienced before the exacerbation

- Any change in concomitant medication(s)
- Any issues using the inhalers/digital sensors or the study portal/app
- Review number of doses/inhalers used and whether new study inhalers are required by the participant
- Healthcare utilization related to asthma and absences from work/school due to asthma

Between visits participants will be advised to contact the Investigator immediately if:

- They need to seek medical help for worsening asthma (eg, go to their General Practitioner, urgent care or hospital) or start SCS
- Their usual healthcare provider makes any changes to their asthma treatment
- They are concerned they will run out of IMP prior to the next study visit
- They are concerned the allocated inhalers and/or digital sensors are not operating correctly
- They wish to withdraw from the study

The study will be completed when the last participant has EOS or premature discontinuation (Early Study/ IMP Discontinuation) visit. Participants who discontinue IMP prematurely from the randomized treatment period will be encouraged to complete all scheduled study visits and assessments.

An Independent DMC is planned for this study to review unblinded data at the time of the Interim Analysis.

## 4.2 Scientific Rationale for Study Design

The Phase III MANDALA study including patients with moderate to severe asthma demonstrated that BDA MDI used as needed, significantly reduced the risk of a severe asthma exacerbation compared with albuterol alone by 27%.

Patients with asthma often rely on SABAs for symptom-relief. Studies with formoterol/budesonide (Bateman, 2018; Beasley, 2019; Hardy, 2019; O'Byrne, 2018;

O'Byrne, 2021) and with albuterol/beclomethasone (Papi, 2007) used as needed in patients who were previously receiving SABAs alone, or a SABA in addition to maintenance treatment with low-dose ICS demonstrated a reduction in exacerbation risk compared with SABA alone. In the proposed study, it is anticipated that BDA MDI used as needed, will reduce the risk of severe asthma exacerbations compared with albuterol as needed alone in patients previously treated with SABA as needed alone or with low-dose ICS or LTRA.

Exacerbations are a significant manifestation of asthma and they are physically threatening and emotionally significant for many patients (Sastre, 2016). The use of SCS to manage exacerbations is associated with undesirable long-term adverse effects, even when used relatively infrequently (Bleecker, 2020; Price, 2018) and the treatment of exacerbations has additional associated healthcare related costs. Time to first severe asthma exacerbation has therefore been chosen as the primary efficacy endpoint, to provide both a reliable and valid measurement of the treatment effect.

A decentralized study design, with all visits conducted virtually and no planned in-clinic visits, has been chosen as a means of widening study participation to patients who might otherwise not have considered enrolling into a clinical trial due to time or geographical constraints. By conducting all the visits virtually, it is hoped to allow participants to attend visits at their convenience, without the need to travel to sites.

All study-related supplies will be delivered directly to the participant's home. As the mono components for BDA MDI, ie, budesonide and albuterol, have been approved for many years and have been widely used in clinical practice for the management of asthma for over 40 years, the safety profiles for both drugs are well documented. The tolerability of BDA MDI was also demonstrated in the Phase III program. Furthermore, all participants will already have been using a SABA (likely to be albuterol) to be eligible for the study. Therefore, it is considered acceptable to deliver the study medication directly to the participant and for safety monitoring to be limited to the collection of AEs and SAEs.

### 4.2.1 Participant Input into Design

Interviews were conducted with 9 individuals with asthma, 4 with mild and 5 with moderate disease. Although the current study is targeted towards milder asthma, the feedback with regards to the decentralized study model was felt to be equally applicable from the participants with mild or moderate asthma.

Participants were enthusiastic about the decentralized model seeing it as way of improving convenience and increasing accessibility to trial participation, although they indicated that there may be some individuals who would prefer more in-person contact and less reliance on technology. Participants highlighted a number of areas of importance to themselves, including the ready availability of study-related information and the importance of data privacy.

Participants mentioned their concern about having their reliever/rescue inhaler replaced with study medication. The participant information will emphasize that the study inhaler will contain similar medication as their current reliever/rescue medication (ie, albuterol) or similar medication but with an additional medication (ie, budesonide) included. Participants also mentioned that visits should be described as 'virtual' rather than 'remote' or 'telemedicine' visits, the meaning of which were less intuitive. The term virtual (rather than remote) to describe the visits will be used in all participants facing material.

## 4.3 Justification for Dose

For this study, the term "dose" refers to 2 inhalations from the MDI.

The MANDALA Phase III study demonstrated that BDA MDI, taken as needed at the now approved dose of budesonide/albuterol 160/180 µg, was both efficacious and well-tolerated in a population with moderate to severe asthma. A reduction in the risk of severe asthma exacerbation and a reduction in total SCS exposure was shown with BDA MDI compared with albuterol 180 µg alone. There was no increase in the frequency of ICS related AEs compared with albuterol alone. The pattern of as-needed usage was similar between BDA MDI and AS MDI.

## 4.4 End of Study Definition

For the majority of participants, they will be considered to have completed the study if they have completed 52 weeks of treatment and the EOS visit. If the target number of the 350 required first severe asthma exacerbations is reached (PCD) before all participants have completed 52 weeks, then participants still in the trial after this timepoint will complete an EOS once they have received ≥12 weeks of treatment. The EOS visit should be completed within 4 weeks of the PCD, provided that the participant has received ≥12 weeks of treatment.

The study completion is defined as the date of the last visit of the last participant in the study.

# 5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

## 5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

**Age**

1. Participant must be ≥12 years of age, at the time of signing the electronic informed consent form (eICF).

   **Note:** For participants from 12 years of age to age of majority, their parents/legal guardian must provide signed consent, as appropriate, and participants will sign an assent form.

**Type of Participant and Disease Characteristics**

2. Diagnosis of asthma by a prescribing healthcare professional (HCP). The asthma diagnosis should be confirmed and documented; suitable documentation includes:
   a. Medical records or electronic medical records
   b. A letter from or documented telephone conversation with the treating HCP office
   c. Electronic medical (health) record (eg, MyChart) documentation of the presence of asthma in a written exchange between the participant and treating HCP
   d. Insurance forms or other equivalent documentation with asthma diagnosis code
   e. Other forms of documentation may be considered for suitability by the Medical Monitor.
3. Participants actively using SABA alone or SABA on a background of either low-dose ICS or LTRA with the following requirements:
   a) **SABA alone**: ≥2 prescriptions for a SABA inhaler in the past 12 months prior to enrollment.
   b) **SABA on a background of low-dose ICS monotherapy**: ≥1 prescription for a SABA inhaler and ≥1 prescription for a low-dose ICS inhaler in the 12 months prior to enrollment.

      **Note**: Refer to Appendix G for doses of ICS
   c) **SABA on a background of a LTRA:** ≥1 prescription for a SABA inhaler and ≥1 prescription for a LTRA in the 12 months prior to enrollment.

Participants must present their medication including any inhaler(s) during Screening Visit 1 and a picture of the medication(s) are required to be captured in the [redacted] platform. For participants on SABA alone, verbal confirmation by the participant that they have used at least one additional inhaler in the past 12 months will be considered acceptable.

4. Self-reported use of a SABA on ≥2 occasions, in response to symptoms (ie, not for exercise prophylaxis only), in the previous 2 weeks prior to enrollment, Visit 2.
5. An AIRQ score of ≥2 at Screening (Visit1/re-screen) and Randomization (Visit2) where applicable. Note, where screening Visit1/re-screen and randomization occur on the same day, AIRQ will only be completed once.

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6. Females of child-bearing potential must have a negative pregnancy test prior to randomization and agree to 1 of the following options to prevent pregnancy:

   (a) Practice complete abstinence defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. Periodic abstinence is not acceptable. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the participant. Therefore, complete abstinence is an acceptable method of contraception only if it is consistent with the preferred and usual lifestyle of the participant.

   (b) If a female of child-bearing potential agrees to prevent pregnancy by using 1 of the following effective methods of birth control from the date the eICF is signed until 2 weeks after the last dose of IMP is taken:

   i. Hormonal contraception (eg, oral contraceptive, contraceptive implant, or injectable hormonal contraceptive)

   ii. Single-barrier birth control (eg, male condom, cap, diaphragm, or sponge with spermicide)

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

   - Highly effective birth control methods include: sexual abstinence (periodic abstinence eg, calendar, ovulation, symptothermal, post-ovulation methods, declaration of abstinence for the duration of exposure to the study IMP and withdrawal are not acceptable methods of contraception), a vasectomized partner, Implanon®, bilateral tubal occlusion, intrauterine device/levonorgestrel

intrauterine system, Depo-Provera™ injections, oral contraceptive, and Evra Patch™, Xulane™, or NuvaRing®.

(c) Note: Females are considered to be of non child-bearing potential if they are physiologically incapable of becoming pregnant, including any female who is 2 years postmenopausal, or surgically sterile, defined as having a bilateral oophorectomy or bilateral salpingectomy, hysterectomy, tubal ligation, or other permanent birth control measures. For purposes of this protocol, menopausal females are defined as females that are amenorrheic for 12 consecutive months or more after cessation of all exogenous hormonal treatment prior to the planned date of randomization.

(d) Participants 12 years and over specific recommendations: if participant is female and has reached menarche or has reached Tanner stage 3 breast developments (even if not having reached menarche), the participant will be considered a female of child-bearing potential.

7. Male participants who are in heterosexual relationships must be surgically sterile or agree to use an effective method of contraception (condom) if the female partner does not use contraception from the date the eICF is signed until 2 weeks after their last dose. Male participants must not donate sperm during their study participation period.

**Informed Consent**

8. Capable of giving signed eICF (including assent with parental / legal guardian consent in 12 years of age to age of majority) as described in Appendix A which includes compliance with the requirements and restrictions listed in the eICF and in this protocol.

## 5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

**Medical Conditions**

1 Any evidence of significant lung disease other than asthma, such as chronic obstructive pulmonary disease, emphysema, idiopathic pulmonary fibrosis, sarcoidosis etc or any other significant disease (like malignancies or severe chronic diseases) that by Investigator judgment would interfere with the participant being able to comply with study procedures or complete the study.

2 Hospitalization due to asthma in the 3 months prior to enrollment or self-reported admission to the Intensive Care Unit with life-threatening asthma at any time in the past. Participants who were screen-failed due to hospitalization within the 3 months prior to enrollment may be re-screened once when the participant is more than 3 months post-hospitalization. Participants who reported an Intensive Care Unit admission with life threatening asthma may not be re-screened.

**Prior/Concomitant Therapy**

3 Self-reported use of inhaled LABA, theophylline, inhaled anticholinergic agent, cromone or medium/high dose ICS daily, as regular maintenance asthma therapy in the 3 months prior to enrollment.
**Note**: Refer to Appendix G for doses of ICS

4 Self-reported use of SCS for the treatment of asthma and any other condition in the 6 weeks prior to enrollment. Participants screen failed for this reason may be re-screened once, with their re-screening visit scheduled >6 weeks after last use of SCS.

5 Participants with a home supply of oral corticosteroids (OCS) to be used in the case of an asthma exacerbation or any other condition that could require a course of OCS, that are not willing to commit to the treating physician to stop using this medication for the duration of the study.

6 Receipt of any marketed (eg, omalizumab, mepolizumab, reslizumab, benralizumab, dupilumab, tezepelumab) or investigational biologic for the treatment of asthma at any time in the past.

7 Receipt of bronchothermoplasty.

8 Use of a SABA prophylactically primarily to prevent exercise induced bronchospasm and not to treat symptoms.

9 Currently receiving systemic treatment with potent cytochrome P3A4 inhibitors (eg, ketoconazole, itraconazole, and ritonavir).

**Prior/Concurrent Clinical Study Experience**

10 Participation in another clinical study with an IMP for any condition administered in the last 3 months or 5 half-lives prior to randomization, whichever is longer.

11 Participants with a known hypersensitivity to albuterol, budesonide or any of the excipients of the IMP.

**Other Exclusions**

12 Involvement in the planning and/or conduct of the study (applies to AstraZeneca, Bond Avillion 2, Avillion LLP, contract research organization (CRO)/third-party vendor staff and/or staff at the study site).

13 Judgment by the Investigator that the participant should not participate in the study if the participant is unlikely to comply with study procedures, restrictions, and requirements.

14 Previous screening enrollment or randomization in the present study, except where re-screening is permitted (see Section 5.5).

15 For females only– currently pregnant (confirmed with positive pregnancy test) or breast-feeding.

16 Participants without access to a smartphone or the internet.

17 Study Investigators, sub-Investigators, coordinators, and their employees or immediate family members, or employees of the Sponsor or any trial site.

18 Participants where a member of their household is currently enrolled in the study.

## 5.3 Diversity and Inclusion of Racial and Ethnic Populations in the Study

Asthma symptoms affect all races and ethnicities. Data collected from 2017 to 2019 indicate that within the racial, non-Hispanic populations of the US, the prevalence of asthma is 7.7% among Whites, 10.6% among Blacks, 3.8% among Asians, 10.7% among native populations (American Indians/Native Americans), and 12.6% among multiple races (identifies with more than one racial group). Prevalence among the ethnic Hispanic population is 6.6% (CDC, 2022). This decentralized study may have greater potential to recruit under-represented populations, which are often limited in enrollment to clinical studies, due in part to the lack of proximity to clinical sites and related transportation challenges. The recruitment strategy is a multi-media outreach campaign across the US including areas in which diverse populations can be found (eg, urban areas, border regions), and Investigators should make every effort to enroll a racially and ethnically diverse population in the study. The Sponsor plans to capture race and ethnicity in the study demographics and report results in the clinical study report, together with gender and age.

## 5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study IMP. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details (reason for screen failure), eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may only be re-screened once for specific reasons as specified within Section 5.1, Section 5.2 and Section 5.5.

## 5.5 Re-screening

Participants may be eligible to re-screen only under the following circumstances:

1. Participants originally consented under protocol version 1.0 who were unable to provide medical records satisfying asthma diagnosis or asthma medications within 28 days of Screening Visit 1 and were therefore screen-failed for this reason.

2. Participants who had been hospitalized due to asthma within 3 months of Screening Visit 1 may re-screen once they are outside the exclusionary window.
3. Participants who had received SCS within 6 weeks of Screening Visit 1 may re-screen once they are outside the exclusionary window.

Participants cannot re-screen for any other reason and can only re-screen once. All procedures at Visit 1 must be repeated and eligibility confirmed during re-screening.

# 6 STUDY INVESTIGATIONAL MEDICINAL PRODUCT

Study IMP is defined as any IMP(s), marketed product(s) or placebo intended to be administered to or medical device(s) utilized by a study participant according to the study protocol.

Study IMP in this protocol includes BDA MDI and AS MDI and will be referred to as IMP.

## 6.1 Study IMP(s) Administered

### 6.1.1 Investigational Medicinal Products

BDA MDI is formulated (Table 4) as micronized budesonide and micronized albuterol co-suspended with spray-dried particles in a hydrofluoroalkane propellant. The co-suspension formulation ensures that participants receive a consistent delivery of the drugs from each actuation of the MDI.

