Clinical Study Protocol	
Study Intervention	PT010
Study Code	D5982C00007
Version	6.0
Date	19 November 2024

A Randomized, Double-Blind, Double Dummy, Parallel Group, Multicenter 24 to 52 Week Variable Length Study to Assess the Efficacy and Safety of Budesonide, Glycopyrronium, and Formoterol Fumarate Metered Dose Inhaler (MDI) Relative to Budesonide and Formoterol Fumarate MDI and Symbicort® Pressurized MDI in Adult and Adolescent Participants with Inadequately Controlled Asthma (KALOS)

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This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The Clinical Study Protocol is publicly registered, and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

Protocol Number: D5982C00007
Amendment Number: 5
Study Intervention(s): PT010, PT009, Symbicort® pMDI
Study Phase: III

Short Title: A Variable Length Efficacy and Safety Study to Assess an Inhaled, Fixed-dose, Triple-combination of Budesonide/Glycopyrronium/Formoterol Fumarate in Adult and Adolescent Participants with Inadequately Controlled Asthma (KALOS)

Medical Monitor Name and Contact Information will be provided separately

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SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
CSP version 6.0	19-Nov-2024
CSP version 5.0	29-Aug-2023
CSP version 4.0	21-Feb-2023
CSP version 3.0	07-Jan-2022
CSP version 2.0	27-Oct-2020
CSP version 1.0	23-Jul-2020

CSP Version 6.0 (Amendment 5): 19 November 2024

This modification is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union and in the EU Clinical Trial Regulation Article 2, 2 (13).

Overall Rationale for the Amendment:

An amendment was required to update the statistical methodological approaches to handling intercurrent events and the Type I error control procedure for CCI and CCI health authorities.

Summary of Changes:

List of Substantial Modifications

Section Number and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis, Section 3 Objectives and Endpoints, Section 9.1.1 Analysis Methods for Estimands, Section 9.1.2.2 CCI Approach, Section 9.4 Statistical Analyses	ICE strategies updated to align with the clinical question. Treatment Policy estimand strategy replaced with Primary strategy for handling ICEs and specified as Primary strategy for superiority analysis of primary and secondary endpoints and supportive strategy of NI analyses as well as selected tertiary endpoints for every Healthy Authority (CCI). While on Treatment strategy specified as a supportive strategy for superiority analysis of all primary and secondary endpoints.	To address FDA feedback on estimand strategies for handling ICEs and align on the clinical question being asked for every Health Authority, instead of different approaches for different Health Authorities.

List of Non-Substantial Modifications

Section Number and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis, Section 9.3 Populations for Analysis, Section 9.4 Statistical Analyses	The term Analysis Population was changed to "Analysis Set".	To align with ICH E9 and AstraZeneca guidance and standards.
Section 1.1 Synopsis, Section 9.3 Populations for Analysis, Section 9.4.2.3 Tertiary/ Exploratory Endpoints	The Rescue Albuterol Use set was removed.	The set would provide insufficient sample size for conducting that analysis.
Section 1.1 Synopsis, Section 9.3 Populations for Analysis	The PP Analysis Set was updated to exclude patients with IPDs impacting efficacy at the date of randomization.	To select only IPDs expected to impact the analysis.
Section 1.1 Synopsis, Section 9.3 Populations for Analysis	The Holter Monitoring Sub-Study Analysis Set was updated to exclude patients with IPD impacting the data prior to receiving study intervention.	To select the appropriate population for analysis.
Section 3 Objectives and Endpoints	EAIR added as an endpoint for AEs.	To reflect analysis and regulatory requirements for safety analyses.
Section 3 Objectives and Endpoints, Section 9.4.2.3 Tertiary/ Exploratory Endpoints, Section 9.4.4.3 Tertiary/ Exploratory Pooled Analyses	Added endpoint: "Time to first ICE of initiation of new asthma therapy or prohibited medications thought to impact efficacy in conjunction with discontinuation from study intervention" to the individual and pooled studies analyses.	Analysis of interest for interpretation of analyses utilizing the Primary strategy for ICEs.

Section Number and Name	Description of Change	Brief Rationale
Section 3 Objectives and Endpoints, Section 9.4.4.3 Tertiary/ Exploratory Pooled Analyses	Added endpoint: "Rate of severe asthma exacerbations resulting in a temporary course of systemic corticosteroids for at least 3 consecutive days" to the pooled study analyses.	Analysis of interest.
Section 3 Objectives and Endpoints	ICEs updated to include: "Initiation of new asthma therapy or administration of any additional prohibited medications thought to impact efficacy, including biological therapy/monoclonal antibodies, LABA, LAMA, or LTRA." The following ICEs were added: Dosing errors (only considered for the PK sub-study analyses) IPDs thought to impact efficacy (only considered for the NI analyses).	To capture medications that may affect the efficacy analyses and to facilitate the utilization of the Primary strategy for handling ICEs. ICEs added for PK and NI analyses as deemed relevant for analyses.
Section 9.1.2.2 CCI Approach	Multiple testing procedure for CCI approach: Clarified that the test for onset of action will only be conducted if both the pooled severe exacerbation rate and FEV_1 AUC0-3 are statistically significant.	Clarification
Section 9.1.2 Type I Error Control	The test conducted for onset of action will be 1-sided.	Update due to error.
Section 9.4.1.3 Baseline	Added definition for baseline reversibility, where data from Visit 2 is used (or Visit 3 in case Visit 2 is missing).	Clarification

Section Number and Name	Description of Change	Brief Rationale
Section 9.4.2.3 Tertiary/ Exploratory Endpoints, Section 9.4.4.2 Secondary Pooled Analyses, Section 9.4.4.4 12-Hour PFT Pooled Sub-Study Analyses	Covariates updated as follows: The 4-week intervals for analysis of eDiary data were updated to 13 intervals instead of 6 to capture entire study duration. For analysis of "Change from Baseline in FVC, PEFR, and FEF_{25-75}. Evaluated using AUC0-3 and AUC0-12", it was clarified that the relevant baseline value for the respective parameter will be used as covariate. For the analysis of "Change from Baseline in Morning/Evening Pre-Dose Trough PEFR", trough FEV_1 was removed as covariate. Study was added as a covariate for pooled analyses.	Covariates relevant for the analysis.
Section 3 Objectives and Endpoints, Section 9.4.3 Safety	QTcF category for analysis was updated from "value $\geq$ 500 msec or change from baseline $\geq$ 60 msec" to "value $>$ 500 msec or change from baseline $\geq$ 60 msec.	To match discontinuation criterion in Section 7.1.
Section 9.4.4.3	Updated censoring timepoints for CCI [redacted].	Clarification
Section 9.4.4.3 Tertiary/Exploratory Pooled Analyses, Table 4 Objectives and Endpoints for Pooled Analyses of Studies D5982C00007 and D5982C00008	Removed endpoint: "Time in days to permanent discontinuation of study intervention due to asthma exacerbation."	Insufficient amount of data expected to perform the analysis.
Section 8.1.2.7 CCI [redacted] (CCI [redacted] Endpoint	Night-time awakenings was removed from the CCI [redacted] criteria.	To align with AstraZeneca company standards.

Section Number and Name	Description of Change	Brief Rationale
Throughout	Minor editorial revisions including updates to Protocol Amendment History Appendix.	Minor, therefore not summarized.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF APPENDICES

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Randomized, Double-Blind, Double Dummy, Parallel Group, Multicenter 24 to 52 Week Variable Length Study to Assess the Efficacy and Safety of Budesonide, Glycopyrronium, and Formoterol Fumarate Metered Dose Inhaler (MDI) Relative to Budesonide and Formoterol Fumarate MDI and Symbicort® Pressurized MDI in Adult and Adolescent Participants with Inadequately Controlled Asthma (KALOS)

Short Title: A Variable Length Efficacy and Safety Study to Assess an Inhaled, Fixed-dose, Triple-combination of Budesonide/Glycopyrronium/Formoterol Fumarate in Adult and Adolescent Participants with Inadequately Controlled Asthma (KALOS)

Rationale: This study will evaluate the efficacy and safety of BGF MDI 320/28.8/9.6 µg and 320/14.4/9.6 µg twice daily (BID) compared with Budesonide and Formoterol Fumarate MDI 320/9.6 µg BID, hereinafter referred to as BFF MDI, and Symbicort® pressurized metered-dose inhaler (pMDI) 320/9 µg BID, hereinafter referred to as Symbicort, over a variable length treatment period, between 24 weeks and a maximum of 52 weeks. The study population will consist of adult and adolescent participants with asthma who remain inadequately controlled, as demonstrated by an Asthma Control Questionnaire (ACQ)-7 total score ≥1.5, despite treatment with a medium or high dose of inhaled corticosteroid (ICS)/long-acting beta$_2$-agonist (LABA).

This study is one of two confirmatory Phase III studies with identical designs (twin studies D5982C00007 and D5982C00008) to demonstrate benefits on improving lung function, health-related quality of life and rate of severe asthma exacerbations. The studies are identical, except for this study, D5982C00007, which has three sub-studies (24-hour Holter Monitor, 12-hour spirometry and 12-hour pharmacokinetic [PK]), and the second study (D5982C00008) which has only the 12-hour spirometry sub-study. The two studies will be combined for exacerbation analyses and 12-hour spirometry sub-study analyses to obtain adequate numbers of participants to support the pooled primary exacerbation endpoint and the pooled 12-hour spirometry endpoints.

Objectives and Endpoints

	Estimand			
Objective	**Population**	**Endpoint**	**Population Summary Measure**	**Strategy for Intercurrent Events**
Primary				
To assess the effect of BGF MDI relative to BFF MDI or Symbicort pMDI on lung function in participants with inadequately controlled asthma.	Participants with inadequately controlled asthma (symptomatic on medium to high-dose ICS with LABA)	CCI Change from baseline in FEV_1 AUC0-3 at Week 24 CCI [redacted]: Change from baseline in morning pre-dose trough FEV_1 over 24 Weeks CCI Change from baseline in morning pre-dose trough FEV_1 over 12 to 24 Weeks	Difference in mean change from baseline	**Primary strategy:** • Premature discontinuations from randomized study intervention: Treatment Policy, ie, all observed data used regardless of ICE. • Prolonged exposure to systemic corticosteroids or increased ICS dose for greater than 28 consecutive days or a single depot corticosteroid injection: Treatment Policy, ie, all observed data used regardless of ICE. • Initiation of new asthma therapy or administration of prohibited medications thought to impact efficacy: Composite (data following ICE will be imputed as treatment failures) if in conjunction with premature IP discontinuation, otherwise Treatment Policy. **Supportive strategy:** • Premature discontinuations from randomized study intervention:

	Estimand			
Objective	**Population**	**Endpoint**	**Population Summary Measure**	**Strategy for Intercurrent Events**
				While on Treatment, ie, data after ICE will not be used. • Prolonged exposure to systemic corticosteroids or increased ICS dose for greater than 28 consecutive days or a single depot corticosteroid injection: While on Treatment, ie, data after ICE will not be used. • Initiation of new asthma therapy or administration of prohibited medications thought to impact efficacy following first dose of randomized IP: While on Treatment, ie, data after ICE will not be used.
Key Secondary				
To assess the effect of BGF MDI relative to BFF MDI or Symbicort pMDI on lung function in participants with inadequately controlled asthma.	Participants with inadequately controlled asthma (symptomatic on medium to high-dose ICS with LABA)	CCI Change from baseline in morning pre-dose trough FEV_1 at Week 24 CCI Change from baseline in FEV_1 AUC0-3 over 12 to 24 Weeks CCI Change from baseline in FEV_1 AUC0-3 over 24 Weeks.	Difference in mean change from baseline	Same as primary and supportive strategy for primary endpoint.

[a] "CCI [redacted] refers to submission strategy with respect to Health Authority responsible for reviewing marketing authorization, not the recruitment location/nationality of the participants.

The data from studies D5982C00007 and D5982C00008 will be pooled and analyzed according to the objectives and endpoints for the pooled analysis listed in the table below.

	Estimand			
Objective	**Population**	**Endpoint**	**Population Summary Measure**	**Strategy for Intercurrent Events**
Primary Pooled Analysis Objective				
To assess the effect of BGF MDI relative to BFF MDI or Symbicort pMDI on asthma exacerbations in participants with inadequately controlled asthma.	Participants with inadequately controlled asthma (symptomatic on medium to high-dose ICS with LABA)	Rate of severe asthma exacerbations over the Treatment Period	Rate ratio	Same as primary and supportive strategy for primary endpoint for individual study.

Overall Design

This is a Phase III randomized, double-blind, double dummy, parallel group, multicenter variable length efficacy and safety study comparing two doses of BGF MDI (320/28.8/9.6 µg and 320/14.4/9.6 µg) to BFF MDI 320/9.6 µg (an ICS/LABA currently under development) and Symbicort pMDI 320/9 µg in adult and adolescent participants who have asthma which remains inadequately controlled (ACQ-7 total score ≥1.5) despite treatment with a medium or high dose of ICS/LABA. All doses represent the sum of two actuations. All study interventions will be administered twice daily (BID) for a minimum of 24 weeks and a maximum of 52 weeks.

This study will be conducted at approximately 420 sites worldwide and will randomize approximately 2200 adult and adolescent participants. The number of participants per treatment arm may be increased based on a blinded sample size re-estimation (BSSR) as described in the Statistical Analysis Plan (SAP).

The study is variable in length, with a planned minimum of 24 weeks and a maximum of 52 weeks on randomized study intervention with up to 15 in-clinic visits during screening and treatment. The study will end when the last randomized participant completes 24 weeks on randomized study intervention and a 2-week safety follow up, telephone call. In addition to a potential sample size increase, the BSSR may also extend the study duration, for example such that all participants complete a 52week dosing period. There is a 12-hour spirometry sub-study in a subset of approximately CCI randomized adult and adolescent participants across the two studies D5982C00007 and D5982C00008 (to ensure completion of CCI participants) at Visit 5 (Day 1) and Visit 8 (Week 12). There is a 12hour Pharmacokinetic (PK) sub-study in a subset of approximately CCI adult and adolescent participants (at least CCI participants per treatment group should be 12 to <18 years of age) who have been confirmed to have taken the last 6 inhalations from each randomized study intervention (3 doses from each) as captured in the daily eDiary prior to Visit 8. Additionally, there is a 24-hour Holter Monitor sub-study in a subset of approximately CCI of the randomized participants. In these participants, a 24-hour Holter monitor will be collected between Visits 4 and 5 (Holter Monitor baseline) and at Visit 6 (Week 4) and Visit 11 (Week 24).

Participants meeting randomization criteria at Visit 5 will discontinue run-in BFF MDI and in previous versions of the protocol were randomized in a 1:1:1:1 scheme to 1 of 4 treatment groups. CCI

Randomization will be assigned based on 2 cohorts: adults and adolescents. For adults, randomization will be stratified by country, baseline pre-bronchodilator percent predicted FEV_1 (≤55% vs. >55%), severe exacerbation history in the 12 months prior to Visit 1 (0, 1, ≥2), and ICS dose (medium vs. high). For adolescents, randomization will be stratified by country and baseline pre-bronchodilator percent predicted FEV_1 (≤75% vs. >75%).

The study has a Data Monitoring Committee and Independent Adjudication Committee(s) (IAC).

Disclosure Statement: This is a parallel group treatment study with 4 arms that is participant and Investigator blinded.

Number of Participants: Approximately 6300 participants will be screened to achieve 2200 randomly assigned to study intervention.

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 in the study, are considered "screen failures", unless otherwise specified by the protocol.

Intervention Groups and Duration: The study is variable in length, with a planned minimum of 24 weeks and a maximum of 52 weeks on randomized study intervention taken as 2 inhalations twice-daily, with up to 15 in-clinic visits during screening and treatment. The study will end when the last randomized participant completes 24 weeks of the randomized study intervention and has a 2-week safety follow-up via telephone. The BSSR may result in increases (but not decreases) to the sample size and/or duration, for example such that all participants complete a 52-week dosing period.

Data Monitoring Committee: Yes

Statistical methods

Primary and Key Secondary Efficacy Analysis: The primary endpoints of change from baseline in FEV_1 AUC_{0-3} (CCI key secondary endpoint for CCI and CCI and change from baseline in morning pre-dose trough FEV_1 (CCI , and CCI key secondary endpoint for CCI will each be analyzed using a repeated measures analysis of covariance model. The model will include treatment, visit, prior ICS dose (medium vs. high), and treatment-by-visit interaction as categorical covariates and baseline trough FEV_1 and percent reversibility as continuous covariates. Contrasts will be used to obtain estimates of the treatment differences at Week 24. Two-sided p-values and point estimates with 2-sided 95% confidence intervals (CIs) will be produced for each treatment difference. The model-based statistics for other visits, over 24 Weeks or over 12 to 24 Weeks will also be reported.

Primary Pooled Analysis: The data from studies D5982C00007 and D5982C00008 will be pooled and analyzed. The rate of severe asthma exacerbations is the primary endpoint for the pooled analysis. It will be analyzed with negative binomial regression. Asthma exacerbations will be considered separate events if more than 7 days are between the recorded stop date of the earlier event and start date of the later event. Time at risk of experiencing a severe exacerbation will be used as an offset variable in the model. Time during a severe exacerbation or in the 7 days following a severe exacerbation will not be included in the calculation of exposure. Treatments will be compared adjusting for baseline trough FEV_1, percent reversibility, baseline severe asthma exacerbation history (0, 1, ≥ 2), prior ICS dose (medium vs. high), region, and study.

Sample Size: A sample size of 2200 participants (approximately 550 participants per treatment group) will provide probabilities of over 99% to detect a CCI mL difference at Week 24, over 12 to 24 Weeks, and over 24 Weeks between BGF MDI 320/28.8/9.6 µg versus BFF MDI 320/9.6 µg or BGF MDI 320/28.8/9.6 µg versus Symbicort pMDI 320/9 µg in the analysis of change from baseline in FEV_1 AUC_{0-3}. The assumed standard deviation (SD) is CCI mL at each visit based on an internal CCI months Phase II/III dose-ranging study of CCI MDI. The effective SD of CCI mL for over 12 to 24 Weeks assumes 2 visits and that the correlation among visits is CCI. The effective SD of CCI mL for over 24 Weeks assumes 3 visits over the interval and that the correlation among visits is CCI. The 2-sided alpha for each pairwise comparison is CCI per the procedure to control Type I error across comparisons for the two BGF MDI dose levels. This sample size assumes that approximately CCI% of randomized participants will have discontinued study intervention prior to Week 4, CCI% prior to Week 12, and CCI% at Week 24.

A sample size of 2200 participants (approximately 550 participants per treatment group) will provide power of 93%, 99%, and 99% to detect a CCI mL difference at Week 24, over 12 to 24 Weeks, and over 24 Weeks, respectively, between BGF MDI 320/28.8/9.6 µg versus BFF MDI 320/9.6 µg or BGF MDI 320/28.8/9.6 µg versus Symbicort pMDI 320/9 µg in the analysis of change from baseline in morning pre-dose trough FEV_1. The assumed SD is CCI mL at each visit based on an internal CCI months Phase II/III dose-ranging study of CCI MDI. For the at Week 24 endpoint, the SD is estimated as CCI mL and assumes CCI% of randomized participants will have discontinued treatment by Week 24. The effective SD of CCI mL for over 12 to 24 Weeks assumes CCI% of randomized participants will have discontinued treatment by Week 12, the remaining participants will complete 3 visits in the interval on average, and that the correlation among visits is CCI. For the interval of over 24 Weeks, the effective SD is estimated as CCI mL assuming CCI% of randomized participants will have discontinued treatment by Week 4, the remaining participants will complete 4 visits on average, and a correlation of CCI between visits. The 2-sided alpha for each pairwise comparison is CCI per the procedure to control Type I error across comparisons for the two BGF MDI dose levels.