**Table 4 Investigational Medicinal Products (IMP)**

| **Arm name** | PT027 | PT007 |
|---|---|---|
| **IMP name** | Budesonide and Albuterol Sulfate Pressurised Inhalation Suspension | Albuterol Sulfate Pressurised Inhalation Suspension |
| **Type** | Combination | Monotherapy |
| **Dose formulation** | Pressurised Inhalation Suspension | Pressurised Inhalation Suspension |
| **Unit dose strength(s)** | 80/90 µg per Actuation | 90 µg per Actuation |
| **Dosage level(s)** | 1 to 6 doses (2 inhalations/dose) per day as needed | 1 to 6 doses (2 inhalations/dose) per day as needed |
| **Route of administration** | Oral inhalation | Oral inhalation |
| **Use** | Experimental | Experimental |
| **Sourcing** | Provided centrally by the Sponsor | Provided centrally by the Sponsor |
| **Packaging and labeling** | Study IMP will be provided in an MDI. Each MDI will be labeled as required in the US | Study IMP will be provided in an MDI. Each MDI will be labeled as required in the US |
| **Current/former name(s) or alias(es)** | PT027, BDA MDI | PT007, AS MDI |

AS: Albuterol Sulfate; BDA: Budesonide and Albuterol; IMP: Investigational Medicinal Products; MDI: metered-dose inhaler; US: United States

## 6.2 Preparation/Handling/Storage/Accountability

1) An order for the study IMP will be raised by the Investigator or designee through the Randomization and Trial Supply Management system (RTSM) and will be automatically sent to a central depot for processing.
2) Participants will be given information about the delivery of their IMP at Visit 2 including what is included in the delivery, expected timelines and IMP storage information.
3) The study IMP, including Instructions for Use (IFU) contained within a Home Study Guide, will be sent directly to the participants' home by designated courier from the central depot.
4) The courier delivering the study IMP to the participant will ensure that appropriate temperature conditions were maintained during transit for all study IMP received. Any study IMP where the temperature conditions were not met will not be handed over by courier to the participant and will be returned by the courier to the central depot to be replaced.
5) Only participants randomized in the study may receive study IMP.
6) The Investigator is responsible for study IMP accountability, reconciliation, and record maintenance (ie, confirming receipt by the participant, and reconciliation/final disposition records from the central depot). The Investigator or designee will check with the participant that they have received the study IMP allocated to them and will check the participant's usage and the remaining quantity of IMP at visits. Should a resupply of IMP or a replacement sensor be required, the Investigator or designee will raise an order within the RTSM system.

### 6.2.1 Dose and Treatment Regimens

Study IMP will be used as needed, either to treat asthma symptoms or prophylactically before exercise to prevent symptoms. No other reliever products will be used during the treatment period.

At randomization (Visit 2), participants who meet the eligibility criteria will be randomly assigned to 1 of the following 2 treatment groups in a 1:1 ratio as reliever therapy on top of usual care:

- BDA MDI 160/180µg (given as 2 inhalations of budesonide/albuterol 80/90 µg per actuation) as needed
- AS MDI 180µg (given as 2 inhalations of albuterol 90 µg per actuation) as needed

Randomization will be stratified by pre-study asthma medication (SABA only, low-dose ICS + SABA and LTRA + SABA) and number of prior severe exacerbations (0, ≥1) in the 12 months

prior to Screening visit.

The maximum daily dosage of study IMP should not exceed 12 inhalations during one calendar day (see Section 8.5 for overdose).

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

### 6.2.2 Labeling

Labels will be prepared in accordance with Good Manufacturing Practice and US regulatory guidelines.

The participant will receive a starter shipment containing a suitable number of IMP kits for that participant to begin treatment. Each kit contains 2 MDI devices individually wrapped in foil bags held within a carton. The MDI devices provided in this study and the packaging and labeling of the kits are visually identical to maintain the blind. Additional kits will only be dispensed if required and will be ordered through the RTSM by the Investigator. Each kit will contain the following blinded labels:

- Single panel canister label (English only)
- Single panel actuator label
- MDI device shield label (single panel, English only)
- Foil bag label (single panel, English only)
- Single panel carton label

The labels will include the following information:

- Investigational medicinal product dosage form, route of administration, and quantity of dosage units (blinded across all arms)
- Storage conditions
- Study Trial Reference
- Medication ID number
- Directions for use

The label will include the following standard statements:

- ‘Caution: New Drug – Limited by Federal (or US) law to investigational use.
- ‘Keep out of reach of children’.

### 6.2.3 Storage

Study IMP, once received by the participant, should be stored under appropriate conditions: at room temperature between 68°F and 77°F (20°C and 25°C, with allowable excursions between 15°C and 30 °C) avoiding humid or wet environments and ensuring the inhaler and attachment are kept out of reach of children. Participants will receive information on IMP storage in a Home Study Guide, and the label in the IMP carton also specifies the appropriate storage temperature.

### 6.2.4 Accountability

Study IMP provided will be used only as directed in the Clinical Study Protocol.

All study IMP will be returned to the approved central depot by the participant at the end of their treatment period. Pre-paid packages will be provided to participants to return IMP upon completion of their study obligations or on withdrawal from the study. The central depot will be responsible for the destruction of IMP after the accountability and reconciliation has been performed by the Investigator.

### 6.2.5 Metered-dose Inhaler: Handling and Cleaning

Detailed handling instructions will be provided to the participant which will cover all aspects of using and handling the MDIs. This 'Instructions for Use' document (Appendix F) focuses on the MDI device.

The importance of the device cleaning and priming requirements should be emphasized to participants. An instructional video will be made available to the participants which will detail the instructions for use and cleaning of the device. This will be shown to the participant at Visit 3.

## 6.3 Measures to Minimize Bias: Randomization and Blinding

### 6.3.1 Methods for Assigning Treatment Groups

All participants will be centrally assigned to randomized study IMP using a RTSM system. Before the study is initiated, the log-in information and directions for the RTSM will be provided to each site. Randomization codes will be assigned strictly sequentially in each stratum as participants become eligible for randomization. Participants will be stratified by background therapy (SABA only, low-dose ICS + SABA and LTRA + SABA) and number of prior severe exacerbations (0, ≥1) in the 12 months prior to Screening visit.

Participants who fail to meet the inclusion/exclusion criteria should not, under any circumstances, be randomized or receive IMP. There can be no exceptions to this rule. If a participant withdraws from the study after randomization, then his/her participant's ID number cannot be reused. Withdrawn participants will not be replaced.

Returned study IMP will not be re-dispensed to participants.

### 6.3.2 Methods for Ensuring Blinding

This is a double-blind study in which BDA MDI and AS MDI are visually identical. Participants will be randomly assigned in a 1:1 ratio to receive IMP. Investigators, investigational site staff, blinded Sponsor and participants will remain blinded to each participant's assigned IMP throughout the course of the study.

The RTSM will provide the Investigator(s) the kit identification number allocated to the participant at the randomization visit and at any subsequent visit where resupply is necessary.

Instructions for this will be described in the RTSM user manual that will be provided to each center.

The randomization code should not be broken except in medical emergencies when the appropriate management of the participant requires knowledge of the treatment randomization. The Investigator will document and report the action to the Sponsor and/or its representative, CRO, without revealing the treatment given to participant to the Sponsor and/or its representing staff.

The Sponsor retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to the IMP and that potentially require expedited reporting to regulatory authorities. Randomization codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual participant have been made and documented and the database is locked.

The RTSM will be programmed with blind-breaking instructions. In case of an emergency, in which the knowledge of the specific blinded study IMP will affect the immediate management of the participant's condition, the Investigator has the sole responsibility for determining if unblinding of a participants' IMP assignment is warranted. Participant safety must always be the first consideration in making such a determination. If a participant's IMP assignment is unblinded, the Sponsor/CRO must be notified within 24 hours after breaking the blind. The Investigator will document and report the action to Sponsor/CRO, without revealing the treatment given to participant to the Sponsor/CRO staff.

## 6.4 Study IMP 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 enough 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 in the Investigator File.

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. Data is collected via the sensor attached to the MDI and transmitted via Bluetooth. The sensor is provided by [redacted]. In the event there is no connection to upload the data in real time, the sensor has offline storage capabilities and will complete the data upload when back online. The usage data generated will be visible to the Investigator via [redacted] portal, but not to the participant. For the Investigator, this portal will provide additional data to any information already provided verbally by the participant as to the how frequently they used the study IMP.

A total of two sensors will be sent to each participant with their initial 'starter-shipment' of IMP to allow more than one study inhaler to be used at once. Instructions on attaching the sensor to an MDI and pairing the sensor attachment to a smartphone will be provided to the participant. Further information on the sensor attachment can be found in the site IMP manual.

## 6.5 Concomitant Therapy

The Investigator/authorized delegate will collect and record any medication taken from the time of Screening (Visit 1) until the final study visit (Visit 8) at virtual study visits. All background asthma medications (eg, SABA, ICS and LTRAs) and all other medications taken for any reason in the 3 months prior to enrollment, and any concomitant medication(s) during the study must be recorded in the electronic Case Report Form (eCRF) along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose, frequency and route

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Participants are prohibited from receiving certain concomitant medications (described in Section 6.5.3).

Medications or therapies that are not prohibited and neither compromise participant safety nor affect study data, as judged by the Investigator, will be permitted and recorded in the appropriate sections of the eCRF.

### 6.5.1 Rescue Medicine

The study IMP will replace the participant's current asthma rescue medication. It is important that the participant is instructed to stop using their current asthma rescue medication (ideally storing it somewhere they are unlikely to use it in error for the duration of their study

participation) and only use the study medication provided as their asthma rescue medication, to be taken as needed, throughout the treatment period.

### 6.5.2 Maintenance Asthma Therapies

Existing low-dose ICS or LTRA asthma maintenance therapy are permitted to be used as maintenance therapy on study as specified in the inclusion criteria.

During the study, participants should maintain stable dosing of their maintenance therapy as presented at baseline, however, dose changes to maintenance therapy are permitted if clinically indicated. Where possible, Investigators should contact the study medical monitors in advance of any proposed change to maintenance therapy for study participants; considerations should be made to participant drug compliance and other factors in advance of making changes to maintenance therapy.

All changes in asthma maintenance therapy should be clearly documented in the eCRF.

### 6.5.3 Allowed and Prohibited Medication

The inclusion and exclusion criteria sections of the protocol define concomitant medications that, if taken in the period prior to randomization, would lead to participant screen failure.

In addition, unless clinically indicated as determined by a physician, the following medications are allowed or prohibited (for the time periods stated):

**Table 5 Allowed and Prohibited Medications**

| Medication | Allowed/Prohibited | Details |
|---|---|---|
| SABA (short-acting $\beta_2$-agonists, eg, albuterol, levalbuterol) | Prohibited | Participants should stop using their existing SABA and replace it with the study IMP MDI provided |
| Background (maintenance) asthma medication:<br><br>Low-dose ICS or a LTRA | Allowed, only for participants receiving maintenance therapy at baseline or if clinically indicated. | Participants should maintain their existing low-dose ICS or their LTRA. If the medication is stopped, or the dose adjusted during the trial this must be recorded in the eCRF |
| Background (maintenance) asthma medication:<br><br>Inhaled LABA, theophylline, inhaled anticholinergic agent, cromone or medium/high dose ICS daily<br><br>(Refer to Appendix G for doses of ICS) | Prohibited | Prohibited as regular maintenance asthma therapy within 3 months of enrollment per exclusion criterion 3. |
| Systemic corticosteroids | Prohibited unless to treat a severe asthma exacerbation or in an equivalent acute situation | Systemic corticosteroid use is only permitted to treat severe asthma exacerbation events or for unavoidable medical events if clinically indicated. Chronic use of systemic corticosteroids is prohibited. Use of systemic corticosteroids is prohibited within 6 weeks of enrollment. |
| Biologics for the treatment of asthma | Prohibited | Receipt of any marketed (eg, omalizumab, mepolizumab, reslizumab, benralizumab, dupilumab, tezepelumab) or investigational biologic for the treatment of asthma at any time in the past |
| Potent cytochrome P3A4 inhibitors | Prohibited | Current treatment with potent cytochrome P3A4 inhibitors (eg, ketoconazole, itraconazole, and ritonavir) |
| Topical (dermal) and intraarticular corticosteroids | Allowed | |

| Medication | Allowed/Prohibited | Details |
|---|---|---|
| Antihistamines | Allowed | |
| Allergen Immunotherapy | Allowed | Stable allergen immunotherapy [a] (AI) is allowed, initiation of AI is not allowed. |

AI: Allergen immunotherapy; eCRF: Electronic Case Report Form; IMP: Investigational Medicinal Product; ICS: Inhaled corticosteroids; LABA: Long-acting $\beta_2$-agonist; LTRA: Leukotriene receptor agonist; MDI: Metered-dose inhaler; OCS: Oral corticosteroids; SABA; Short-acting $\beta_2$ agonist

[a] Stable allergen immunotherapy is defined as when the participant has reached the target dose and is on regular maintenance dosing for at least 4 weeks.

## 6.6 IMP After the End of the Study

Following the completion of the EOS or the Early Study/IMP Discontinuation visit, the participant should revert to the rescue medication they were using prior to enrollment. All further treatment will be at the discretion of the participant's regular treating physician.

# 7 DISCONTINUATION OF STUDY IMP AND PARTICIPANT WITHDRAWAL FROM STUDY

## 7.1 Discontinuation of Study IMP

### 7.1.1 Planned Discontinuation of Study IMP

Participants receive IMP for a minimum of 12 weeks and a maximum of 52 weeks. Unless participants prematurely discontinue IMP, they will continue treatment until 52 weeks of treatment or until the PCD has been achieved. If the PCD is achieved before a participant reaches 52 weeks of treatment, provided they have received at least 12 weeks of treatment, the participant will be asked to discontinue IMP within 4 weeks of the PCD and to complete an EOS.

The date of last IMP dose, the date of IMP discontinuation decision, and the reason(s) for discontinuation should be documented in eSource documentation and recorded in the eCRF.

### 7.1.2 Premature Discontinuation of IMP

All participants who prematurely discontinue study IMP should contact the study center and complete the procedures described in the EOS or Early Study/IMP Discontinuation visit as soon as possible from discontinuing the study IMP. See the SoA (Section 1.3) for data to be collected at the time of IMP discontinuation, follow-up and for any further evaluations that need to be completed. A participant who decides to prematurely discontinue IMP will always be asked about the reason(s) for discontinuation and the presence of any AEs.

All participants who prematurely discontinued IMP will be asked to continue in the study until they complete the EOS visit or until the study completes. It is strongly recommended that all scheduled virtual study visits and procedures are continued until the EOS visit if possible. However, participants will be provided with the following follow-up options and will be asked to provide consent for their preferred follow-up schedule:

**Option 1**: Ideally the participant should continue with all the regular virtual study visits and continue to respond to the bi-weekly messages from the [redacted] app asking if they had a need to seek medical help as a result of their asthma worsening or had any asthma-related unscheduled healthcare contacts/visits as per the SoA (Section 1.3) until EOS at Week 52 or within 4 weeks if the PCD has been reached.

**Option 2:** (If the participant cannot comply or does not wish to comply with Option 1 above). The participant agrees to receive and respond to the bi-weekly messages from the [redacted] app and perform an unscheduled visit to collect follow-up details if applicable. The participant agrees to be contacted for an EOS visit at 52 weeks or within 4 weeks if the PCD has been reached.

**Option 3:** (If the participant cannot comply or does not wish to comply with Options 1 and 2 above). The participant agrees to be contacted for an EOS visit at 52 weeks or within 4 weeks if the PCD has been reached.

**Option 4**: (If the participant cannot comply with Option 1, 2 or 3 above). The participant may withdraw consent for further follow-up and may proceed to perform the EOS visit prematurely upon withdrawal.

Unscheduled visits following a response of 'YES' to the bi-weekly [redacted] app message will be performed in accordance with the details recorded in Section 8.7.

If a participant becomes pregnant during the course of the study, IMP should be discontinued and a conversation between the Investigator, and, if needed, the participant's regular treating physician and/or obstetrician should be arranged as soon as possible to determine whether continuation in the study is in the best interest of the participant and their unborn fetus. If a participant becomes pregnant during the study, they should be re-consented before continuing in the study.

In the event an ineligible participant was randomized in error, the Investigator together with the medical monitor should determine if it is safe for the participant to continue or if she/he needs to be withdrawn from study IMP. If the decision is made that the participant can continue on study treatment the rationale should be clearly documented.

## 7.2 Participant Withdrawal from the Study

- Participants who withdraw will not be replaced.
- 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, behavioral, compliance, or administrative reasons.
- At the time of withdrawal from the study, if possible, an Early Study/IMP Discontinuation visit should be conducted (equivalent to the EOS visit), as shown in the SoA (Section 1.3). See SoA for data to be collected at the time of study withdrawal and follow-up and for any further evaluations that need to be completed.
  - The participant will discontinue the study IMP and be withdrawn from the study at that time.
- 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.

## 7.3 Lost to Follow-up

A participant will be considered lost to follow-up if they repeatedly fail to attend the scheduled virtual visits and are unable to be contacted by the study site.

The following actions must be taken if a participant fails to attend a required virtual study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known email or postal address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix A.

# 8 STUDY ASSESSMENTS AND PROCEDURES

This study will be decentralized. All assessments and procedures for this study are performed virtually with no planned in-person contact between the participant and the Investigator or their staff. The following systems and procedures are used to enable this decentralized approach:

- Media advertising including social media for participant recruitment
- [redacted] website for study pre-screener
- [redacted] platform for the site and the participants enabling the eConsent process, telemedicine visits (virtual visits), eSource and collection of participant reported data related to their asthma, concomitant medications and questionnaire completion
- Direct to participants shipment of IMP and device sensors
- [redacted] portal app for participants to register their device sensor for capture of actuation information
- [redacted] will provide a patient concierge service (Patient Navigator) with end-to-end participant and caregiver support to assist with any study related questions by telephone. Patient Navigator contact details can be accessed via the [redacted] app and additional information on the service will be available within the [redacted] app.

In general study procedures and their timing are summarized in the SoA (Section 1.3).

Protocol waivers or exemptions are not allowed.

- The Investigator will ensure that the eSource information is captured in [redacted] platform and the data are recorded in the eCRF. The Electronic Data Capture (EDC) system will be used for data collection and query handling.
- The Investigator ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement. The Investigator will sign the completed eCRF. A copy of the completed eCRF will be archived at the study site.
- Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study IMP.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. A list of participants screened is maintained within [redacted].

- Procedures conducted as part of the participant's routine clinical management and obtained before signing of the eICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

## 8.1 Screening and Critical Baseline Assessments

Informed consent will be obtained using the eConsent tool provided by [redacted] app.

Medical/medication history will be assessed as related to the inclusion/exclusion criteria listed in Section 5. Relevant medical and surgical history will be captured at Screening, including all background asthma medications (eg, SABA, ICS and LTRAs) and all other medications taken for any reason in the 3 months prior to enrollment. Any concomitant medication(s) taken during the study must also be recorded in the eCRF. In addition, smoking history will also be collected as relevant medical history. Adverse events are captured from the signature of eICF.

The following demographic parameters will be captured: year of birth, sex (genetically female or male), race and ethnicity.

Evaluation of the participant's asthma at Screening includes:

- Date of diagnosis and/or approximate duration since diagnosis
- Requirement for therapy (eg, SABA and ICS or LTRA use) including requirement for OCS treatment for the management of asthma during the 12 months prior to Screening (Visit 1).
- Number of participant-reported severe asthma exacerbations experienced during the 12 months prior to Screening (Visit 1). Details of whether the severe asthma exacerbation required systemic steroids only, an emergency room / urgent care visit lasting <24 hours requiring systemic steroids or in-patient hospitalization lasting ≥24 hours, will be captured.

Participants should be enrolled into the [redacted] portal (Section 8.6) and then complete the AIRQ (Section 8.2.2.1) in the [redacted] app on their smartphone.

Participants who meet all the inclusion criteria and none of the exclusion criteria and who are not females of child-bearing potential may progress directly to randomization (Visit 2).

For females of child-bearing potential, a negative pregnancy test result must be received before proceeding to randomization (a picture of the negative test should be uploaded to the [redacted] portal).

At randomization, both the AIRQ and the EuroQol-5 Dimension 5 Level (EQ-5D-5L) questionnaire (Section 8.2.2.2) will be completed in the [redacted] app. Where Screening Visit 1/re-screen and randomization (Visit 2) occur on the same day, AIRQ will only be captured once and this will be considered the baseline assessment.

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.

## 8.2 Efficacy Assessments

### 8.2.1 Asthma Exacerbation Definition

All protocol defined exacerbations need to fulfill the symptom criteria as defined in Section 8.2.1.1 or be supported by an Investigator justification (Section 8.2.1.2). The Investigator will inquire to the participant as to which of the worsening/onset of signs/symptoms listed in Section 8.2.1.1 they experienced prior to/during the exacerbation.

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

- worsening of asthma signs/symptoms (refer to Section 8.2.1.1)
- increased use of ‘as needed’ reliever medication

#### 8.2.1.1 Definition of Worsening of Asthma Signs/Symptoms

The worsening/onset of signs/symptoms include at least one of the following:

- shortness of breath
- wheezing
- chest tightness
- cough
- sputum
- night-time awakening due to asthma
- activity limitation and tiredness due to asthma

Inquiries as to any signs of worsening or new symptoms of asthma will be made at each contact with the participant.

#### 8.2.1.2 Investigator Justified Asthma Exacerbations

A vast majority of asthma exacerbations are associated with worsening of the signs and symptoms described in Section 8.2.1.1. Clinical presentations may, however, vary among patients. If in the Investigator’s opinion, a participant’s symptoms and overall clinical findings support the diagnosis of an asthma exacerbation, but the signs and symptoms do not meet the

definition in Section 8.2.1.1, the Investigator must justify the decision for defining the event as an exacerbation and document the reasoning in the eCRF.

#### 8.2.1.3 Severe Asthma Exacerbations

All protocol defined asthma exacerbations will be classified as **severe** based on the following treatment criteria.

An asthma exacerbation will be considered **severe** if it results in at least 1 of the following:

- A temporary bolus/burst of SCS for at least 3 consecutive days to treat symptoms of asthma worsening; a single depo-injectable dose of corticosteroids will be considered equivalent to a 3-day bolus/burst of SCS.
- An emergency room or urgent care visit (defined as evaluation and treatment for <24 hours in an emergency department or urgent care center) due to asthma that required SCS (as per the above).
- An in-patient hospitalization (defined as admission to an inpatient facility and/or evaluation and treatment in a healthcare facility for ≥ 24 hours) due to asthma.
- Death

Any of the events above will need to be supported through relevant documentation in the eSource records, eg, a copy of a record of a prescription for OCS for asthma, evidence from a hospital that the participant was treated for an asthma exacerbation etc.

#### 8.2.1.4 Onset and Duration of Asthma Exacerbations

**For severe** exacerbations, the duration is defined by the **prescribed treatment:**

- The start date will be defined as the start date of prescribed treatment with a SCS.
- The stop date will be defined as the last day of prescribed treatment with a SCS.
- A single depot injectable dose of corticosteroids will be considered equivalent to a 3-day course of SCS. The corresponding stop date for this treatment will consequently be determined as the date of administration plus 2 days.
- If multiple treatments are prescribed for the same exacerbation, the earliest start date and the latest stop date will be used.
- For a severe asthma exacerbation requiring hospitalization with no documented corticosteroid treatment, hospitalization admission/discharge dates, or emergency visit date will be used as start/stop dates.

#### 8.2.1.5 Approach for Capturing Asthma Exacerbations

All severe asthma exacerbations following randomization (including Investigator justified asthma exacerbations) must be captured using the Asthma Exacerbation eCRF.

If an asthma exacerbation requires hospitalization, the exacerbation should be reported as a SAE as well as on the Asthma Exacerbation eCRF.

Severe asthma exacerbations will be considered study efficacy endpoints and will not be reported as AEs unless considered a SAE.

Associated symptoms of asthma are considered as symptoms of disease under study (DUS) and will not be recorded as AEs unless considered an SAE.

All asthma-related SAEs will also be recorded on the SAE eCRF.

### 8.2.2 Patient-Reported Outcomes

#### 8.2.2.1 Asthma Impairment and Risk Questionnaire (AIRQ)™

The Asthma Impairment and Risk Questionnaire (AIRQ)™ is a patient-reported outcome (PRO) tool intended to identify patients 12 years and older 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 severe 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, and 5-10 is very poorly controlled. Thus, a higher score indicates worse control status (Appendix C).

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 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.

The AIRQ™ will be administered within the [redacted] app and completed on the participant's smartphone by the participant as per the SoA. The AIRQ™ is estimated to take approximately 3 minutes to complete.

#### 8.2.2.2 EuroQol-5 Dimension 5 Level (EQ-5D-5L)

The EQ-5D-5L is a 5-level standardized instrument for use as a measure of health outcome. 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). The descriptive system comprises of the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 severity levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. EQ-5D-5L index score can be calculated based upon participants' 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, which will be further described

in the SAP.

The EQ-5D VAS records the respondent's self-rated health on a 0 to 100 vertical scale with endpoints labeled "the best health you can imagine" and "the worst health you can imagine", with higher scores corresponding to a better health state. This information is used as a quantitative measure of health as judged by the individual respondents.

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

## 8.3 Safety Assessments

Planned time points for all safety assessments are provided in the SoA.

## 8.4 Adverse Events and Serious Adverse Events

In this study all AEs will be collected.

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

The definitions of an AE or SAE can be found in Appendix B.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The Investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE.

### 8.4.1 Time Period and Frequency for Collecting AE and SAE Information

AEs will be collected from the signing of eICF throughout the treatment period and last contact.

SAEs will be recorded from the time of signing of the eICF.

If the Investigator becomes aware of a SAE with a suspected causal relationship to the IMP that occurs after the end of the clinical study in a participant treated by him or her, the Investigator shall immediately report the SAE to the Sponsor.

### 8.4.2 Follow-up of AEs and SAEs

Any AEs/SAEs that are unresolved at the participant's last AE assessment in the study will be followed up by the Investigator for as long as medically indicated, but without further recording in the eCRF. The CRO and the Pharmacovigilance Department retains the right to request additional information for any participant with ongoing AE(s)/SAE(s) at the end of the

study, if judged necessary.

**Adverse event variables**

The following variables will be collected for each AE;

- AE (verbatim)
- The date when the AE started and stopped
- Maximum intensity
- Whether the AE is serious or not
- Investigator causality rating against the IMPs (yes or no)
- Action taken with regard to IMPs
- AE caused participant's withdrawal from study (yes or no)
- Outcome

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

- Date AE met criteria for SAE
- Date Investigator became aware of SAE
- AE is serious due to
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Severity grade (mild, moderate, severe)
- Causality assessment to other medication

### 8.4.3 Causality Collection

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

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

A guide to the interpretation of the causality question is found in Appendix B to the Clinical

Study Protocol.

### 8.4.4 Adverse Events Based on Signs and Symptoms

All AEs spontaneously reported by the participant (including those reported during the interactions with the Patient Navigator service) or reported in response to the open question from the study site staff: 'Have you had any health problems since the previous visit/you were last asked?', or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

### 8.4.5 Adverse Events of Special Interest

There are no AEs of special interest for this product.

### 8.4.6 Disease Under Study (DUS)

Symptoms of DUS are those which might be expected to occur as a direct result of daily or seasonal variations in asthma. Events which are unequivocally due to DUS should not be reported as an AE during the study unless they meet SAE criteria of the IMP.

### 8.4.7 Reporting of Serious Adverse Events

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

If any SAE occurs in the course of the study, Investigators or other site personnel will inform the appropriate CRO representatives within one day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated CRO representative will work with the Investigator to ensure that all the necessary information is provided to the CRO Patient Safety data entry site **within one calendar day** of initial receipt for fatal and life-threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up will be undertaken immediately. Investigators or other site personnel will inform CRO representatives of any follow-up information on a previously reported SAE within one calendar day, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

Once the Investigators or other site personnel indicate an AE is serious in the EDC system, an automated email alert is sent to the designated CRO representative.

If the EDC system is not available, then the Investigator or other study site staff must complete the SAE form and submit it to the appropriate CRO representative via email or via fax. In the event that the site is unable to complete the SAE form to report the event within 24 hours of their knowledge of the event, the Investigators may report the SAE over the telephone via SAE answering service, and then provide the completed SAE form via fax or email.

The CRO representative will advise the Investigator/study site staff how to proceed.

For further guidance on the definition of a SAE, see Appendix B of the Clinical Study Protocol.

The reference document for definition of expectedness/listedness is the IB for BDA MDI and AS MDI.

### 8.4.8 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to CRO except for:

- If the pregnancy is discovered before the study participant has received any study IMP

#### 8.4.8.1 Maternal Exposure

If a participant becomes pregnant during the course of the study, IMP should be discontinued and a conversation between the Investigator, and, if needed, the participant's regular treating physician and/or obstetrician should be arranged as soon as possible to determine whether continuation in the study is in the best interest of the participant and their unborn fetus. If a participant becomes pregnant during the study, they should be re-consented before continuing in the study.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IMP under study may have interfered with the effectiveness of a contraceptive medication. Congenital anomalies/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as Aes. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital anomaly/birth defect) should be followed up and documented even if the participant was discontinued from the study.

If any pregnancy occurs in the course of the study, then the Investigator or other site personnel will inform the appropriate CRO representatives within **1 day**, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated CRO representative will work with the Investigator to ensure that all relevant information is provided to the CRO Patient Safety data entry site **within 1 or 5 calendar days**

for SAEs (see Section 8.4.7) and **within 30 days** for all other pregnancies.

The same timelines apply when outcome information is available.

The Pregnancy report in the eCRF is used to report the pregnancy and the Pregnancy form is used to report the outcome of the pregnancy.

### 8.4.9 Medication Error

If a medication error occurs in the course of the study, then the Investigator or other site personnel informs the appropriate CRO representatives within **1 day**, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated CRO representative will work with the Investigator to ensure that all relevant information is completed within **1** (Initial Fatal/Life-Threatening or follow-up Fatal/Life-Threatening) **or 5** (other serious initial and follow-up) **calendar days** if there is an SAE associated with the medication error (see Section 8.4.7) and **within 30 days** for all other medication errors.