A BSSR may be conducted approximately three months prior to last-patient-in in the study considered to be completing earlier (of the two replicate studies). The primary/key secondary lung function endpoints (FEV_1 AUC_{0-3} and morning pre-dose trough FEV_1) will be analyzed. In addition, the underlying rate of severe asthma exacerbations and negative binomial shape parameter will be predicted and the sample size potentially increased (but not decreased) using information from both studies. The increase in sample size will be capped at CCI participants per arm for the 2 combined studies, such that the total number of randomized participants will not exceed CCI for the 2 combined studies. The operating characteristics of the BSSR will be fully detailed in the BSSR SAP, if it is decided to conduct a BSSR.

Pooled Analyses: The data from studies D5982C00007 and D5982C00008 will be pooled and analyzed for severe asthma exacerbations. A sample size of 1100 participants per arm will also provide 80% probability to detect a CCI% reduction in the rate of severe asthma exacerbations for BGF MDI 320/28.8/9.6 µg versus BFF MDI 320/9.6 µg or BGF MDI 320/28.8/9.6 µg versus Symbicort pMDI 320/9 µg. The assumed 2-sided alpha for each pairwise comparison is CCI per the Type I error control procedure. This calculation assumes a dispersion parameter of CCI and an annualized event rate for BFF MDI 320/9.6 µg or Symbicort pMDI 320/9 µg of CCI [Virchow 2019, Kerstjens 2020, Lee 2021]. An average exposure time of CCI years is also assumed.

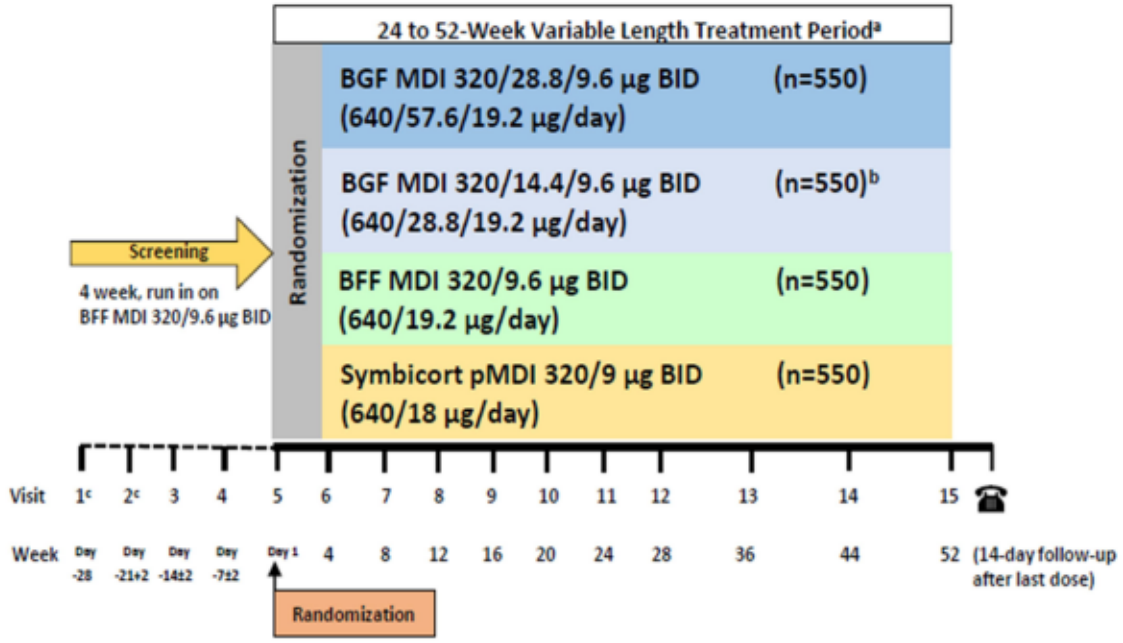
The secondary endpoints, percentage responders in ACQ-5, ACQ-7, and AQLQ(s)+12, will also be analyzed using the pooled data from both studies. The results from the pooled analyses of ACQ-5 and ACQ-7 will be included for all regulatory submissions. The results from the AQLQ(s)+12 pooled analysis will only be included in the submission to the EU Health Authority.

Populations for Analyses: The following analysis sets are defined for this study, Enrolled, Randomized, Efficacy, Safety, Per Protocol (PP), Pharmacokinetic (PK), Pulmonary Function Test (PFT) sub-study, and Holter Monitor sub-study. The Efficacy Analysis Set is defined as all participants who are randomized to study intervention and receive any amount of study intervention. The Safety Analysis Set is defined as all participants who are randomized to treatment and receive any amount of randomized study intervention. The PP Analysis Set is defined as all participants in the Efficacy Set without an important protocol deviation (IPD) impacting efficacy at the date of randomization. The PK Analysis Set is defined as all participants in the Efficacy Analysis Set who enrolled in the PK sub-study, who have at least one post-dose PK measurement and who have correctly self-administered the last 3 doses of study intervention (6 inhalations) in order to have achieved steady state by their Visit 8. The PFT Sub-Study Analysis Set is defined as all participants who are randomized to the PFT sub-study and have at least one post-baseline spirometry assessment (after the first dose of study intervention). The Holter Monitor Sub-Study Analysis Set is defined as all participants in the Safety Analysis Set who enrolled in the Holter Monitoring sub-study, had no IPD

impacting the data prior to receiving study intervention, and had at least 18 hours of acceptable quality Holter monitoring data at both Visit 4 (Holter baseline) and at least one of Visit 6 (Week 4) and Visit 11 (Week 24).

1.2 Schema

Figure 1 Study Design



[a] This study is variable in length with a planned minimum of 24 weeks and a maximum of 52 weeks on randomized treatment.

[b] CCI

n.

[c] CCI

BGF= Budesonide, Glycopyrronium, and Formoterol Fumarate, BFF= Budesonide and Formoterol Fumarate, MDI= Metered Dose Inhaler, BID= twice daily, pMDI= pressurized MDI

1.3 Schedule of Activities

Table 1 Schedule of Activities

	Screening[a]				Treatment Period											F/U TC	
Visit[b,c]	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15/Final/ WD Visit	UNSCH (as-needed activities)	2 weeks (±2 days) after last dose	Details in CSP Section or Appendix
Week					Rand	4	8	12	16	20	24	28	36	44	52			
Study Day[d]	-28	-21 (+2)	-14 (±2)	-7 (±2)	1	29 (±2)	57 (±5)	85 ±5)	113 (±5)	141 (±5)	169 (±5)	197 (±5)	253 (±5)	309 (±5)	365 (±5)			
Informed consent/assent[q]	X																	Section 4.1, Section 5.1, Appendix A 3
Inclusion /exclusion criteria	X	X	X	X	X													Section 5.1, Section 5.2
Verify continuing eligibility						X	X	X	X	X	X	X	X	X	X	X		Section 7.1
Randomization criteria					X													Section 5.3
Calculate PEFR stability limits					X													Section 8.1.3.3
Routine clinical procedures																		
Demography and medical/surgical history	X																	Section 8.2.1
Respiratory medical history	X	X																Section 8.2.1.1
Prior/concomitant medication review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 6.5
Dispense/collect eDiary	X[e]														X			Section 8.1.3
eDiary training and review	X[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		Section 8.1.3

Table 1 Schedule of Activities

	Screening[a]				Treatment Period											F/U TC	
Visit[b,c]	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15/Final/ WD Visit	UNSCH (as-needed activities)	2 weeks (±2 days) after last dose	Details in CSP Section or Appendix
Week					Rand	4	8	12	16	20	24	28	36	44	52			
Study Day[d]	-28	-21 (+2)	-14 (±2)	-7 (±2)	1	29 (±2)	57 (±5)	85 ±5)	113 (±5)	141 (±5)	169 (±5)	197 (±5)	253 (±5)	309 (±5)	365 (±5)			
Peak flow meter training and dispensed/collected	X[e]														X	X		Section 8.1.3.3
Reversibility to albuterol		X	X[f]															Table 2, Section 8.1.1.3
FeNO (Pre-dose at Visit 5)	X				X													Section 8.1.5
Dispense/collect albuterol (as needed)	X[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		Section 4.1, Section 6, Section 6.5.1
Discontinue ICS/LABA	X[e]																	Section 4.1, Section 6
Dispense/collect Run-in BFF MDI	X[e]				X													Section 4.1, Section 6
Dispense/collect blinded study intervention					X	X	X	X	X	X	X	X	X	X	X	X		Section 4.1, Section 6
Safety assessments																		
Adverse Events (AE) (Including asthma exacerbations that meet the serious AE definition)[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 8.1.2, Section 8.3, Section 8.4, Appendix B
Pregnancy testing (urine)[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			Section 5.1

Table 1 Schedule of Activities

	Screening[a]				Treatment Period											UNSCH (as-needed activities)	F/U TC	Details in CSP Section or Appendix
Visit[b,c]	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15/Final/ WD Visit		2 weeks (±2 days) after last dose	
Week					Rand	4	8	12	16	20	24	28	36	44	52			
Study Day[d]	-28	-21 (+2)	-14 (±2)	-7 (±2)	1	29 (±2)	57 (±5)	85 ±5)	113 (±5)	141 (±5)	169 (±5)	197 (±5)	253 (±5)	309 (±5)	365 (±5)			
Safety laboratory assessments (blood collection)	X				X						X				X	X		Section 8.2.7
Physical examination	X				X						X				X	X		Section 8.2.2
Height/Weight	X										X[h]				X[h]			Section 8.2.3
Vital signs (Blood pressure/pulse)	X				X	X					X				X	X		Section 8.2.4
12-lead ECG (full study population)[j]	X					X		X			X				X	X		Section 8.2.5
Holter monitor placement/removal (sub-study)				X		X					X							Section 8.2.6
ECGs for participants in Holter monitor sub-study					X[l, m]	X[m]		X[m]			X[m]		X[m]		X[m]			Section 8.2.5
Other assessments and exploratory measurements																		
Exploratory biomarker sampling (serum)					X										X			Section 8.6
Genomics Initiative, optional exploratory genetic sample (except for adolescent participants)					X													Section 8.7, Appendix D

Table 1 Schedule of Activities

	Screening[a]				Treatment Period												F/U TC	
Visit[b,c]	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15/Final/ WD Visit	UNSCH (as-needed activities)	2 weeks (±2 days) after last dose	Details in CSP Section or Appendix
Week					Rand	4	8	12	16	20	24	28	36	44	52			
Study Day[d]	-28	-21 (+2)	-14 (±2)	-7 (±2)	1	29 (±2)	57 (±5)	85 ±5)	113 (±5)	141 (±5)	169 (±5)	197 (±5)	253 (±5)	309 (±5)	365 (±5)			
Efficacy measurements[r]																		
Asthma exacerbations					X	X	X	X	X	X	X	X	X	X	X	X		Section 8.1.2
Serial spirometry[i]					X	X		X			X				X			Table 2, Section 8.1.1
Pre-dose spirometry[i]	X[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X			Table 2, Section 8.1.1
ACQ (Pre-dose)	X		X		X	X	X	X	X	X	X	X	X	X	X			Section 8.1.4.1
AQLQ(s)+12 (Pre-dose)					X	X		X		X	X	X	X	X	X			Section 8.1.4.2
SGRQ (Evening prior to visit)					X	X					X							Section 8.1.3.7
PGIC (Pre-dose)								X			X				X			Section 8.1.4.4
EQ-5D (Pre-dose)					X	X	X	X	X	X	X	X	X	X	X			Section 8.1.4.3
Weekly 5-item OEQ at home (12-hour spirometry sub-study only)[k]					X	X		X										Section 8.1.3.8
Healthcare resource utilization				X		X	X	X	X	X	X	X	X	X	X			Section 8.8
Serial spirometry (and OEQ item) 12-hrs post-dose (12-hour spirometry sub-study)					X			X										Table 2, Section 8.1.1
12-hour PK profile (sub-study)								X										Table 2, Section 8.5.1

Table 1 Schedule of Activities

	Screening[a]				Treatment Period											F/U TC	
Visit[b,c]	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15/Final/ WD Visit	UNSCH (as-needed activities)	2 weeks (±2 days) after last dose	Details in CSP Section or Appendix
Week					Rand	4	8	12	16	20	24	28	36	44	52			
Study Day[d]	-28	-21 (+2)	-14 (±2)	-7 (±2)	1	29 (±2)	57 (±5)	85 ±5)	113 (±5)	141 (±5)	169 (±5)	197 (±5)	253 (±5)	309 (±5)	365 (±5)			
Study intervention administration																		
Check inhalation device technique and training	X[e]	X	X	X	X	X	X	X	X	X	X	X	X	X		X		Section 6
Administer Run-in BFF MDI in clinic [e,j,n]	X	X	X	X														Section 4.1, Section 6
Administer blinded study intervention in clinic[n]					X	X	X	X	X	X	X	X	X	X	X[p]			Section 4.1, Section 6
Provide prednisolone or equivalent as needed for severe asthma exacerbations[o]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		Section 6.5.2, Section 8.1.2.4

[a] Screening period can be extended for participants who experience a respiratory tract infection or asthma exacerbation (see Section 5.5.2).

[b] Risk assessments for the SARS-CoV-2 pandemic must be made prior to every in-clinic visit in-line with the Study Disruptions Mitigation Instructions.

[c] Sites should call participants 1 to 2 days before each scheduled visit to remind them of the upcoming visit and required timings (See Section 4.1 and Section 8.1.1.2). Participants will be required to return to the clinic at approximately the same time ±1 hr as Visit 1 throughout study. For all visits after Visit 1, if albuterol and study intervention have not been withheld for the specified timeframes (see Section 8.1.1.2), then visits should be rescheduled and conducted within the specified visit windows.

[d] Site should make every effort to maintain participants within the scheduled visit windows. Participants who fall outside the visit window should be placed in the protocol-defined window at the next scheduled visit.

[e] At Visit 1, issue/train participants on eDiary/peak flow meter use, discontinue ICS/LABA, and dispense albuterol and run-in BFF MDI **only** after the participant has been found eligible to proceed to Visit 2. Should there be any concern that the ICS/LABA was taken prior to Visit 1, this visit should be rescheduled within two business days.

[f] If reversibility criterion is not met at Visit 2, participants may continue to Visit 3. Reversibility criterion must be met either in the 12 months prior to Visit 1 or at Visit 2 or Visit 3, otherwise the participant will be screen-failed.

[g] For all screen failures, an assessment of AEs and highly sensitive urine pregnancy testing (for women of childbearing potential) must be performed within 7 days of the screen failure date.

[h] For adolescent participants only, height and weight will be assessed at Visits 11 and Visit 15/Study Intervention Discontinuation and/or Study Withdrawal.

[i] All pre-dose (trough) spirometry will be required to be conducted in the morning (0800 ±2 hours).

[j] Participants who have not withheld asthma medications prior to Visit 1 and failed spirometry testing per Inclusion #6 at Visit 1 should return to the clinic to repeat spirometry testing and ECG within two business days. If repeat spirometry failed, then participant must be screen-failed. There must be a minimum of 7 days between Visit 1 and Visit 2.

[k] The weekly 5-item OEQ is only for participants in the 12-hour spirometry sub-study. The weekly 5-item OEQ will be completed at home on the eDiary weekly at Weeks 1, 2, 3, 4, and 12 after randomization.

[l] Six pre-dose ECGs readings should be taken for participants in the Holter monitor sub-study at Visit 5.

[m] Triplicate ECG readings should be taken for participants in the Holter monitor sub-study at Visit 5 post-dose, Visit 8 pre-dose and post-dose, and Visits 6, 11, 13, and 15/Final pre-dose. See Table 2 for timings of post-dose assessments.

[n] All in-clinic dosing must occur prior to 1000 (+1-hour allowance). Study intervention will be provided in a double dummy fashion whereby participants randomized to BGF MDI or BFF MDI are given placebo pMDI to match Symbicort pMDI and participants randomized to Symbicort pMDI are given placebo MDI to match BGF/BFF MDI. In-clinic dosing time is recorded as the time of the second puff of the last device used.

[o] Prednisolone or equivalent can be dispensed to a participant experiencing a severe asthma exacerbation at any visit. If the participant has signed the informed consent and receives prednisolone or equivalent at Visit 1 up to Visit 5, they should not be randomized to a blinded study intervention at Visit 5 until at least 4 weeks after the last dose of prednisolone or equivalent. The Screening Period can be extended as detailed in Section 5.5.2.

[p] Not applicable at a Study Intervention Discontinuation and/or Study Withdrawal Visit.

[q] Informed Consent Form can be signed at or prior to Visit 1.

[r] The suggested order of assessments is vital signs, AE/SAE assessments, 60-minute pre-dose spirometry, PRO questionnaires, 30-minute pre-dose spirometry, ECG, blood draw, and then study intervention administration. **Spirometry MUST be performed in accordance with the specified timing.**

Abbreviations: ACQ=Asthma Control Questionnaire; AEs=adverse events; AQLQ(s)+12=Asthma Quality of Life Questionnaire for 12 years and older; BFF=budesonide and formoterol fumarate; CSP=clinical study protocol; ECG=electrocardiogram; eDiary=electronic diary; EQ-5D=European Quality-of-Life-5 Dimensions Questionnaire; FeNO=fractional exhaled nitric oxide; F/U=follow-up; ICS/LABA=inhaled corticosteroid/long-acting beta$_2$-agonist; MDI=metered-dose inhaler; OEQ=Onset of Effect Questionnaire; PEFR=peak expiratory flow rate; PGIC=patient global impression of change; PK=pharmacokinetic; PRO=patient reported outcome; Rand=randomization; SAE=serious adverse event; SGRQ=St. George's Respiratory Questionnaire; TC=telephone call; UNSCH=unscheduled; WD= Study Intervention Discontinuation and/or Study Withdrawal Visit

Ensure pre-dose spirometry assessments are conducted as close to the specified timepoints as possible. All study procedures will be conducted prior to dosing at the visit, except for post-dose spirometry, post-dose pharmacokinetic (PK) sampling, and Onset of Effect Questionnaire (OEQ) item.

Table 2 provides timing of specific assessments during visits. For the Holter, 12-hour spirometry and PK sub-studies, if spirometry or the OEQ item occur at the same time as ECG or PK assessments, then the ECG should be performed first, followed by drawing the PK sample and then the spirometry maneuvers and finally the OEQ item.

Table 2 Timing of Spirometry, ECG (for Holter Monitor Sub-Study), and Pharmacokinetic Measurements

	Visits	Pre-dose[a]		Post-dose[a]														
		Minutes		Minutes						Hours								
		-60 (±10)	-30 (±10)	2	5 (±2)	15 (±5)	20	30 (±5)	40	1 (±10 min)	2 (±10 min)	3 (±10 min)	4	6 (±10 min)	8	9 (±10 min)	10	12 (±10 min)
Spirometry	1, 4, 7, 9, 10, 12, 13, 14	X	X															
	2 (reversibility to albuterol) and 3 (reversibility to albuterol, if needed)	X	X					X		X[b]								
	5, 6, 8, 11, 15/Final, Treatment Discontinuation/Study Withdrawal	X	X		X[c]	X		X		X	X	X						
Sub-study spirometry	12-hour spirometry sub-study at Visits 5 and 8	X	X		X[c]	X		X		X	X	X		X		X		X
OEQ item[d]	12-hour spirometry sub-study at Visits 5 and 8			X	X	X		X		X								
PK	12-hour PK sub-study at Visit 8		X	X	X		X		X	X	X		X		X		X	X
ECG	Holter Monitor sub-study at Visits 6, 11, 13, 15/Final		X[f]															
	Holter Monitor sub-study at Visit 5		X[e]					X[f]					X[f]					
	Holter Monitor sub-study at Visit 8		X[f]			X[f]												

[a] Time windows apply to spirometry assessments only.
[b] For reversibility to albuterol **only**,1-hour spirometry post-dose may be assessed, if not reversible at 30 minutes post dose.
[c] Only applies to Visit 5.
[d] Only for participants in the 12-hour spirometry sub-study and will be the last assessment performed at each specified timepoint. See Section 8.1.4.5.
[e] Six ECG readings will be recorded pre-dose.
[f] Three ECG reading will be recorded at these timepoints.