The definition of a Medication Error can be found in Appendix B 4.

## 8.5 Overdose

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

All overdoses will be recorded in the overdose eCRF.

An overdose with associated AEs is recorded if the AE is serious and the AE diagnosis/symptoms will be reported on the relevant AE modules in the eCRF.

For the purpose of this study, any accidental or deliberate intake of blinded treatment of more than 12 inhalations during 1 calendar day is defined as an overdose.

If an overdose of IMP resulting in a SAE occurs in the course of the study, the Investigator or other site personnel will inform appropriate Sponsor/CRO representatives immediately, but **no later than 24 hours** of when he or she becomes aware of it.

The designated Sponsor/CRO representative will work with the Investigator to ensure that all relevant information is provided to the Sponsor/CRO Patient Safety data entry site **within 1 or 5 calendar days** for overdoses associated with an SAE (see Section 8.4.7).

## 8.6 [redacted] Mobile Software Application

The [redacted] mobile software application, and associated website system, will provide digital support to participants and Investigators/site staff from screening through to study completion for eConsent, ePRO completion, telemedicine visits and eSource activities (eSource is defined in Appendix A 7). In addition, the system will provide participants and site staff with information and tools relevant to the conduct of the study in accordance with the protocol, including educational content related to asthma and the study medication. This will include messages at bi-weekly intervals to inquire as to whether during the previous 14 days the participant has needed to seek medical help as a result of their asthma worsening. If the participant replies yes, a message will be sent to the Investigator to indicate a Health Event has occurred. The Investigator/site staff should contact the participant to collect further information. The app will be used to administer and collect the participant's responses to the AIRQ and EQ-5D-5L, at the relevant virtual visits, and will allow the participant to confirm if they received the study medication. In addition, the participants can contact the Investigators/site staff via the [redacted] app study contacts section at any time during the study including when they require an unscheduled visit.

After eConsent has been obtained, the Investigator/site staff will enter the participant's ID number and user details into the [redacted] portal. Once enrolled in [redacted] app, the participant will receive an invitation e-mail and will need to download the [redacted] app on their smartphone, setting their password and watching a short instructional video. The participant will then be able to complete the AIRQ to determine their eligibility for the study.

The Sponsor will own any system data collected which may be used after the trial to make improvements to [redacted] app. System data collected will be retained for a period of 15 years after trial closure.

## 8.7 Unscheduled Visits following 'Yes' Response to [redacted] bi-weekly Message

Between scheduled visits, participants will receive a message via a smartphone app ([redacted]) bi-weekly to inquire as to whether they have needed to seek medical help as a result of their asthma worsening or any asthma-related unscheduled healthcare related contacts/ visits. If the participant replies yes, then the Investigator/site staff will receive an email notification to contact the participant to collect further information. Where a scheduled visit is within 2 weeks of the notification, sites may (at their discretion) wait for the scheduled visit to collect follow-up information from the participant; however, they are encouraged to contact the participants as soon as possible. Where the next scheduled visit is > 2 weeks following the notification, an unscheduled visit should be conducted as soon as possible to obtain the follow-up information below.

During the next scheduled or unscheduled contact, the Investigator or site staff will review and query the participant regarding:

- AEs and SAEs
- Any documentation available suggesting or supporting of a severe asthma exacerbations including:
  - Any medical review (primary care/ER/hospitalization)
  - Any SCS use
  - Whether any other medications were used for asthma (other than IMP) and whether their ICS dose was changed or their ICS or LTRA was stopped, or other asthma controllers were started
  - The details of any asthma signs/symptoms experienced before the exacerbation
- Any change in concomitant medication(s)
- Any issues using the inhalers/digital sensors or the study portal/app
- Number of doses/inhalers used and whether new study inhalers are required by the participant
- Healthcare utilization related to asthma and absences from work/school due to asthma

## 8.8 [redacted] Sensor, Portal and App

Sensors which attach to the MDI devices will be provided to record each actuation of the device in order to monitor IMP usage. Sensors are manufactured by [redacted] and two sensors will be provided within the initial shipment of IMP to each participant following randomization. Replacement sensors in case of damage or loss can be provided if required. Sensors will be specific for each participant and who will activate the sensors by downloading the [redacted] app to their mobile device and pairing the app and the sensors. After initial download and pairing, the sensor and the app will remain connected and data transfers will be automatic, with no further action required by the participant. Instructions will be provided to the participant. Data from the sensors will be available to the sites and Sponsor within the [redacted] portal for real time data review as required and regular data transfers conducted to support the data analysis.

## 8.9 Medical Resource Utilization and Health Economics

Medical resource utilization data, associated with medical encounters, will be collected in the eCRF by the Investigator and study site personnel for all participants throughout the study.

Protocol-mandated procedures, tests, and encounters are excluded.

The data collected may be used to conduct exploratory economic analyses and will include:

- Number and duration of medical care encounters, including surgeries, and other selected procedures (inpatient and outpatient)
- Duration of hospitalization (total days or length of stay, including duration by wards [eg, intensive care unit])
- Number and type of diagnostic and therapeutic tests and procedures
- Outpatient medical encounters (including physician or emergency room visits, tests and procedures, and medications).

# 9 STATISTICAL CONSIDERATIONS

## 9.1 Statistical Hypotheses

The primary objective of this study is to evaluate the efficacy of BDA MDI (used at a dose of budesonide/albuterol 160/180 µg) as needed compared with AS MDI as needed (used at a dose of 180 µg) on the risk of a severe asthma exacerbation in participants receiving SABA alone or with a background of low-dose ICS or a LTRA. This is a superiority study to demonstrate the benefit of adding budesonide in the combination BDA MDI when used as needed compared with AS MDI as needed. The primary efficacy endpoint is the time to first severe exacerbation from the start of the IMP period, up to the EOS, as a measure of risk of experiencing a severe asthma exacerbation. The primary and secondary analyses will be based on a two-sided hypothesis testing approach.

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

H0: Hazard ratio (BDA MDI versus AS MDI) = 1,

HA: Hazard ratio (BDA MDI versus AS MDI) $\neq$ 1.

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

H0: Annualized rate ratio (Annualized $\text{rate}_{BDA}$ /Annualized $\text{rate}_{AS}$) = 1

HA: Annualized rate ratio (Annualized $\text{rate}_{BDA}$ / Annualized $\text{rate}_{AS}$) $\neq$ 1

All p-values will be reported as two-sided.

See Section 9.4.2.3 for further statements on the hypotheses testing.

## 9.2 Sample Size Determination

In order 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, and LTRA +SABA and number of 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 secondary endpoint time to first severe asthma exacerbation targeting an estimand utilizing a Treatment Policy strategy.

The primary endpoint of time to first severe exacerbation that targets the estimand utilizing the While on Treatment strategy assumes a 30% reduction in the risk of first severe exacerbation with BDA MDI versus AS MDI and is supported by results from the MANDALA study where the reduction in the rate of severe asthma exacerbations was 27% 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 90.8% power, with a 2-sided significance of 5%.

For the secondary endpoint of time to first severe asthma exacerbation that targets an estimand utilizing a 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 severe exacerbation with BDA MDI compared to AS MDI and a 1 year first severe exacerbation event rate of 21% in the AS MDI arm, 350 first severe exacerbation 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 events. However, if during the study the observed first severe exacerbation 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 first exacerbation rate is lower than predicted, the number of participants randomized may be increased to approximately 2500 to ensure the required number of first severe exacerbations is achieved. Any assessment of accumulating data will be performed on pooled, blinded data. The timing and procedure for blinded sample size assessment will be documented in the SAP.

An unblinded interim analysis for efficacy is planned once 50% of the events have been observed (172 first severe exacerbation events total, prior to treatment discontinuation or a step-up in maintenance therapy), based on the primary analysis of the primary endpoint. Alpha spending will be governed through the O'Brien-Fleming approach, where 0.003 will be spent at the interim to assess significance. If efficacy cannot be established at the 50% of target number of event threshold, the study will continue until 350 total first events are observed or approximately 2500 participants have been randomized and completed treatment and assessed at alpha=0.049. If more than 172 first events are available, the alpha will be adjusted accordingly (DeMets, 1994). The interim analysis, with unblinding firewalls, will be addressed in the Data Review Committee charter and administered by a separate unblinded analysis team.

If the study completes, ie, all participants are treated for one year, without reaching the required number of events then all planned analyses will be conducted with the number of

events that have occurred as of completion of the study.

**Note**: "Enrolled" means a participant's, or their legally acceptable representative's, agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study, but are not randomly assigned/assigned in the study, are considered" screen failures", unless otherwise specified by the protocol.

## 9.3 Populations for Analyses

The following populations are defined:

**Table 6 Populations for Analysis**

| Population/Analysis sets | Description |
|---|---|
| Enrolled | All participants who sign the electronic informed consent form (eICF). |
| Full analysis set | All participants who are randomized to treatment and receive any amount of study treatment (ie, at least 1 actuation). Participants will be analyzed according to the treatment they were assigned at randomization, regardless of the actual treatment received. |
| Safety analysis set | All participants who are randomized to treatment and receive any amount of the study treatment (ie, at least 1 actuation). Participants will be analyzed according to the actual treatment received rather than randomized. |

## 9.4 Statistical Analyses

The SAP will be finalized prior to database lock and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints. Additional analyses assessing the impact of coronavirus disease 2019 (COVID-19) pandemic or any other natural event may be included in the SAP.

### 9.4.1 General Considerations

Demographic and baseline characteristics data will be summarized by treatment for the Full and Safety analysis sets.

No study time windows will be derived by visit and data will be presented according to the scheduled study visit. For endpoints with repeated measures values collected at premature discontinuation visits should be assigned to the next available visit.

Baseline is defined as the 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.

### 9.4.2 Efficacy

#### 9.4.2.1 Primary Endpoint

The primary endpoint is the time to first severe asthma exacerbation and is defined as the length in days from start of the IMP period until the first date when the event occurs, up to the EOS. The primary estimand will adopt a While on Treatment strategy in the FAS. The following five attributes describe the estimand that will be used to define the treatment effect of interest for the primary efficacy analysis:

- Treatment Condition = Randomized IMP alone or usual Maintenance therapy + randomized IMP

- Population = Adults and adolescents (≥12 years) with asthma who are taking SABA as needed alone or with low-dose ICS or LTRA.

- Participant-level outcome = Time to first severe asthma exacerbation from start of the IMP period until the first date when the event occurs, up to the EOS.

- IE handling =Two IEs are defined: a) a step-up in maintenance therapy and b) all-cause discontinuation of study treatment. A While on Treatment strategy will be implemented for both IEs, such that the data will be censored at the time at which the IE occurred.

- Summary measure = Adjusted hazard ratio comparing BDA MDI administered as needed versus AS MDI as needed.

In order to ensure that the same event is not counted twice, concurrent severe asthma exacerbations with start and stop dates ≤ 7 days apart will be considered the same event.

Participants that do not experience a severe asthma exacerbation event or an IE and complete the study will be censored at the date of their EOS visit.

Participants that discontinue from study will be censored at the date of withdrawal from study or in the case of lost to follow-up the date of last contact.

The primary analysis will be based on a two-sided hypothesis testing approach. The statistical null hypothesis for the primary efficacy summary measure is that the adjusted hazard ratio for the primary treatment comparison is equal to 1 versus the alternative hypothesis that it is not equal to 1.

The time to first severe asthma exacerbation from start of IMP period up to the end of treatment will be analyzed using a Cox proportional hazards regression model. Treatment comparison will be performed using a model including treatment, pre-study asthma therapy (SABA only, low-dose ICS + SABA, LTRA + SABA) and the number of prior severe exacerbations (0, ≥1) in the 12 months prior to Screening visit. The estimated adjusted hazard

ratio for the treatment comparison will be displayed along with the associated Wald two-sided 95% confidence interval and p-value.

Kaplan-Meier plots of time to first severe asthma exacerbation will be presented by treatment group.

Censoring times will be assumed to be at random however, sensitivity analyses in which censored results will have event times imputed under an informative censoring assumption will be performed. Details will be provided in the SAP.

#### 9.4.2.2 Multiplicity adjustments

**Interim Analyses**

An interim analysis is planned for assessing efficacy. Only the primary and first secondary endpoint of time to first severe exacerbation based on the estimands utilizing a While on Treatment strategy (participants ≥12 years) and a Treatment Policy strategy (participants ≥12 years), respectively, will be tested. Please refer to Section 9.5 for the strategy for hypothesis testing of the primary and first secondary endpoint that are part of the interim decision criteria for stopping for efficacy and the methods to control the overall type-I error rate.

Testing of the remaining secondary endpoints of time to first severe exacerbation (While on Treatment strategy, participants ≥18 years), annualized severe exacerbation rate (While on Treatment strategy) and total systemic glucocorticoid exposure (While on Treatment strategy), that are not part of the interim decision criteria for stopping will be tested. Details of the hypothesis testing and alpha level for these endpoints will be provided in the SAP.

**Final Analyses (decision is not to stop for efficacy at interim analyses)**

In order to account for the multiple tests across multiple endpoints, a hierarchical testing strategy will be employed to control the 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, participants ≥12 years (While on Treatment strategy);

2) Time to first severe asthma exacerbation, participants ≥12 years (Treatment Policy strategy);

3) Time to first severe asthma exacerbation, participants ≥18 years (While on Treatment strategy);

4) Time to first severe asthma exacerbation, participants ≥18 years (Treatment Policy strategy);

5) Annualized rate of severe asthma exacerbation rates, participants ≥12 years (While on Treatment strategy);

6) Annualized rate of severe asthma exacerbation rates, participants ≥18 years (While on Treatment

strategy);

7) Total amount (mg/year) per participant of SCS exposure, participants ≥12 years (While on Treatment strategy), and

8) Total amount (mg/year) per participant of SCS exposure, participants ≥18 years (While on Treatment strategy).

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.

#### 9.4.2.3 Secondary Endpoint(s)

The first secondary endpoint, time to first severe exacerbation in participants ≥ 12 years, will also be analyzed based on an estimand utilizing a Treatment Policy strategy in which all observed data while participants are in the study, regardless of whether or not they are on randomized study treatment, will be included in the analyses. This is a secondary analysis and will be included in the hierarchical testing strategy (Section 9.4.2.2). The estimand adopting a treatment policy handling of intercurrent events will be evaluated in the FAS. The following five attributes describe the estimand that will be used to define the treatment effect of interest for this secondary analysis of effectiveness:

- Treatment Condition = Randomized IMP alone or usual Maintenance therapy at Day 1 + randomized IMP, including any other additional medication/therapy.

- Population = Adults and adolescents (≥12 years) with asthma who are taking SABA as needed alone or with a stable low-dose ICS or LTRA.

- Participant-level outcome = Time to first severe asthma exacerbation from start of the IMP period until the first date when the event occurs, or up to EOS.

- IE handling = An IE is defined as a step-up in maintenance therapy or discontinuation of study treatment. A treatment policy strategy will be implemented such that the value for the participant-level outcome will be used regardless of whether or not the IEs occurs.

- Summary measure = Adjusted hazard ratio comparing BDA MDI administered as needed versus AS MDI as needed.

Participants that do not experience a severe asthma exacerbation event or an IE and complete the study will be censored at the date of their EOS visit. Participants that discontinue from

study will be censored at the date of withdrawal from study or in the case of lost to follow-up the date of last contact.

The statistical model used to analyze the time to severe asthma exacerbation from start of the IMP period up to EOS and associated hypothesis test will be the same as specified for the primary efficacy analysis.

In order to ensure that the same event is not counted twice, concurrent severe asthma exacerbations with start and stop dates ≤ 7 days apart will be considered the same event and assigned the maximum severity between the two events.

The second secondary endpoint is the time to first severe exacerbation based on the estimand utilizing a While on Treatment strategy in the adult population, defined as participants aged ≥18 years. The estimand attributes of treatment condition, participant-level outcome, IE handling, and summary measure are defined as per the primary estimand utilizing a While on Treatment strategy. The population attribute is adults (≥18 years) with asthma who are taking SABA as needed alone or with a stable low-dose ICS or LTRA. The statistical model used to analyze the time to severe asthma exacerbation from start of the IMP period up to EOS and associated hypothesis test will be the same as specified for the primary efficacy analysis.

The third secondary efficacy endpoint is the time to first severe exacerbation based on an estimand utilizing a Treatment Policy in the adult population, defined as participants aged ≥18 years. The estimand attributes of treatment condition, participant-level outcome, IE handling, and summary measure are defined as per the estimand for time to first severe asthma exacerbation in the ≥12 years population. The population attribute is adults (≥18 years) with asthma who are taking SABA as needed alone or with a stable low-dose ICS or LTRA. The statistical model used to analyze the time to severe asthma exacerbation from start of the IMP period up to EOS and associated hypothesis test will be the same as specified for the primary efficacy analysis.

The fourth secondary efficacy endpoint is the annualized rate of severe asthma exacerbations, participants ≥12 years. Severe asthma exacerbations from the start of the IMP period up to the end of treatment will be used in the analysis. Intercurrent events will be defined as per the primary efficacy endpoint (While on Treatment strategy). Intercurrent events will be handled such that severe asthma exacerbations occurring post an IE will be excluded from the analysis and the time on study will be calculated up to the date at which the IE occurred. Time during a severe asthma exacerbation and the 7 days after a severe exacerbation will not be included in the calculation. As per the primary efficacy endpoint, exacerbations separated by less than 7 days will be treated as a continuation of the same exacerbation. The annualized rate of severe asthma exacerbations will also be evaluated based on the estimand utilizing a Treatment Policy strategy, where all data collected from the start of the IMP period up to the EOS participation, regardless of the occurrence of IEs, will be used.

The annualized 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 on study (years) will be used as an offset variable. The model will include covariates for treatment, pre-study asthma therapy (SABA only, low-dose ICS + SABA, LTRA + SABA) and the number of prior severe exacerbations (0, ≥1) in the 12 months prior to screening/enrollment. The treatment comparison will be as per the primary efficacy analysis. From the negative binomial model, the annualized severe asthma exacerbation rates will be estimated along with the associated 95% confidence intervals, for each treatment group. The summary measure for the comparison of BDA MDI versus AS MDI will be the estimated rate ratio which will be presented with the corresponding 95% confidence interval and two-sided p-value. The analysis of annualized exacerbation rate assessed under the While on Treatment strategy will be included in the type-I error controlled testing strategy. The analysis based on the estimand utilizing a Treatment Policy strategy will be considered a supplemental analysis. Details will be provided in the SAP.

The fifth secondary endpoint is the annualized rate of severe asthma exacerbations. The analysis will target the estimand utilizing a While on Treatment strategy in the adult population, defined as participants aged ≥18 years. This analysis will be the same as the analyses described for the fourth secondary endpoint except the population is adults (≥18 years) with asthma who are taking SABA as needed alone or with a stable low-dose ICS or LTRA.

The sixth secondary endpoint is total SCS exposure (participants ≥12 years) will be expressed as the annualized total dose of SCS (mg/year). Intercurrent events will be handled such that only SCS doses related to severe asthma exacerbation events that occurred while on treatment during the IMP period will be included in the analysis (While on Treatment strategy). Total SCS exposure will also be evaluated based on an estimand utilizing a Treatment Policy strategy, where all data collected from the start of the IMP period up to the EOS participation, regardless of IE occurrence, will be used.

Total amount (mg/year) of SCS exposure (per participant) = {Total SCS dose (mg) received during IMP treatment period / (Date of treatment completion/discontinuation - Date of start of IMP period + 1)} × 365.25

Annualized total dose of SCS will be presented descriptively by treatment group. A comparison of the treatment groups will be performed using a Wilcoxon rank sum test and associated p-values will be presented. For this endpoint, additional descriptive statistics of the difference between treatment arithmetic means, percentage reduction in the treatment arithmetic means, 2.5$^{th}$, 5$^{th}$, 75$^{th}$, 80$^{th}$, 95$^{th}$, and 97.5$^{th}$ percentiles will be presented. Further details of these and other summary measures will be provided in the SAP.

The analysis of total SCS exposure assessed under the While on Treatment strategy will be included in the type-I error controlled testing strategy. The analysis of total SCS exposure assessing the estimand utilizing a Treatment Policy strategy will be considered a supplemental analysis.

Additionally, the total SCS exposure will be expressed as the total number of days taking SCS treatment due to asthma and will be summarized descriptively.

Further details will be provided in the SAP.

The seventh secondary endpoint is total SCS exposure, which will be expressed as the annualized total dose of SCS (mg/year), based on an estimand utilizing a While on Treatment strategy in the adult population, defined as participants aged ≥18 years. This analysis will be the same as the analyses described for the sixth secondary endpoint except the population is adults (≥18 years) with asthma who are taking SABA as needed alone or with a stable low-dose ICS or LTRA.

#### 9.4.2.4 Tertiary/Exploratory Endpoint(s)

Tertiary/Exploratory endpoint efficacy analyses will be conducted based on estimand utilizing a While on Treatment Policy strategy only. Further details for all analyses will be provided in the SAP.

### 9.4.3 Safety

All safety summarizes will be performed on the Safety analysis set and will include all data obtained before participants discontinue randomized treatment. Participants will be analyzed according to the actual treatment received.

#### 9.4.3.1 Adverse Events

Adverse events during the treatment period will be summarized by the number of participants experiencing the event. AEs will be tabulated at the level of the Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term. The version of the MedDRA current at the time of database lock will be used in the tabulations and listings.

#### 9.4.3.2 Other Safety Endpoint(s)

Not applicable.

### 9.4.4 Other Analyses

Analyses of the primary, secondary, and tertiary endpoints may be performed by various subgroups. In addition to baseline and demographic subgroups, other factors will be used to create subgroups of interest. All subgroup analyses will be described fully in the SAP.

## 9.5 Interim Analyses

An unblinded interim analysis for efficacy is planned once 50% of the target number of first severe exacerbation events 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.

Only the primary and first secondary analysis of time to first severe exacerbation evaluating the estimands utilizing a While on Treatment strategy (participants ≥12 years) and a Treatment Policy strategy in (participants ≥12 years), respectively, will be tested at the interim analysis. No minimum exposure time is required and all participants in the FAS will be analyzed. Participants who are on-going at the time of the interim analysis, who have not had a severe exacerbation event or IE will be censored at the date of their last known contact.

Members of the DMC (see Section 9.6) 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, corresponding to a rejection of both the primary and secondary null hypotheses each at alpha=0.003.

In the event that the DMC recommends to stop the study due to overwhelming efficacy, 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, enrollment 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.

If efficacy cannot be established at the 50% of target number of events threshold, the study will continue until 350 total first events are observed or approximately 2500 participants have been randomized and completed treatment. In this scenario, the primary and key secondary analyses will be assessed at alpha=0.049.

If more than 172 first severe exacerbation events total, prior to treatment discontinuation or a step-up in maintenance therapy are available at the interim analysis, the alpha will be adjusted accordingly (DeMets, 1994). Similarly, the final analysis will take account of the number of observed events at that time to ensure that the type-I error rate is controlled at 5%.

## 9.6 Data Monitoring Committee

An independent, external DMC will be set up to review safety data at three time points during the study. At a single time point (Interim Analysis) DMC will review the primary efficacy

endpoint and the first secondary endpoint to determine stopping early for overwhelming efficacy. One safety review will occur before the interim analysis, with a second safety review at the time of the interim analysis, and a third safety review will occur at a later timepoint following the interim analysis if the study was not closed early for efficacy. The committee will operate in accordance with a DMC Charter. The DMC will have access to the individual treatment codes and will be able to merge these with the collected study data while the study is ongoing as required. The personnel involved in the clinical study at the Sponsor and/or its designee will remain blinded to these analyses and will have no knowledge of the results presented to the DMC.

Members of the DMC will review efficacy data generated externally and independently from the Sponsor, unblinded, once 50% of the events have been observed. The number of events will be monitored by the Sponsor in a blinded manner and the DMC triggered once the required 172 first events have been achieved.

# 10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

## Appendix A Regulatory, Ethical, and Study Oversight Considerations

### A 1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, eICF, IB, and other relevant documents (eg, advertisements) must be submitted to an Institutional Review Board (IRB) / Independent Ethics Committee (IEC) by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The Sponsor will be responsible for obtaining the required authorizations to conduct the study from the concerned Regulatory Authority. This responsibility may be delegated to a CRO but the accountability remains with the Sponsor.
- The Investigator will be responsible for providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European Regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

**Regulatory Reporting Requirements for SAEs**

- Prompt notification by the Investigator to the Sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study IMP under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study IMP under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and Investigators.

- For all studies except those utilizing medical devices, Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.
  - European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations
- An Investigator who receives an Investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

## A 2 Financial Disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

## A 3 Informed Consent Process (eConsent)

- The Investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary and they are free to refuse to participate and may withdraw their consent/assent at any time and for any reason during the study. Participants or their legally authorized representative [defined as parent or legal guardian] will be required to sign a statement of informed consent and participants not at age of majority will be required to sign a statement of assent, that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The participants source record for the study must include a statement that informed consent was obtained electronically before any study related procedures are performed and the date the eConsent was obtained. The authorized person obtaining the informed eConsent must also electronically sign the eICF.
- If any changes occur to the eICF that may affect participant ongoing participation, the changes to the eICF must be IRB/IEC-approved and participants must be re-consented to the most current version of the eICF(s) during their participation in the study.
- A copy of the eICF(s) must be provided to the participant or the participant’s legally authorized representative.

- Participants who become pregnant who have discontinued IMP during the study and agree to remain in the study (following discussion with the Investigator, the Study Physician and their treating physician and/or obstetrician) will be required to be re-consented.
- Assent forms will be provided electronically to participants ≥12 years who have not reached the age of majority at the time of entry to the trial.

## A 4 Data Protection

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure and use of their data must also be explained to the participant in the eICF.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The participant will have to provide personal information to the investigational site via the [redacted] e-source platform who will in turn share some of this information with the following vendors: the IMP vendor ([redacted]) for shipment of study materials (IMP devices, IMP sensors), [redacted] who enable [redacted] Support to create a password for the app, [redacted] to process participant's payment, and Patient Navigator to support participants. This information will be kept confidential by all providers.

## A 5 Dissemination of Clinical Study Data

A description of this clinical study will be available on http://www.clinicaltrials.gov as will the summary of the study results when they are available. The clinical study and/or summary of study results may also be available on other websites according to the regulations of the countries in which the study is conducted.

## A 6 Data Quality Assurance

- All participant data relating to the study will be recorded on eCRF unless transmitted to the Sponsor or designee electronically (eg, [redacted] actuation data). The Investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- The Investigator must maintain accurate documentation (eSource data) in the [redacted] platform that supports the information entered in the eCRF.

- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to the eSource data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring plan.
- CRO is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, CROs).
- Study monitors will perform ongoing eSource data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from the eSource documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including a record of the electronically signed eICFs, pertaining to the conduct of this study must be retained by the Investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

## A 7 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are stored in the [redacted] portal and filed at the Investigator's site.
- Data entered in the eCRF that are transcribed from the eSource documents must be consistent with the eSource documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study.
  - AIRQ and EQ5D-5L questionnaires are available within the [redacted] portal. Completion of the questionnaires will be entered directly into the [redacted] portal by the participants and are considered eSource data with no transcription requirement.
  - Dosing data will be automatically captured using the sensor with no transcription requirement into the eCRF.

- Pictures / uploads of medical records into the [redacted] portal will be required eSource documents for information including pregnancy tests, asthma diagnosis, asthma medication and asthma exacerbations.
- A full definition of what constitutes source data can be found in the source data agreements for each site.

## A 8 Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first site open and will be the study start date.

The Sponsor reserves the right to close a study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion (or early if they are unable to comply with study procedures or meeting study objectives). A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The Investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the Investigator
- Discontinuation of further study IMP development

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Participants from terminated sites will have the opportunity to be transferred to another site to continue the study.

# Appendix B Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

## B 1 Definition of Adverse Events

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

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

## B 2 Definition of Serious Adverse Events

A serious adverse event is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfills one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-participant hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect
- Is an important medical event that may jeopardize the participant or may require medical treatment to prevent one of the outcomes listed above.

Adverse Events (AEs) for **malignant tumors** reported during a study should generally be assessed as **Serious AEs**. If no other seriousness criteria apply, the ‘Important Medical Event’ criterion should be used. In certain situations, however, medical judgment on an individual event basis should be applied to clarify that the malignant tumor event should be assessed and reported as a **non-serious AE**. For example, if the tumor is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumor, the AE may not fulfill the attributes for being assessed as serious, although reporting of the progression of the malignant tumor as an AE is valid and should occur. Also, some types of malignant tumors, which do not spread remotely after a routine treatment that does not require hospitalization, may be assessed as non-serious; examples in adults include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

**Life-threatening**

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

**Hospitalization**

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

**Important Medical Event or Medical Treatment**

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

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

- Angioedema not severe enough to require intubation but requiring IV hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalization
- Development of drug dependency or drug abuse

**Intensity Rating Scale:**

- Mild (awareness of sign or symptom, but easily tolerated)
- Moderate (discomfort sufficient to cause interference with normal activities)
- Severe (incapacitating, with inability to perform normal activities)

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Appendix B 2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE unless it meets the criteria shown in Appendix B 2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Appendix B 2.

## B 3 A Guide to Interpreting the Causality Question

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

- Time Course. Exposure to suspect drug. Has the participant actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another etiology such as the underlying disease, other drugs, other host or environmental factors.
- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? The Sponsor would not normally recommend or support a re-challenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

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

- Is this a recognized feature of overdose of the drug?
- Is there a known mechanism?

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

The causality assessment is performed based on the available data including enough information to make an informed judgment. With no available facts or arguments to suggest a causal relationship, the event(s) will be assessed as 'not related'.

Causal relationship in cases where the DUS has deteriorated due to lack of effect should be classified as no reasonable possibility.

## B 4 Medication Error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for study IMP that either causes harm to the participant or has the potential to cause harm to the participant.

A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study site staff or participant.