2 INTRODUCTION

AstraZeneca is developing a family of orally inhaled drug products containing budesonide, glycopyrronium, and formoterol fumarate as dual and triple combination products. These drug products are formulated as a suspension with micronized active pharmaceutical ingredients and Co-Suspension™ Delivery Technology delivered in metered-dose inhalers (MDIs). The Co-Suspension Delivery Technology consists of spray-dried porous particles comprised of the phospholipid 1,2-distearoyl-sn-glycero-3-phosphocholine and calcium chloride suspended in a hydrofluoroalkane (HFA) propellant. When used in combination MDI products, these particles form strong non-specific associations with the active pharmaceutical ingredients, preventing the drugs from interacting with each other in the suspension and providing reproducible drug delivery and long-term stability.

The test formulation to be evaluated in this study is an MDI with a CCI containing a fixed-dose triple combination of budesonide (an inhaled corticosteroid, ICS), glycopyrronium (a long-acting muscarinic antagonist, LAMA), and formoterol fumarate (a long-acting beta$_2$-agonist, LABA). The MDI used for Budesonide, Glycopyrronium, and Formoterol Fumarate and Budesonide and Formoterol Fumarate is different than that for Symbicort; therefore, the study is set up as a double dummy design for blinding purposes.

2.1 Study Rationale

Budesonide, Glycopyrronium, and Formoterol Fumarate MDI, hereinafter referred to as BGF MDI, is being fully developed for use in the treatment of asthma. There are adult and adolescent patients with asthma who remain inadequately controlled despite treatment with a medium or high dose of ICS/LABA, and the Global Initiative for Asthma (GINA) guidelines [GINA 2020] recommend a step-up in therapy. The addition of LAMA to ICS/LABA is an appropriate treatment option in this population. The aim of this study is to demonstrate benefit of the fixed-dose triple combination of ICS/LAMA/LABA in reducing severe asthma exacerbations and improving lung function and health-related quality of life measures.

This study will evaluate the safety and efficacy of BGF MDI 320/28.8/9.6 µg and 320/14.4/9.6 µg twice daily (BID) compared with Budesonide and Formoterol Fumarate MDI 320/9.6 µg BID, hereinafter referred to as BFF MDI, and Symbicort® pressurized metered-dose inhaler (pMDI) 320/9 µg BID, hereinafter referred to as Symbicort, over a variable length treatment period, between 24 weeks and a maximum of 52 weeks. The study population will consist of adult and adolescent participants with asthma who remain inadequately controlled, as demonstrated by an Asthma Control Questionnaire (ACQ)-7 total score ≥1.5, despite treatment with a medium or high dose of ICS/LABA.

This study is one of two confirmatory Phase III studies with identical designs (twin studies D5982C00007 and D5982C00008) to demonstrate benefits on improving lung function,

health-related quality of life and rate of severe asthma exacerbations. The studies are identical, except for this study, D5982C00007, which has three sub-studies (24-hour Holter Monitor, 12-hour spirometry and 12-hour pharmacokinetic [PK]), and Study D5982C00008 which has only the 12-hour spirometry sub-study. The two studies will be combined for exacerbation analyses and 12-hour spirometry sub-study analyses to obtain adequate numbers of participants to support the pooled primary exacerbation endpoint and the pooled 12-hour spirometry endpoints.

2.2 Background

Asthma is a heterogeneous disease that is characterized by chronic airway inflammation and bronchial hyperreactivity. It is defined by a history of respiratory symptoms such as wheeze, shortness of breath, chest tightness, and cough that vary over time and in intensity, together with variable expiratory airflow obstruction. The variations in symptoms and airflow obstruction are often triggered by factors such as exercise, allergen or irritant exposure, changes in weather, noxious fumes, or viral respiratory infections. These responses are more likely when asthma is uncontrolled. Symptoms and airflow obstruction may resolve spontaneously or in response to therapy. Importantly, worsening asthma symptoms/airway obstruction can be severe, resulting in an asthma exacerbation that may be life-threatening. Such events pose a significant burden to patients and result in significant direct and indirect economic costs [GINA 2020].

Asthma affects approximately 339 million people in all regions of the world. Globally, there are roughly 1000 asthma-related deaths per day, and this condition is among the leading causes of disability [Global Asthma Network 2018]. Contextually, in the United States (US), the prevalence of current asthma is estimated at 7.7% in adults as of 2017 [CDC 2017]. Among these individuals, asthma is uncontrolled (based on the degree of impairment and while on treatment [NAEPP Expert Report 3, 2007]) in an estimated 61.9% of adults [CDC 2016]. Approximately 43.6% of adults with current asthma have had at least 1 asthma exacerbation in the previous 12 months [CDC 2017].

The long-term goals of asthma management are risk reduction and symptom control. The aim is to reduce the patient burden and risk of asthma-related death, exacerbations, airway damage, and medication side effects. The patient's own goals regarding their asthma and its treatment should also be identified [GINA 2020]. This concept encompasses 2 components: (1) patient's recent clinical status and current disease impact which includes assessment of symptoms, night awakenings, use of rescue medication, and lung function and (2) patient assessment for future risk of exacerbations, decline in lung function, or treatment-related side effects.

Poor asthma symptomatic control is a risk factor for future asthma exacerbations [GINA 2020]. According to the GINA guidelines, asthma is controlled when patients can avoid

troublesome symptoms during the night and day; need little to no reliever medication; have productive, physically active lives; have normal or near normal lung function; and avoid serious flare-ups (exacerbations or attacks) [GINA 2020].

The GINA guidelines specify 5 treatment steps for asthma, each step outlining options for higher levels of treatment for controlling asthma in patients 12 years of age and older [GINA 2020]. Within this stepwise approach, GINA proposes a classification of asthma severity based on the type and intensity of controller medication required for the control of the disease (Steps 1 to 5). This classification of asthma severity is then assessed retrospectively once the patient is on regular controller treatment for several months.

For patients whose asthma is not well controlled despite the use of a medium to high dose ICS/LABA, treatment options include adding a LAMA, such as tiotropium, and in certain subsets of patients, biologic agents (eg, benralizumab, omalizumab, mepolizumab, dupilumab), low-dose oral corticosteroids, azithromycin and bronchial thermoplasty [GINA 2020]. Subsequently, LAMAs can provide an important step up in care before escalation to systemic or invasive therapies such as bronchial thermoplasty, thus having a significant role in the management of asthma when used in combination with other controller medications.

A detailed description of the chemistry, pharmacology, efficacy, and safety of BGF MDI, BFF MDI, and Symbicort pMDI is provided in the Investigator's Brochures.

2.3 Benefit/Risk Assessment

Budesonide, glycopyrronium, and formoterol fumarate are approved in many countries worldwide in multiple formulations for different indications, such as the treatment of chronic obstructive pulmonary disease (COPD) and asthma.

In order to evaluate the clinical benefit/risk balance, efficacy and safety data are available from Phase I, II, and III studies (AstraZeneca COPD/asthma program) evaluating data with budesonide, glycopyrronium, and formoterol fumarate as single agents or in dual or triple combinations. Budesonide, glycopyrronium, and formoterol fumarate have been well tolerated with favorable safety profiles identified in studies to date. The recently completed dose ranging study with different glycopyrronium doses in participants with asthma over 6 months (PT001102) did not identify any new safety concerns. Glycopyrronium doses of 28.8 µg and 14.4 µg administered twice-daily with an ICS/LABA in the PT001102 study are being evaluated in this study as part of the fixed-dose triple combination of BGF MDI.

Potential risks with BGF MDI will be mitigated by the selected inclusion/exclusion criteria and continuous monitoring of safety data during the study. Benefits of BGF MDI over BFF MDI and Symbicort in this study are expected to include an improvement in lung function, a decrease in severe asthma exacerbations, and an improvement in patient reported outcomes (PROs), and quality of life measures.

More detailed information about the known and expected benefits, and potential risks of BGF MDI, BFF MDI, and Symbicort pMDI is provided in the Investigator's Brochures.

This global study may be initiated or conducted during the SARS-CoV-2 pandemic, another civil crisis, natural disaster, or public health crisis; the regional and/or country level risk may vary during the conduct of the study. Guidance will be ratified with local regulations, health authority and relevant professional bodies to minimize the expected direct risks to site personnel and study participants. Alternative measures and procedures may be implemented during the conduct of the study as described in Section 4.2. Risk assessments for the SARS-CoV-2 pandemic must be made prior to every in-clinic visit in-line with the Study Disruptions Mitigation Instructions.

3 OBJECTIVES AND ENDPOINTS

Table 3 Objectives and Endpoints

	Estimand			
Objective	**Population**	**Endpoint**	**Population Summary Measure**	**Strategy for Intercurrent Events[a]**
Primary				
To assess the effect of BGF MDI relative to BFF MDI or Symbicort pMDI on lung function in participants with inadequately controlled asthma.	Participants with inadequately controlled asthma (symptomatic on medium to high-dose ICS with LABA)	CCI Change from baseline in FEV_1 AUC0-3 at Week 24 CCI [redacted]: Change from baseline in morning pre-dose trough FEV_1 over 24 Weeks CCI Change from baseline in morning pre-dose trough FEV_1 over 12 to 24 Weeks	Difference in mean change from baseline	**Primary strategy:** • Premature discontinuations from randomized study intervention: Treatment Policy, ie, all observed data used regardless of ICE. • Prolonged exposure to systemic corticosteroids or increased ICS dose for greater than 28 consecutive days or a single depot corticosteroid injection: Treatment Policy, ie, all observed data used regardless of ICE. • Initiation of new asthma therapy or administration of prohibited medications thought to impact efficacy: Composite (data following ICE will be imputed as treatment failures) if in conjunction with premature IP

Table 3 Objectives and Endpoints

	Estimand			
Objective	**Population**	**Endpoint**	**Population Summary Measure**	**Strategy for Intercurrent Events[a]**
				discontinuation, otherwise Treatment Policy. **Supportive strategy:** • Premature discontinuations from randomized study intervention: While on Treatment, ie, data after ICE will not be used. • Prolonged exposure to systemic corticosteroids or increased ICS dose for greater than 28 consecutive days or a single depot corticosteroid injection: While on Treatment, ie, data after ICE will not be used. • Initiation of new asthma therapy or administration of prohibited medications thought to impact efficacy following first dose of randomized IP: While on Treatment, ie, data after ICE will not be used.

Table 3 Objectives and Endpoints

	Estimand			
Objective	**Population**	**Endpoint**	**Population Summary Measure**	**Strategy for Intercurrent Events[a]**
Secondary				
To assess the effect of BGF MDI relative to BFF MDI or Symbicort pMDI on lung function in participants with inadequately controlled asthma.	Participants with inadequately controlled asthma (symptomatic on medium to high-dose ICS with LABA)	CCI (Key secondary): Change from baseline in morning pre-dose trough FEV_1 at Week 24 CCI Change from baseline in FEV_1 AUC0-3 over 24 Weeks CCI (Key secondary): Change from baseline in FEV_1 AUC0-3 over 24 Weeks CCI (Key secondary): Change from baseline in FEV_1 AUC0-3 over 12 to 24 Weeks	Difference in mean change from baseline	Same as primary endpoint
To assess the effect of BGF MDI relative to BFF MDI or Symbicort pMDI on lung function, PROs, and symptoms in participants with inadequately controlled asthma.	Participants with inadequately controlled asthma (symptomatic on medium to high-dose ICS with LABA)	Percentage of responders in ACQ-7 (≥0.5 decrease equals response) at Week 24, over 24 Weeks or over 12 to 24 Weeks	Odds ratio	**Primary strategy:** • Premature discontinuations from randomized study intervention: Treatment Policy, ie, all observed data used regardless of ICE. • Prolonged exposure to systemic corticosteroids or increased ICS dose for greater than 28 consecutive days or a single depot corticosteroid injection: Treatment Policy,

Table 3 Objectives and Endpoints

	Estimand			
Objective	**Population**	**Endpoint**	**Population Summary Measure**	**Strategy for Intercurrent Events[a]**
				ie, all observed data used regardless of ICE. • Initiation of new asthma therapy or administration of prohibited medications thought to impact efficacy: Composite if in conjunction with IP discontinuation, non-responder status will be assumed for participants from (and including) day of ICE, otherwise Treatment Policy. **Supportive Composite:** • Premature discontinuation from randomized study intervention: – For reasons related to global/country situation, data following such ICE will be considered missing and will not be imputed. – For other reasons, non-responder status will be assumed for

Table 3 Objectives and Endpoints

	Estimand			
Objective	**Population**	**Endpoint**	**Population Summary Measure**	**Strategy for Intercurrent Events[a]**
				participants from (and including) the day of first ICE (Composite strategy). • Prolonged exposure to systemic corticosteroids or increased ICS dose for greater than 28 consecutive days or a single depot corticosteroid injection: Non-responder status will be assumed for participants from (and including) day of first ICE (Composite strategy). • Initiation of new asthma therapy or administration of prohibited medications thought to impact efficacy following first dose of randomized IP: Non-responder status will be assumed for participants from (and including) day of first ICE (Composite strategy).

Table 3 Objectives and Endpoints

	Estimand			
Objective	**Population**	**Endpoint**	**Population Summary Measure**	**Strategy for Intercurrent Events[a]**
		Percentage of responders in ACQ-5 (≥0.5 decrease equals response) at Week 24, over 24 Weeks or over 12 to 24 Weeks	Odds ratio	Same as for percentage of responders in ACQ-7
		Percentage of responders in the Asthma Quality of Life Questionnaire for 12 years and older (AQLQ(s)+12) (≥0.5 increase equals response) at Week 24, over 24 Weeks or over 12 to 24 Weeks	Odds ratio	Same as for percentage of responders in ACQ-7
		Percentage of responders in the St. George's Respiratory Questionnaire (SGRQ) (≥4.0 unit decrease equals response) at Week 24 or over 24 Weeks	Odds ratio	Same as for percentage of responders in ACQ-7
		Onset of action on Day 1: Absolute change in FEV_1 at 5 minutes on Day 1	Mean change from baseline	Same as Primary strategy for primary endpoint
		CCI only: Rate of severe asthma exacerbations over the Treatment Period	Rate ratio	Same as Primary strategy for primary endpoint

Table 3 Objectives and Endpoints

	Estimand			
Objective	**Population**	**Endpoint**	**Population Summary Measure**	**Strategy for Intercurrent Events[a]**
To assess the effect of BFF MDI relative to Symbicort pMDI on lung function, PROs, and symptoms in participants with inadequately controlled asthma [non-inferiority][c]	Participants with inadequately controlled asthma (symptomatic on medium to high-dose ICS with LABA)	Change from baseline in FEV_1 AUC0-3 over 24 Weeks	Difference in mean change from baseline	Primary: Principal Stratum: All data following an ICE (including data on the same day of the event) will be excluded. • Any ICEs listed for the superiority analyses. • IPDs impacting efficacy. Supportive #1: Same as Primary strategy for handling ICEs for the primary endpoint Supportive #2: While on Treatment (per supportive strategy for the primary endpoint)
		Change from baseline in morning pre-dose trough FEV_1 over 24 Weeks	Difference in mean change from baseline	Same as for the non-inferiority analysis of change from baseline in FEV_1 AUC_{0-3} over 24 weeks

Table 3 Objectives and Endpoints

	Estimand			
Objective	**Population**	**Endpoint**	**Population Summary Measure**	**Strategy for Intercurrent Events[a]**
		Percentage of responders in ACQ-7 (≥ 0.5 decrease equals response) over 24 Weeks	Odds ratio	Mix of Principal Stratum and Composite: • All data following a permanent ICE or an IPD impacting efficacy (including data on the same day of the event) will be excluded: Principal Stratum. • All data following a permanent ICE or an IPD due to efficacy (including data on the same day of the event) will then be imputed to a non-responder status: Composite strategy. • Discontinuation from randomized study intervention for reasons related to global/country situation: Data following such ICE will be considered missing and will not be imputed.

Table 3 Objectives and Endpoints

	Estimand			
Objective	**Population**	**Endpoint**	**Population Summary Measure**	**Strategy for Intercurrent Events[a]**
		Percentage of responders in ACQ-5 (≥ 0.5 decrease equals response) over 24 Weeks	Odds ratio	Same as for the non-inferiority analysis of percentage of responders in ACQ-7
		Percentage of responders in the AQLQ(s)+12 (≥ 0.5 increase equals response) over 24 Weeks	Odds ratio	Same as for the non-inferiority analysis of percentage of responders in ACQ-7
		Percentage of responders in the SGRQ (≥ 4.0 unit decrease equals response) over 24 Weeks	Odds ratio	Same as for the non-inferiority analysis of percentage of responders in ACQ-7
		Onset of action on Day 1: Absolute change in FEV_1 at 5 minutes on Day 1	Mean change from baseline	Principal Stratum: Same as for Primary strategy for change from baseline in FEV_1 AUC_{0-3} over 24 weeks of NI analysis
Safety				
To assess the safety of BGF MDI relative to BFF MDI or Symbicort pMDI in participants with inadequately controlled asthma.	Participants with inadequately controlled asthma (symptomatic on medium to high-dose ICS with LABA)	Adverse events (AEs)	Percentage EAIR	AEs will be analyzed by study/treatment periods defined in the Statistical Analysis Plan (SAP)
		Vital signs	Mean absolute value and mean change from baseline	On-treatment observations will be analyzed
		Clinical laboratory values	Mean absolute value and mean change from baseline	On-treatment observations will be analyzed

Table 3 Objectives and Endpoints

	Estimand			
Objective	**Population**	**Endpoint**	**Population Summary Measure**	**Strategy for Intercurrent Events[a]**
		Electrocardiograms (ECGs)	Mean absolute value and mean change from baseline	On-treatment observations will be analyzed
To assess the safety of BFF MDI relative to Symbicort pMDI in participants with inadequately controlled asthma[c]	Participants with inadequately controlled asthma (symptomatic on medium to high-dose ICS with LABA)	AEs	Percentage EAIR	AEs will be analyzed by study/treatment periods defined in the SAP
		Vital signs	Mean absolute value and mean change from baseline	On-treatment observations will be analyzed
		Clinical laboratory values	Mean absolute value and mean change from baseline	On-treatment observations will be analyzed
		ECGs	Mean absolute value and mean change from baseline	On-treatment observations will be analyzed
Tertiary/Exploratory				
To further assess the effect of BGF MDI relative to BFF MDI or Symbicort pMDI on lung function, PROs, and symptoms in participants with	Participants with inadequately controlled asthma (symptomatic on medium to high-dose ICS with LABA)	Change from baseline in the mean number of puffs of rescue medication use (puffs/day) over 24 Weeks or over 12 to 24 Weeks	Difference in mean change from baseline	While on Treatment
		Percentage of rescue-free days (24-hour period without rescue medication use)	Difference in mean percentage	While on Treatment