Medication error includes situations where an error:

- Occurred
- Was identified and intercepted before the participant received the drug
- Did not occur, but circumstances were recognized that could have led to an error

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

- Drug name confusion
- Dispensing error eg, medication prepared incorrectly, even if it was not actually given to the participant
- Drug not administered as indicated, for example, wrong route or wrong site of administration
- Drug not taken as indicated eg, tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed eg, kept in the fridge when it should be at room temperature
- Wrong participant received the medication (excluding Interactive Response Technology (IRT)/RTSM errors)
- Wrong drug administered to participant (excluding IRT/RTSM errors)

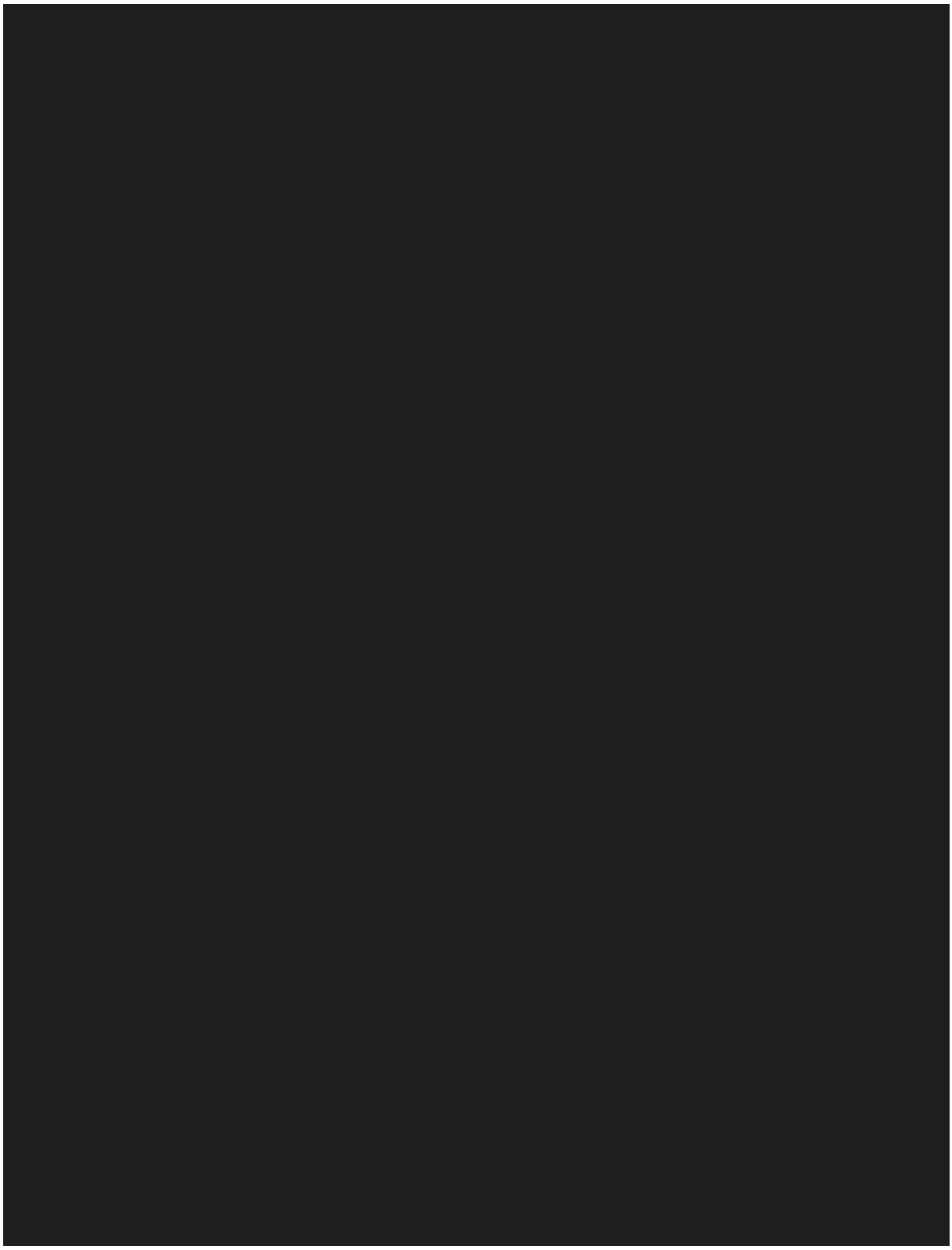
Examples of events that **do not** require reporting as medication errors in clinical studies:

- Errors related to or resulting from IRT/RTSM - including those which lead to one of the above listed events that would otherwise have been a medication error

- Participant accidentally missed drug dose(s) eg, forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Participant failed to return unused medication or empty packaging
- Errors related to background and rescue medication, or standard of care medication in open label studies.

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

# Appendix C Asthma Impairment and Risk Questionnaire (AIRQ™)



# Appendix D Avillion Protocol Signature Page

Avillion Signature Form for the Clinical Study Protocol

We, the undersigned, to the best of our knowledge and ability attest to the accuracy and validity of the contents of the Clinical Study Protocol.

_____ _____

Name: [redacted] Date
Title: Senior Global Medical Lead
Company: Avillion LLP

_____ _____

Name: [redacted] Date
Title: Statistician
Company: Avillion LLP

# Appendix E Primary Investigator Signature Page

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

Principal Investigator's Name (print)

Principal Investigator's Signature Date

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

# Appendix F Instructions for Use

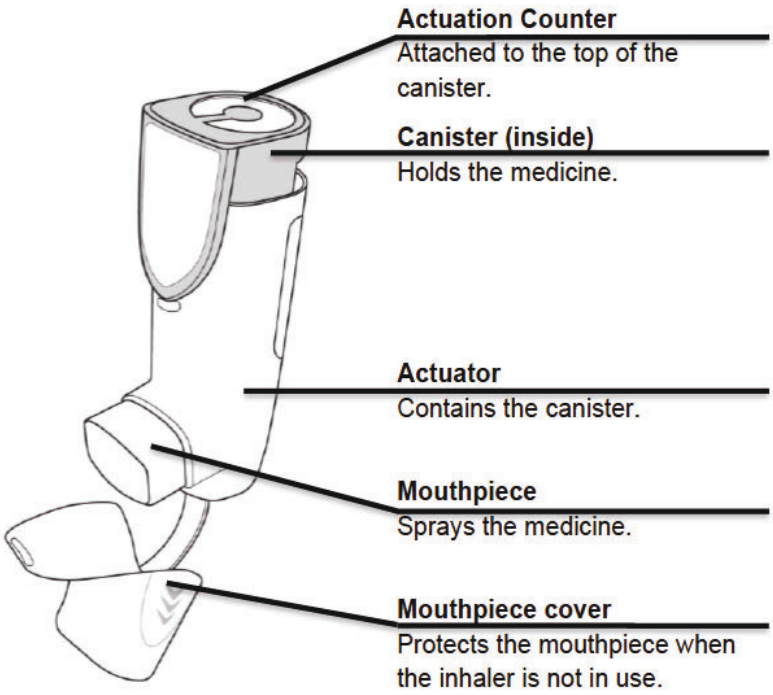
## Instructions for use for MDI

***Handling and cleaning instructions for MDI devices***

### 1. Use of Study Drug and MDI

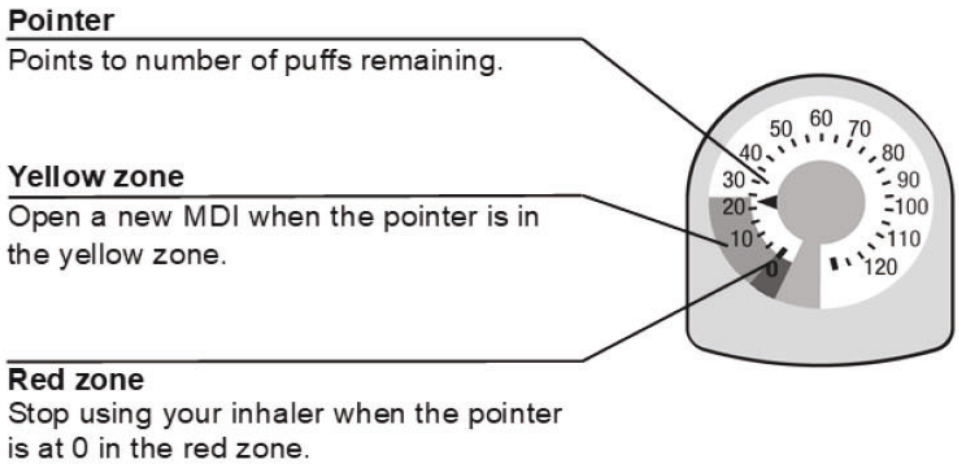
- The parts that make up the MDI are presented in Figure 2.
- The actuation counter presents the number of puffs left in the MDI and is part of the MDI that is pressed to dispense an actuation of medication. Figure 3 presents the dial of the actuation counter.
- The actuation counter has numbers for every 10 actuations and tick marks for every 5 actuations, as shown in Figure 3. For a new MDI, the actuation counter will start with the pointer to the left of the “120” mark.
- The actuation counter pointer will move with every actuation. For example, if the actuation counter pointer is pointing to 120 and 10 actuations are dispensed, the pointer of the actuation counter will move from 120 to 110. This means that there are 110 actuations of medicine left.
- When the pointer on the actuation counter approaches 20, the color behind the number changes to yellow, indicating that it is time to change to a new MDI.
- When the number on the actuation counter dial reaches 0 and the color behind the number is red, this means that the MDI should no longer be used, and it needs to be replaced with a new MDI.

**Figure 2 Metered Dose Inhaler (MDI)**




The actuation counter will count down by 1 each time you spray a puff of medicine.

**Figure 3 Actuation Counter Dial**



**2. Preparation and first use priming of the MDI**

- Take the MDI out of the foil pouch. Safely throw away the desiccant packet that comes inside the pouch. Do not eat or inhale the content of the desiccant packet. Retain the pouch and any other packaging for return at the end of the study.
- Take the cap off the MDI by gently squeezing the sides of the dust-cap and pulling off, as presented in Figure 4.

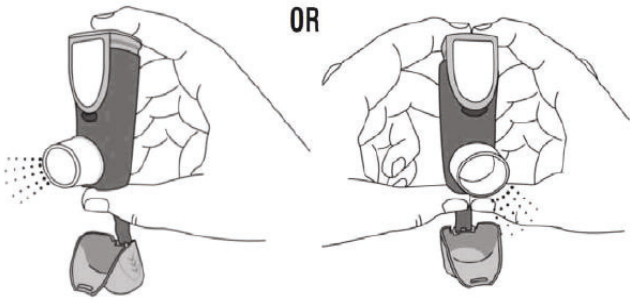
**Figure 4 Instructions for Removing the Cap from the MDI**

- Inspect the front of the MDI and make sure there is nothing inside the mouthpiece of the MDI. Make sure the canister is fully and firmly inserted into the actuator.
- The MDI must be primed before first use. First use priming involves releasing 4 sprays into the air before using the MDI; shaking is required prior to each priming spray. Shaking and priming the MDI fills a chamber inside the canister with the correct dose and mix of medication so that the MDI is ready to use.
- For each priming spray of the MDI, gently shake the MDI for 5-10 seconds and then spray once into the air away from yourself and others.
- **NOTE**: an audible "**click**" may be heard when the spray is released, which is advancement of the actuation counter and considered normal.
- Wait approximately 5-10 seconds and then repeat three more times.

**Using the MDI**

- The MDI can be used for 12 months once the foil pouch has been opened.
- The MDI should be held upright with the mouthpiece at the bottom and the actuation counter at the top as pictured in Figure 5.

**Figure 5 Ways to Hold the MDI for Use**




- Shake the MDI for 5 to 10 seconds.
- Breathe out fully through your mouth, expelling as much air from your lungs as possible. Tilt your head back slightly, placing the mouthpiece into your mouth, holding the MDI with the mouthpiece down, and closing your lips around it, as presented in Figure 6. To allow the medication to enter your lungs, keep your tongue flat on the bottom of your mouth.

**Figure 6 Diagram of How to Use the MDI**

- While breathing in deeply and slowly through your mouth, fully depress the top of the actuation counter with your index finger. Immediately after the spray is delivered, release your finger from the canister. When you have breathed in fully, remove the MDI from your mouth and close your mouth.
- Hold your breath as long as possible, up to 10 seconds, and then breathe normally.
- Repeat steps above for the second inhalation to complete the full dose.
- After you finish taking 2 inhalations, rinse your mouth with water. Spit out the water. Do not swallow it.
- Place the dust-cap back onto the device.

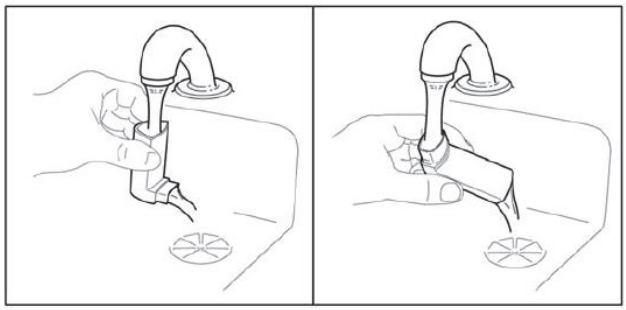
**Using the MDI (Children)**

- Children should use the MDI with an adult's help, as instructed by the child's healthcare provider.

**Cleaning the actuator**

- The actuator should be cleaned once per week if used in the last 7 days. The sensor should be removed from the MDI and the canister should be gently pulled from the top of the actuator. Do not clean the canister or let it get wet.
- Pull the canister out of the actuator and set the canister aside where it will not get wet.
- Take the dust cap off of the mouthpiece.
- Rinse the actuator through the top with warm running water for 30 seconds, as shown in Figure 7.

**Figure 7 Cleaning the Actuator**



- Shake all of the water droplets out of the actuator.
- Then rinse the actuator again through the mouthpiece with warming running water for 30 seconds.
- Shake all of the water droplets out of the actuator.
- Look in the actuator and mouthpiece and make sure it is clean and clear. Repeat steps above until the actuator and mouthpiece are clean and clear.
- Let the actuator dry completely, such as overnight. Do not put the canister back into the actuator if the actuator or dust cap is still wet.