Table 3 Objectives and Endpoints

	Estimand			
Objective	**Population**	**Endpoint**	**Population Summary Measure**	**Strategy for Intercurrent Events[a]**
inadequately controlled asthma.		Percentage of symptom-free days (24-hour period without symptoms)	Difference in mean percentage	While on Treatment
		Peak change from baseline in FEV_1 at each visit	Mean difference	While on Treatment
		Time to peak FEV_1 on Day 1	Mean difference	While on Treatment
		Forced vital capacity (FVC), peak expiratory flow rate (PEFR), and forced expiratory flow at 25-75% (FEF_{25-75}) evaluated using AUC0-3	Difference in mean change from baseline	While on Treatment
		Change from baseline in morning pre-dose PEFR	Difference in mean change from baseline	While on Treatment
		Change from baseline in evening pre-dose PEFR	Difference in mean change from baseline	While on Treatment
		Percentage of responders in ACQ-6 (≥ 0.5 decrease equals response)	Odds ratio	Same as Primary strategy for ACQ-7
		Change from baseline in ACQ-5, ACQ-6, ACQ-7 and AQLQ(s)+12	Difference in mean change from baseline	Same as Primary strategy for the primary endpoint
		Change from baseline in SGRQ	Difference in mean change from baseline	Same as Primary strategy for the primary endpoint
		Time to Clinically Important Deterioration (CID)	Hazard ratio	While on Treatment

Table 3 Objectives and Endpoints

	Estimand			
Objective	**Population**	**Endpoint**	**Population Summary Measure**	**Strategy for Intercurrent Events[a]**
		CCI	Hazard ratio	While on Treatment
		CCI	Rate ratio	While on Treatment
		Time to first intercurrent event (ICE)	Hazard ratio	While on Treatment
		Time to first ICE of initiation of new asthma therapy or prohibited medications thought to impact efficacy in conjunction with discontinuation from study intervention	Hazard ratio	Same as Primary strategy for the primary endpoint
		Patient Global Impression of Change (PGIC)	Percentage	While on Treatment
		European Quality-of-Life-5 Dimensions (EQ-5D) Questionnaire index score and Visual Analogue Scale (VAS) Questionnaire score at each post-randomization visit and end of study visit	Mean absolute value and mean change from baseline	While on Treatment
		The percentage of participant's categorical responses to each of the 5-dimensions in EQ-5D	Percentage	While on Treatment

Table 3 Objectives and Endpoints

	Estimand			
Objective	**Population**	**Endpoint**	**Population Summary Measure**	**Strategy for Intercurrent Events[a]**
		Percentage of participants with fractional exhaled nitric oxide (FeNO) less than 25 ppb, between 25 ppb and less than 50 ppb, and at least 50 ppb	Percentage	While on Treatment
		Percentage of peak FEV_1 improvement achieved at 5 minutes on Day 1	Percentage	While on Treatment
Healthcare Resource Utilization Objective				
To assess the overall and asthma-specific Healthcare Resource Utilization of BGF MDI relative to BFF MDI or Symbicort pMDI in participants with inadequately controlled asthma.	Participants with inadequately controlled asthma (symptomatic on medium to high-dose ICS with LABA)	Days missed school/work per patient-year	Mean Annualized Rate	While on Treatment
		Days that primary caregivers of participants missed from work as a result of the participant's asthma per patient year	Mean Annualized Rate	While on Treatment
		Percentage of participants with telephone calls to healthcare providers - Calls to Primary Care Physician (PCP) - Calls to specialist - Calls to other healthcare providers	Percentage	While on Treatment

Table 3 Objectives and Endpoints

	Estimand			
Objective	**Population**	**Endpoint**	**Population Summary Measure**	**Strategy for Intercurrent Events[a]**
		Number of telephone calls to healthcare providers per patient-year - Calls to PCP - Calls to specialist - Calls to other healthcare providers	Mean Annualized Rate	While on Treatment
		Percentage of participants with visits to healthcare providers - Visits to PCP - Visits to specialist - Visits to other healthcare providers	Percentage	While on Treatment
		Number of visits to healthcare providers per patient-year - Visits to PCP - Visits to specialist - Visits to other healthcare providers	Mean Annualized Rate	While on Treatment
		Percentage of participants with Emergency Room (ER) visits	Percentage	While on Treatment
		Number of visits to ERs per patient-year	Mean Annualized Rate	While on Treatment

Table 3 Objectives and Endpoints

	Estimand			
Objective	**Population**	**Endpoint**	**Population Summary Measure**	**Strategy for Intercurrent Events[a]**
		Percentage of participants hospitalized	Percentage	While on Treatment
		Number of participant hospitalizations per patient-year	Mean Annualized Rate	While on Treatment
		Number of days in the hospital per patient-year	Mean Annualized Rate	While on Treatment
		Number of days in Intensive Care Units (ICU) per patient-year	Mean Annualized Rate	While on Treatment
		Percentage of participants in the ICU	Percentage	While on Treatment
		Number of days in Coronary Care Units (CCU) per patient-year	Mean Annualized Rate	While on Treatment
		Percentage of participants in CCU	Percentage	While on Treatment
		Percentage of participants who required ambulance transport	Percentage	While on Treatment
		Number of times ambulance transport was required per patient-year	Mean Annualized Rate	While on Treatment
12-Hour Pharmacokinetic Sub-Study Objective				
To characterize the steady state pharmacokinetics (PK)	Participants with inadequately controlled asthma	Steady-state partial area under the concentration-time curve from 0 to 12 hours post dose (AUC0-12)	Mean	While on Treatment

Table 3 Objectives and Endpoints

	Estimand			
Objective	**Population**	**Endpoint**	**Population Summary Measure**	**Strategy for Intercurrent Events[a]**
of budesonide, glycopyrronium, and formoterol fumarate based on PK assessments in participants with inadequately controlled asthma.	(symptomatic on medium to high-dose ICS with LABA) who consent to PK Sub-study	Steady-state AUClast.	Mean	While on Treatment
		Steady-state Cmax	Mean	While on Treatment
		Steady-state Cavg	Mean	While on Treatment
		Steady-state Tmax	Mean	While on Treatment
		Pre-dose PK value (Ctrough)	Mean	While on Treatment
24-Hour Holter Monitor Sub-Study Objective				
To assess the cardiovascular safety of BGF MDI relative to BFF MDI or Symbicort pMDI as evaluated by 24-hour Holter monitoring.	Participants with inadequately controlled asthma (symptomatic on medium to high-dose ICS with LABA) who consent to Holter Monitor Sub-study	Change from baseline in mean heart rate (HR) over 24 hours	Difference in mean change from baseline	While on Treatment
		Change from baseline in nighttime (2200 to 0600) and daytime (0600 to 2200) HR	Difference in mean change from baseline	While on Treatment
		Change from baseline in the maximum 24-hour HR	Difference in mean change from baseline	While on Treatment
		Change from baseline in the minimum 24-hour HR	Difference in mean change from baseline	While on Treatment
		Change from baseline in the frequency of isolated ventricular events (premature ventricular contractions [PVCs])	Difference in mean change from baseline	While on Treatment

Table 3 Objectives and Endpoints

	Estimand			
Objective	**Population**	**Endpoint**	**Population Summary Measure**	**Strategy for Intercurrent Events[a]**
		Change from baseline in the frequency of ventricular couplets (defined as 2 PVCs preceded or followed by regular beats)	Difference in mean change from baseline	While on Treatment
		Change from baseline in the frequency of ventricular runs (defined as 3 or more PVCs preceded or followed by regular beats)	Difference in mean change from baseline	While on Treatment
		Change from baseline in the frequency of supraventricular couplets	Difference in mean change from baseline	While on Treatment
		Change from baseline in the frequency of isolated supraventricular events	Difference in mean change from baseline	While on Treatment
		Change from baseline in the frequency of supraventricular ectopic beats	Difference in mean change from baseline	While on Treatment
		Change from baseline in the frequency of supraventricular runs	Difference in mean change from baseline	While on Treatment
		Incidence of atrial fibrillation with rapid ventricular response (>100 bpm)	Incidence	While on Treatment

Table 3 Objectives and Endpoints

	Estimand			
Objective	**Population**	**Endpoint**	**Population Summary Measure**	**Strategy for Intercurrent Events[a]**
		Proportion of participants with maximum HR >180, >160 to 180, >140 to 160, >120 to 140, >100 to 120, and 100 bpm or less	Percentage	While on Treatment
		Proportion of participants with minimum HR >60, >50 to 60, >40 to 50, and <40 bpm	Percentage	While on Treatment
		Proportion of participants in each category of change from baseline in the number of PVCs per hour (no change; increase of >0 to <60, 60 to <120, and ≥120; and decrease of >0 to <60, 60 to <120, and ≥120)	Percentage	While on Treatment
		Number of cases and percentages in each category of QTcF ≥450 msec, QTcF ≥480 msec, and QTcF ≥500 msec; change from baseline QTcF ≥30 msec, change from baseline QTcF ≥60 msec; value of > 500 msec or change from baseline ≥ 60 msec	Percentage	While on Treatment

[a] For specific details on ICEs, see Section 9.1.1.

[b] CCI refers to submission strategy with respect to Health Authority responsible for reviewing marketing authorization and not the recruitment location/nationality of the participants.

[c] To support the CCI of CCI MDI in CCI

The data from studies D5982C00007 and D5982C00008 will be pooled and analyzed according to the objectives and endpoints for the pooled analysis listed in Table 4.