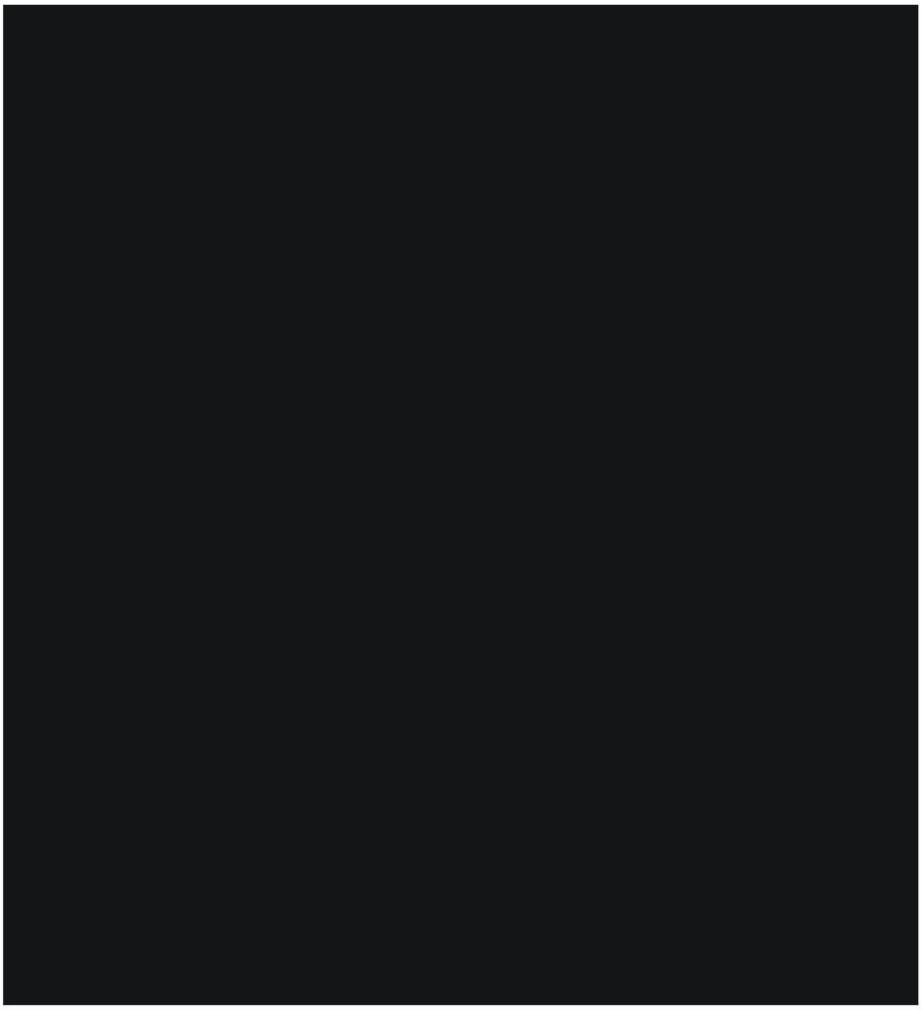
**Reassembling the MDI and instructions for use after**

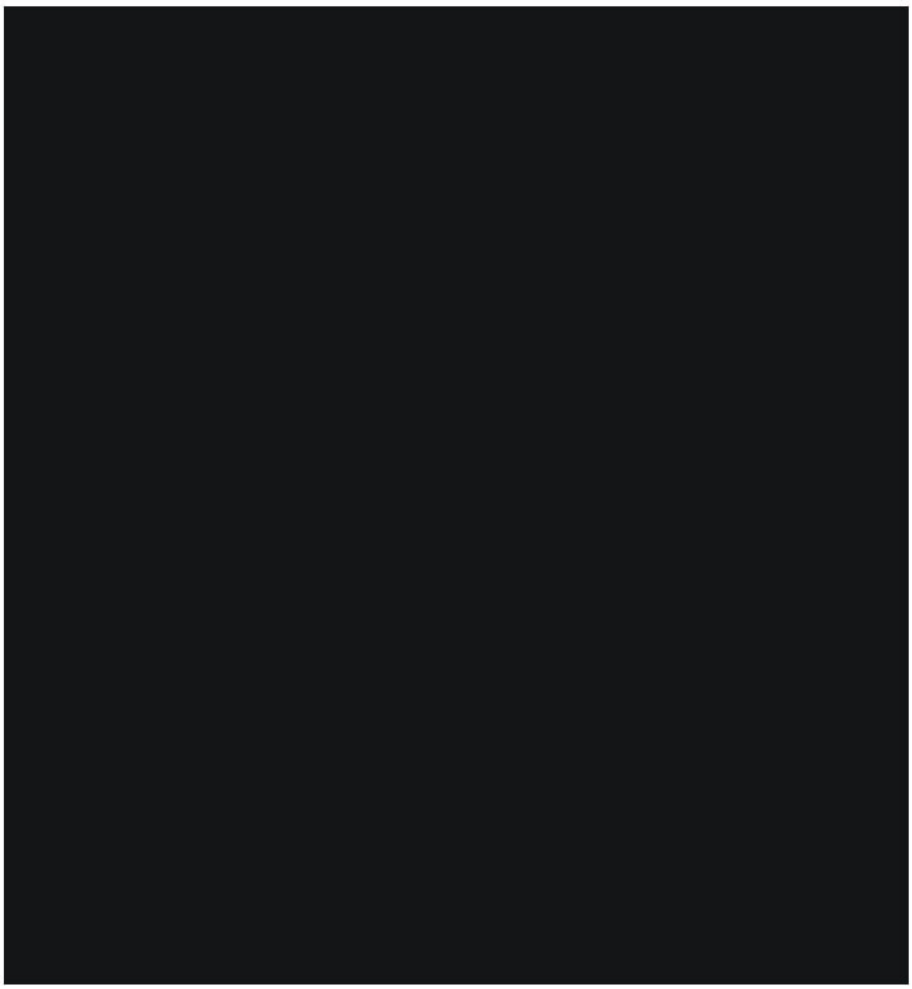
- After the actuator and dust cap are completely dry, gently press the canister down in the actuator. It is not necessary to press down on the canister hard enough to cause a puff to be released.
- The MDI must be re-primed after each cleaning. Re-priming involves releasing 2 sprays into the air. To do this, gently shake the MDI for 5-10 seconds and then spray once into the air away from yourself and others.
- NOTE: an audible “click” may be heard when the spray is released, which is the advancement of the actuation counter and is considered normal.
- Wait approximately 5-10 seconds and then repeat the above two steps, one more time.
- After re-priming the MDI two times, the MDI is ready for use.

**Re-priming the MDI after periods of non-use or when dropped**

- The MDI must be re-primed if it has not been used in more than 7 days or when it has been dropped.
- Re-priming involves releasing 2 sprays into the air. To do this, gently shake the MDI for 5-10 seconds and then spray once into the air away from yourself and others.
- NOTE: an audible “click” **may** be heard which is advancement of the actuation counter and is considered normal.
- To complete re-priming, wait approximately 5-10 seconds and then release 2 more sprays into the air as before.
- After re-priming the MDI, the MDI is ready for use.

**Instructions for Use for [redacted] Sensor**





# Appendix G Daily Metered doses of Inhaled Corticosteroids in Adults/Adolescents 12 years and older

| **Inhaled corticosteroid** | **Total daily ICS dose (mcg)** | | |
|---|---|---|---|
| | **Low** | **Medium** | **High** |
| Beclometasone dipropionate (pMDI, standard particle, HFA) | 200-500 | >500-1000 | >1000 |
| Beclometasone dipropionate (DPI or pMDI, extrafine particle, HFA) | 100–200 | >200–400 | >400 |
| Budesonide (DPI, or pMDI, standard particle, HFA) | 200–400 | >400–800 | >800 |
| Ciclesonide (pMDI, extrafine particle, HFA) | 80–160 | >160–320 | >320 |
| Fluticasone furoate (DPI) | 100 | | 200 |
| Fluticasone propionate (DPI) | 100–250 | >250–500 | >500 |
| Fluticasone propionate (pMDI, standard particle, HFA) | 100–250 | >250–500 | >500 |
| Mometasone furoate (DPI) | Depends on DPI device – see product information | | |
| Mometasone furoate (pMDI, standard particle, HFA) | 200-400 | | >400 |

DPI: dry powder inhaler; HFA: hydrofluoroalkane propellant; ICS: inhaled corticosteroid; pMDI: pressurized metered-dose inhaler.
ICS by pMDI should preferably be used with a spacer.
Source: GINA, 2022

# Appendix H Abbreviations

| Abbreviation or special term | Explanation |
|---|---|
| AE | Adverse event |
| AIRQ | Asthma Impairment and Risk Questionnaire |
| AS | Albuterol Sulfate |
| BDA | Budesonide/albuterol |
| CFR | Code of Federal Regulations |
| CRO | Contract Research Organization |
| DUS | Disease Under Study |
| eCRF | electronic Case Report Form |
| EDC | Electronic Data Capture |
| EOS | End of Study |
| EQ-5D-5L | EuroQol-5 Dimension 5 Level |
| FAS | Full Analysis Set |
| GCP | Good Clinical Practice |
| GINA | Global Initiative for Asthma |
| HCP | Healthcare professional |
| IB | Investigator's Brochure |
| (e) ICF | (Electronic) informed consent form |
| ICH | International Council for Harmonisation |
| ICS | Inhaled Corticosteroid |
| IE | Intercurrent Event |
| IEC | Independent Ethics Committee |
| IFU | Instructions for Use |
| IMP | Investigational Medicinal Product |
| IRB | Institutional Review Board |
| IRT | Interactive Response Technology |
| LABA | Long-acting $\beta$ 2-agonist |
| LTRA | Leukotriene receptor agonist |
| MDI | Metered-dose inhaler |
| MedDRA | Medical Dictionary for Regulatory Activities |
| NDA | New Drug Application |
| OCS | Oral Corticosteroids |
| PCD | Primary Completion Date |
| PI | Principal Investigator |

| Abbreviation or special term | Explanation |
|---|---|
| RTSM | Randomization and Trial Supply Management |
| SABA | Short/rapid-acting $\beta_2$agonist |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SCS | Systemic corticosteroids |
| SoA | Schedule of Activities |
| US | United States |
| VAS | Visual Analog Scale |

# 11 SUMMARY OF CHANGES

## 11.1 Changes to Protocol Amendment 2 (Version 3.0)

The overall rationale for this amendment is to update the testing hierarchy to test each of the key endpoints also on adult participants (participants ≥18 years) in line with the approved product label.

The following table provides a brief summary of major changes. It does not include all non-substantial changes (eg, formatting, minor clerical, and typographical corrections).

| Section | Changes to Protocol Amendment 2 (Version 3.0) |
|---|---|
| Version History | Date and version changed; brief summary of changes added as Section 11. |
| 1.1 Synopsis | **Objectives and Endpoints:**<br><br>Updated primary and secondary objectives for clarity to specify where testing is performed in relation to participants ≥12 years or ≥18 years respectively.<br><br>The following secondary objectives were added:<br><br>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 (While on Treatment strategy and Treatment Policy strategy).<br><br>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 (While on Treatment strategy).<br><br>To evaluate the effect of BDA MDI as needed compared with AS MDI as needed on systemic glucocorticoid exposure associated with asthma management, participants ≥18 years (While on Treatment strategy).<br><br>**Overall Design:**<br><br>Flexibility was introduced to permit enrolment of ‘approximately’ 2500 participants. |

| Section | Changes to Protocol Amendment 2 (Version 3.0) |
|---|---|
| 3.0 Objectives and Endpoints | Changes were implemented in line with the changes made to section 1.1 for consistency. |
| 9.2 Sample Size Determination | Flexibility was introduced to permit enrolment of 'approximately' 2500 participants. |
| 9.4.2.2 Multiplicity adjustments | In line with section 1.1. and 3.0, the testing hierarchy was updated to include the endpoints indicated in bold font below:<br><br>1) Time to first severe asthma exacerbation, **participants ≥12 years** (While on Treatment strategy);<br><br>2) Time to first severe asthma exacerbation**, participants ≥12 years** (Treatment Policy strategy);<br><br>**3) Time to first severe asthma exacerbation, participants ≥18 years (While on Treatment strategy);**<br><br>**4) Time to first severe asthma exacerbation, participants ≥18 years (Treatment Policy strategy);**<br><br>5) Annualized rate of severe asthma exacerbation rates, participants ≥12 years (While on Treatment strategy);<br><br>**6) Annualized rate of severe asthma exacerbation rates, participants ≥18 years (While on Treatment strategy);**<br><br>7) Total amount (mg/year) per participant of SCS exposure, participants ≥12 years (While on Treatment strategy), and<br><br>**8) Total amount (mg/year) per participant of SCS exposure, participants ≥18 years (While on Treatment strategy).**<br><br>Additional details relating to the new endpoints were provided within the body text. |
| 9.4.2.3 Secondary Endpoints | Details provided for new secondary objectives. Clarifications provided confirming when analyses will be performed for participants ≥12 years or ≥18 years respectively. |

| Section | Changes to Protocol Amendment 2 (Version 3.0) |
|---|---|
| 9.5 Interim Analysis | Clarification provided that only the primary and first secondary endpoint will be tested at the interim analysis. |
| Throughout document | Minor administrative changes have been made. |

## 11.2 Changes to Protocol Amendment 1 (Version 2.0)

The overall rationale for this amendment is to update the eligibility criteria based on label approval and experience to date. Further, the updates have been done to provide clarification in the protocol language.

The following table provides a brief summary of major changes. It does not include all non-substantial changes (eg, formatting, minor clerical, and typographical corrections).

| Section | Changes to Protocol Amendment 1 (Version 2.0) |
|---|---|
| Version History | Date and version changed; brief summary of changes added as Section 11. |
| 1.1 Synopsis | **Objectives and Endpoints:**<br><br>Updated primary objective as "To evaluate the efficacy of as-needed BDA MDI compared with **as-needed** AS MDI on the risk of severe asthma exacerbations."<br><br>Updated treatment as "Randomized Investigational Medicinal Product (IMP) **alone** or **usual** Maintenance therapy + randomized IMP."<br><br>**Investigational Medicinal Product (IMP) Groups and Duration:**<br><br>Updated that for females of child-bearing potential, following the initial screening assessment, a urine pregnancy test with high sensitivity **is required**.<br><br>Updated that the Treatment Initiation Visit (Visit 3) will occur once the participant is in receipt of the **study medication** (expected to be **within 7 days** following randomization). |

| Section | Changes to Protocol Amendment 1 (Version 2.0) |
|---|---|
| | Removed digital training material from the additional training materials available.<br><br>**Data Monitoring Committee**<br><br>Deleted text "If needed, two other reviews will occur for safety review only" from the synopsis to briefly present in the synopsis and add further details on safety review in Section 9.6. |
| 1.2 Schema | Number of participants for PT027 and PT007 in Figure 1 updated as **955** instead of 959.<br><br>Note in Figure 1 updated as "Note: All visits conducted **remotely**/virtually with no in-person clinic visits" |
| 1.3 Schedule of activities | Updated in the header of Table 1 that IMP will be delivered within **7 days** instead of 3-5 days and the same change is reflected in the footnote b.<br><br>Medical and surgical row updated in Table 1 to include **any smoking history**.<br><br>Inclusion/exclusion criteria added at Visit 2 in Table 1 and the respective footnote f was updated to recheck eligibility status before randomization and/or **before IMP is dispensed**.<br><br>Footnote j updated as "AIRQ version with 12-month recall period will be used at Screening, Randomization and EOS or Early Study/ IMP Discontinuation visits. AIRQ version with a 3-month recall will be used at other visits **as indicated above**. AIRQ is performed at both screening/**re-screen** and randomization, however, where screening/**re-screen** and randomization is performed on the same day, the AIRQ questionnaire will only be completed once.<br><br>**Footnote p** added "**The interval between screening and randomization may be up to 28 days. The screening period may be extended to collect documentation to confirm the asthma diagnosis only in the event that information has not been received within 28 days of** |

| Section | Changes to Protocol Amendment 1 (Version 2.0) |
|---|---|
| | **consent. The screening period cannot be extended >56 days for any reason. See Section 5.1 for details**."<br><br>**Footnote q** added "**Participants who initially screen failed due to failure to receive confirmatory medical records within the original 28-day screening period, use of corticosteroids within 6 weeks of Screening visit 1 or who were hospitalized for asthma within 3 months of screening Visit 1 may re-screen once. Participants who re-screen must complete all Visit 1 procedures during re-screening and satisfy eligibility criteria before being permitted to randomize into the study. Participants who fail to satisfy eligibility criteria during re-screening cannot be re-screened for a second time.**" |
| 2 Introduction | Updated to include that the study will be conducted **in patients with asthma, in partnership with AstraZeneca**.<br><br>Updated to add "**BDA MDI was approved by the Food and Drug Administration on 10 Jan 2023 for the as-needed treatment or prevention of bronchoconstriction and to reduce the risk of exacerbations in patients with asthma 18 years of age and older (NDA 214070); AstraZeneca Pharmaceuticals LP is the NDA holder**." |
| 2.3.1 Risk Assessment | Updated that the participants using >12 inhalations daily may potentially be at an increased risk of local or systemic corticosteroids side effects including adrenal suppression and, in **adolescent** participants, growth retardation. |
| 3. Objectives and endpoints | Updated primary objective as "To evaluate the efficacy of as-needed BDA MDI compared with **as-needed** AS MDI on the risk of severe asthma exacerbations."<br><br>Updated treatment as "Randomized IMP **alone** or **usual** Maintenance therapy + randomized IMP. " |
| 4.1 Overall Design | Updated that for females of child-bearing potential, following the initial screening assessment, a urine pregnancy test with |

| Section | Changes to Protocol Amendment 1 (Version 2.0) |
|---|---|
| | high sensitivity **is required**.<br><br>Updated that the interval between screening and randomization may be up to 28 days.<br><br>Added "**screening period may be extended to collect documentation to confirm the asthma diagnosis only in the event that information has not been received within 28 days of consent. The screening period cannot be extended > 56 days for any reason. See Section 5.1 and Schedule of Activities (SoA) (Table 1) for details."**<br><br>Updated that the Treatment Initiation Visit (Visit 3) will occur once the participant is in receipt of the study medication (expected to be **within 7 days** following randomization).<br><br>Removed digital training material, including a training video from the additional training materials available. |
| 4.2 Scientific Rationale for Study Design | Updated that the Phase III MANDALA study demonstrated that BDA MDI as needed significantly reduced the risk of a severe asthma exacerbation compared with albuterol alone **by 27%**. |
| 4.3 Justification for Dose | Updated the text as "The MANDALA Phase III study demonstrated that BDA MDI, taken as needed at **the now approved** dose of budesonide/albuterol 160/180 µg, was both efficacious and well-tolerated in a population with moderate to severe asthma." |
| 5.1 Inclusion Criteria | <u>Inclusion criteria 1</u><br>Note updated as "For participants from **12 years of age to age of majority**, their parents/legal guardian must provide signed consent, as appropriate, and participants will sign an assent form."<br><br><u>Inclusion criteria 2</u><br><br>Updated to included list of suitable documentation for confirmation on asthma diagnosis. |

| Section | Changes to Protocol Amendment 1 (Version 2.0) |
|---|---|
| | Inclusion criteria 3<br><br>Point no. a updated to remove text "at least 70% of participants should be on SABA alone."<br><br>Prescriptions to be considered instead of filled prescriptions.<br><br>Added that "**Participants must present their medication including any inhaler(s) during Screening Visit 1 and a picture of the medication(s) are required to captured in the [redacted] platform. For participants on SABA alone, verbal confirmation by the participant that they have used at least one additional inhaler in the past 12 months will be considered acceptable**."<br><br>Inclusion Criteria 5<br><br>Updated as "An AIRQ score of ≥2 at Screening (Visit1/**re-screen**) and Randomization (Visit2) where applicable. Note, where screening **Visit1/re-screen** and randomization occur on the same day, AIRQ will only be completed once."<br><br>Inclusion criteria 6<br><br>Females of sexually active in heterosexual relationships removed and updated that females of child-bearing potential must have a negative pregnancy test prior to randomization and agree to follow 1 of the options listed under this criterion to prevent pregnancy.<br><br>Point number b (ii) updated as **single-barrier** birth control method instead of double-barrier.<br><br>Specific recommendations for participants 12 years and over has been separated from point c and updated as point d.<br><br>Inclusion criteria 7<br><br>Updated as "Male participants who are in heterosexual relationships must be surgically sterile or agree to use an |

| Section | Changes to Protocol Amendment 1 (Version 2.0) |
|---|---|
| | effective method of contraception (condom) **if the female partner does not use contraception** from the date the eICF is signed until 2 weeks after their last dose. Male participants must not donate sperm during their study participation period."<br><br>Inclusion criteria 8<br><br>Updated as "Capable of giving signed eICF (including assent with parental / legal guardian consent in 12 years of age **to age of majority** as described in Appendix A which includes compliance with the requirements and restrictions listed in the eICF and in this protocol." |
| 5.2 Exclusion Criteria | Exclusion Criteria 1<br><br>Added "**or any significant disease (like malignancies or severe chronic diseases) that by Investigator judgment would interfere with the participant being able to comply with study procedures or complete the study.**"<br><br>Exclusion Criteria 2<br><br>Added "**Participants who were screen-failed due to hospitalization within the 3 months prior to enrollment may be re-screened once when the participant is more than 3 months post-hospitalization. Participants who reported an Intensive Care Unit admission with life threatening asthma may not be re-screened.**"<br><br>Exclusion Criteria 3<br><br>Updated as **inhaled** LABA and **inhaled** anticholinergic agent.<br><br>Exclusion Criteria 4<br><br>Updated as "Self-reported use of SCS for the treatment of asthma **and any other condition** in the 6 weeks prior to enrollment. **Participants screen failed for this reason may** |

| Section | Changes to Protocol Amendment 1 (Version 2.0) |
|---|---|
| | **be re-screened once, with their re-screening visit scheduled >6 weeks after last use of SCS**."<br><br>Exclusion Criteria 5<br><br>Updated as "Participants with a home supply of oral corticosteroids (OCS) to be used in the case of an asthma exacerbation **or any other condition that could require a course of OCS**, that are not willing **to commit** to the treating physician **to stop using this medication** for the duration of the study."<br><br>Exclusion Criteria 6<br><br>Added **Tezepelumab** as an example.<br><br>Exclusion Criteria 14<br><br>Updated as "Previous screening enrollment or randomization in the present study, **except where re-screening is permitted (see Section 5.5)**." |
| 5.4 Screen Failures | Updated that the Individuals who do not meet the criteria for participation in this study (screen failure) **may only be re-screened once for specific reasons as specified within Section 5.1, Section 5.2 and Section 5.5.** |
| 5.5 Re-screening | New section for re-screening added. |
| 6.2 Preparation/Handling/ Storage/ Accountability | Point no. 2 added "**Participants will be given information about the delivery of their IMP at Visit 2 including what is included in the delivery, expected timelines and IMP storage information**."<br><br>Point no. 3 (previously point no. 2) was updated to include that the Instructions for Use (IFU) is **contained within a Home Study Guide**. |
| 6.2.1 Dose and Treatment Regimens | Updated that the handling instructions for the MDI device will be available for the site to train participants and also for |

| Section | Changes to Protocol Amendment 1 (Version 2.0) |
|---|---|
| | the participants to refer to throughout the study. |
| 6.2.2 Labeling | Updated that additional kits will be ordered through the **RTSM** by the Investigator. |
| 6.2.3 Storage | Updated that the participants will receive information on IMP storage in a Home Study Guide, and the label in the IMP carton also specifies the appropriate storage temperature. |
| 6.2.4 Accountability | Updated that the central depot will be responsible for the destruction of IMP after the accountability and reconciliation has been performed **by the Investigator**. |
| 6.2.5 Metered-dose Inhaler: Handling and Cleaning | Updated that an instructional video with details on the instructions for use and cleaning of the device will be shown to the participant at **Visit 3**. |
| 6.3.1 Methods for Assigning Treatment Groups | Updated as **participant's ID number** instead of enrollment/randomization code. |
| 6.4 Study IMP Compliance | Updated that the number of MDIs sent to the participant and returned by the participant to the central depot will be documented and stored in the Investigator **File** instead of Investigator Site. |
| 6.5.3 Allowed and Prohibited Medication | Table 5 was updated for the Background (maintenance) asthma medication, systemic corticosteroids, biologics for the treatment of asthma, and allergen immunotherapy.<br><br>Background (maintenance) asthma medication (Low-dose ICS or a LTRA) was updated **to allow only for participants receiving maintenance therapy at baseline or if clinically indicated.**<br><br>Background (maintenance) asthma medication (**Inhaled** LABA, theophylline, **inhaled** anticholinergic agent, cromone |

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|---|---|
| | or medium/high dose ICS daily) was updated to prohibit as **per exclusion criterion 3**.<br><br>Systemic corticosteroids were updated to prohibit **unless to treat a severe asthma exacerbation or in an equivalent acute situation.** Details regarding use of systemic corticosteroid were updated.<br><br>Biologics for the treatment of asthma was updated to add **tezepelumab** as an example to any marketed products.<br><br>Added **Footnote a** "**Stable allergen immunotherapy is defined as when the participant has reached the target dose and is on regular maintenance dosing for at least 4 weeks."** |
| 7.1.1 Planned Discontinuation of Study IMP | The following statement was updated as "If the PCD is achieved before a participant reaches 52 weeks of treatment, **provided they have received at least 12 weeks of treatment**, the participant will be asked to discontinue IMP within 4 weeks of the PCD and to complete an EOS." |
| 7.1.2 Premature Discontinuation of IMP | Updated that the participants who prematurely discontinue study IMP should complete the procedures described in the **EOS** or Early Study/ IMP Discontinuation visit as soon as possible from discontinuing the study IMP.<br><br>Updated option 4: (If the participant cannot comply with Option 1, 2 or 3 above) "The participant may withdraw consent for further follow-up and may proceed to perform the EOS visit **prematurely** upon withdrawal." |
| 7.2 Participant Withdrawal from the Study | Updated that at the time of withdrawal from the study, if possible, Early Study/IMP Discontinuation visit should be conducted (**equivalent to the EOS visit**). |
| 8 Study Assessments and Procedures | Updated that all assessments and procedures will be performed virtually with no planned in-person contact **between the participant and** the Investigator or their staff.<br><br>Updated that the [redacted] portal app will capture **actuation** |

| Section | Changes to Protocol Amendment 1 (Version 2.0) |
|---|---|
| | information instead of dose information.<br><br>Updated that the Patient Navigator **contact details** can be accessed via the [redacted] app and additional information on the service will be available within the [redacted] app.<br><br>Updated that the **list of participants screen is maintained within** [redacted] instead of a screening log maintained by the Investigator. |
| 8.1 Screening and Critical Baseline Assessments | Updated that the relevant medical and surgical history will be captured at Screening, **including all background asthma medications (eg, SABA, ICS and LTRAs) and all other medications taken for any reason in the 3 months prior to enrollment. Any concomitant medication(s) taken during the study must also be recorded in the eCRF. In addition, smoking history will also be collected as relevant medical history.**<br><br>Updated that where Screening **Visit 1/re-screen** and **randomization** (Visit 2) occur on the same day, AIRQ will only be captured once and this will be considered the baseline assessment. |
| 8.6 [redacted] Mobile Software Application | eCode updated as participant's **ID number.**<br><br>Updated that the System data collected will be retained for a period of **15** years after trial closure instead of 10 years. |
| 8.7 Unscheduled Visits following 'Yes' Response to [redacted] bi-weekly Message | Updated that the Investigator/site staff will receive an **email** notification to contact the participant to collect further information.<br><br>Added "**Where a scheduled visit is within 2 weeks of the notification, sites may (at their discretion) wait for the scheduled visit to collect follow-up information from the participant; however, they are encouraged to contact the participants as soon as possible. Where the next scheduled visit is > 2 weeks following the notification, an** |

| Section | Changes to Protocol Amendment 1 (Version 2.0) |
|---|---|
| | **unscheduled visit should be conducted as soon as possible to obtain the follow-up information below**."<br><br>Updated that during the **next scheduled** or unscheduled contact, the Investigator or site staff will review and query the participant regarding the items listed as bullet points in this section. |
| 8.9 Medical Resource Utilization and Health Economics | Updated as "Outpatient medical encounters (including physician or emergency room visits, tests and procedures, and medications)." |
| 9.4.2.1 Primary Endpoint | Updated as "Treatment condition= Randomized IMP **alone** or **usual** Maintenance therapy + randomized IMP" |
| 9.4.2.3 Primary Endpoint | Updated as "Treatment Condition = Randomized IMP **alone** or **usual** Maintenance therapy at Day 1 + randomized IMP, including any other additional medication/therapy." |
| 9.6 Data Monitoring Committee | Updated that one safety review will occur before the interim analysis, **with a second safety review at the time of the interim analysis, and a third safety review will occur at a later timepoint following the interim analysis if the study was not closed early for efficacy**.<br><br>Updated that the members of the DMC will review **efficacy** data generated externally and independently from the Sponsor, unblinded, once 50% of the events have been observed. |
| 10 Supporting Documentation and Operational Considerations | **A 3 Informed Consent Process (eConsent)**<br><br>Updated that the participants may withdraw their consent/**assent** at any time and for any reason during the study.<br><br>Added that the **participants not at age of majority will be required to sign a statement of assent.**<br><br>Updated that the participants **source** record for the study must include a statement that informed consent was obtained |

| Section | Changes to Protocol Amendment 1 (Version 2.0) |
|---|---|
| | electronically before any study related procedures are performed and the date the eConsent was obtained.<br><br>**A 4 Data Protection**<br><br>Updated that the participant will have to provide personal information **to the investigational site via the [redacted] e-source platform who in turn share some of this information with the following vendors: the IMP vendor ([redacted])** for shipment of study materials (IMP devices, IMP sensors), [redacted] **who** enable [redacted] Support to create a password for the app, [redacted] **to process participant's payment, and Patient Navigator to support participants**. This information will be kept confidential **by all providers**.<br><br>**A 6 Data Quality Assurance**<br><br>Updated example in the first bullet point as [redacted] **actuation** data instead of [redacted] dosing data.<br><br>**A 7 Source Documents**<br><br>Deleted text "Also, current medical records must be available."<br><br>**A 8 Study and Site Start and Closure**<br><br>Updated that the study sites will be closed upon study completion **(or early if they are unable to comply with study procedures or meeting study objectives)**.<br><br>**B 2 Definition of Serious Adverse Events**<br><br>Under "Important Medical Event or Medical Treatment" added text "**Examples of important medical events include but are not limited to:"**<br><br>**Appendix F Instructions for Use**<br><br>Updated the appendix with instructions for use for MDI and |

| Section | Changes to Protocol Amendment 1 (Version 2.0) |
|---|---|
| | [redacted] Sensor.<br><br>**Appendix H**<br><br>Updated Appendix with new abbreviation. |
| Throughout document | Updated as **CRO** instead of [redacted] across the document.<br><br>Updated as early study/IMP discontinuation instead of early study IMP discontinuation or early discontinuation.<br><br>Updated as participants instead of patients in relevant places. |

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