Table 4 Objectives and Endpoints for Pooled Analysis of Studies D5982C00007 and D5982C00008

	Estimand			
Objective	**Population**	**Endpoint**	**Population Summary Measure**	**Strategy for Intercurrent Events[a]**
Primary Pooled Analysis Objective				
To assess the effect of BGF MDI relative to BFF MDI or Symbicort pMDI on asthma exacerbations in participants with inadequately controlled asthma.	Participants with inadequately controlled asthma (symptomatic on medium to high-dose ICS with LABA)	Rate of severe asthma exacerbations	Rate ratio	Same as primary and supportive strategies for primary endpoint for individual studies
Secondary Pooled Analysis Objective				
To assess the effect of BGF MDI relative to BFF MDI or Symbicort pMDI on asthma exacerbations, PROs, and symptoms in participants with	Participants with inadequately controlled asthma (symptomatic on medium to high-dose ICS with LABA)	Rate of severe asthma exacerbations for participants with percent predicted $FEV_1 \leq 55\%$ at baseline	Rate ratio	Same as primary and supportive strategies for primary endpoint for individual studies
		Rate of severe asthma exacerbations for participants with ≥ 1 severe exacerbation in the 12 months prior to Visit 1	Rate ratio	Same as primary and supportive strategies for primary endpoint for individual studies

Table 4 Objectives and Endpoints for Pooled Analysis of Studies D5982C00007 and D5982C00008

	Estimand			
inadequately controlled asthma.		Time to first severe asthma exacerbation	Hazard ratio	Same as primary and supportive strategies for primary endpoint for individual studies
		Rate of moderate/severe asthma exacerbations	Rate ratio	Same as primary and supportive strategies for primary endpoint for individual studies
		Time to first moderate/severe asthma exacerbation	Hazard ratio	Same as primary and supportive strategies for primary endpoint for individual studies
		Percentage of responders in ACQ-7 (≥ 0.5 decrease equals response) at Week 24, over 24 Weeks or over 12 to 24 Weeks	Odds ratio	Same as for percentage of responders in ACQ-7 for individual study
		Percentage of responders in ACQ-5 (≥ 0.5 decrease equals response) at Week 24, over 24 Weeks or over 12 to 24 Weeks	Odds ratio	Same as for percentage of responders in ACQ-7 for individual study
		Percentage of responders in AQLQ(s)+12 (≥ 0.5 increase equals response) at Week 24 and over 24 Weeks	Odds ratio	Same as for percentage of responders in ACQ-7 for individual study

Table 4 Objectives and Endpoints for Pooled Analysis of Studies D5982C00007 and D5982C00008

	Estimand			
To assess the effect of BFF MDI relative to Symbicort pMDI on asthma exacerbations in participants with inadequately controlled asthma [non-inferiority][b]	Participants with inadequately controlled asthma (symptomatic on medium to high-dose ICS with LABA)	Rate of severe asthma exacerbations over the Treatment Period	Rate ratio	Principal Stratum, same as for the non-inferiority analysis of change from baseline in FEV_1 AUC_{0-3} over 24 Weeks
		Time to first severe asthma exacerbation (assessed over the Treatment Period only)	Hazard ratio	Principal Stratum, same as Primary strategy for the non-inferiority analysis of change from baseline in FEV_1 AUC_{0-3} over 24 Weeks
		Rate of moderate/severe asthma exacerbations over the Treatment Period	Rate ratio	Principal Stratum, same as Primary strategy for the non-inferiority analysis of change from baseline in FEV_1 AUC_{0-3} over 24 Weeks
		Time to first moderate/severe asthma exacerbation (assessed over the Treatment Period only)	Hazard ratio	Principal Stratum, same as Primary strategy for the non-inferiority analysis of change from baseline in FEV_1 AUC_{0-3} over 24 Weeks
Tertiary/Exploratory Pooled Analysis Objective				
To further assess the effect of BGF MDI	Participants with inadequately controlled	Time to first hospitalization for asthma exacerbation	Hazard ratio	While on Treatment

Table 4 Objectives and Endpoints for Pooled Analysis of Studies D5982C00007 and D5982C00008

	Estimand			
relative to BFF MDI or Symbicort pMDI on asthma exacerbations in participants with inadequately controlled asthma.	asthma (symptomatic on medium to high-dose ICS with LABA)	Rate of hospitalization for asthma exacerbations	Rate ratio	While on Treatment
		Rate of severe asthma exacerbations resulting in a temporary course of systemic corticosteroids for at least 3 consecutive days	Rate ratio	While on Treatment
		Time to first clinically important deterioration (CID)	Hazard ratio	While on Treatment
		CCI [redacted]	Hazard ratio	While on Treatment
		CCI [redacted]	Rate ratio	While on Treatment
		Time to first ICE	Hazard ratio	While on Treatment
		Time to first ICE of initiation of new asthma therapy or prohibited medications thought to impact efficacy in conjunction with discontinuation from study intervention	Hazard ratio	Same as Primary strategy for the primary endpoint
		Percentage of participants who permanently discontinued study intervention due to asthma exacerbation	Percentage	While on Treatment
		Total number of days on systemic corticosteroids to treat asthma exacerbations	Mean	While on Treatment

Table 4 Objectives and Endpoints for Pooled Analysis of Studies D5982C00007 and D5982C00008

		Estimand		
		Rate of severe asthma exacerbations treated with systemic corticosteroids only (assessed over the Treatment Period only)	Rate ratio	While on Treatment
		Rate of asthma deteriorations treated with ICS and/or antibiotics (assessed over the Treatment Period only)	Rate ratio	While on Treatment
		Rate of asthma deteriorations treated with antibiotics (assessed over the Treatment Period only)	Rate ratio	While on Treatment
		Time to first severe asthma exacerbation treated with systemic corticosteroids only (assessed over the Treatment Period only)	Hazard ratio	While on Treatment
		Time to first asthma deterioration treated with ICS and/or antibiotics (assessed over the Treatment Period only)	Hazard ratio	While on Treatment
		Time to first asthma deterioration treated with antibiotics (assessed over the Treatment Period only)	Hazard ratio	While on Treatment
12-Hour Pulmonary Function Test Pooled Sub-Study Objective				
To assess the effect of BGF MDI relative to BFF MDI or	Participants with inadequately controlled asthma (symptomatic on	FEV_1 AUC_{0-12} at Day 1 and Week 12	Difference in mean change from baseline	Same as for the primary endpoint

Table 4 Objectives and Endpoints for Pooled Analysis of Studies D5982C00007 and D5982C00008

		Estimand		
Symbicort pMDI on pulmonary function test (PFT) parameters over 12 hours in participants with inadequately controlled asthma.	medium to high-dose ICS with LABA) who consent to PFT Sub-study	FEV_1 at each timepoint at Day 1 and Week 12	Mean absolute value and mean change from baseline	While on Treatment
		FEV_1 AUC_{0-6}, FEV_1 AUC_{6-12}, and peak FEV_1	Difference in mean change from baseline	While on Treatment
		FVC, PEFR, and FEF_{25-75} evaluated using AUC_{0-12}	Difference in mean change from baseline	While on Treatment
		Percentage of perceivers and non-perceivers for weekly onset of effect questionnaire (OEQ) 5-item PRO at home	Percentage	While on Treatment
		Percentage of perceivers and non-perceivers for repeat OEQ item in clinic (post-dose)	Percentage	While on Treatment
		Time for the participant to first perceive the medication as working	Hazard ratio	While on Treatment

[a] For specific details on ICEs, see Section 9.1.1.
[b] To support the CCI of CCI MDI in CCI

Intercurrent Events (ICEs)

- Premature discontinuation from randomized study intervention (may be further broken down for lack of efficacy or for tolerability as well as for reasons related or unrelated to global/country situation).
- Prolonged exposure to systemic corticosteroids or increased ICS dose for greater than 28 consecutive days or having received at least a single depot corticosteroid injection. Furthermore, use of systemic corticosteroids or increased ICS dose for 28 consecutive days or less will be considered an ICE for concurrent lung function assessments (or lung function assessments performed within 7 days following exposure to systemic corticosteroid or increased ICS). The start date of this ICE is defined as the first day of the additional treatment or increased dose. This ICE will only be considered for the efficacy analyses.
- Initiation of new asthma therapy or administration of any additional prohibited medications thought to impact efficacy, including biological therapy/monoclonal antibodies, LABA, LAMA, or LTRA (for further details, refer to the SAP). This ICE will only be considered for the efficacy analyses.
- Administration of any additional prohibited medications recognized to impact interpretation of the Holter data. This ICE will only be considered for the Holter Monitoring sub-study analyses and will not be considered for any other analyses.
- Administration of any additional prohibited medications recognized to impact interpretation of the PK data or dosing errors. This ICE will only be considered for the PK sub-study analyses and will not be considered for any other analyses.
- Dosing errors. This ICE will only be considered for the PK sub-study analyses and will not be considered for any other analyses.
- Important protocol deviations thought to impact efficacy. This ICE will only be considered for the NI analyses and will not be considered for any other analyses.

4 STUDY DESIGN

4.1 Overall Design

This is a Phase III randomized, double-blind, double dummy, parallel group, multicenter variable length efficacy and safety study comparing two doses of BGF MDI (320/28.8/9.6 µg and 320/14.4/9.6 µg) to BFF MDI 320/9.6 µg (an ICS/LABA currently under development) and Symbicort pMDI 320/9 µg in adult and adolescent participants who have asthma which remains inadequately controlled (ACQ-7 total score ≥1.5) despite treatment with a medium or high dose of ICS/LABA. All doses represent the sum of two actuations. All study interventions will be administered twice daily (BID) for a minimum of 24 weeks and a maximum of 52 weeks.

For an overview of the study design see Figure 1. For details on study interventions given during the study, see Section 6.1 Study Intervention(s) Administered.

The study is variable in length, with a planned minimum of 24 weeks and a maximum of 52 weeks on randomized study intervention. Participants will complete a 52-week dosing period with the exception of those randomized within 28 weeks of the last randomized participant that completes in the study period. The study will end when the last randomized participant completes 24 weeks on randomized study intervention and a 2-week safety follow up, phone call (see Section 4.5).

This study will be conducted at approximately 420 sites worldwide and will randomize approximately 2200 adult and adolescent participants. The number of participants per treatment arm may be increased based on a BSSR. For details on the BSSR, see Section 9.2.

At Visit 1, participants (or the parents or legal guardians of participants <18 years of age) will sign an informed consent form (ICF) and participants <18 years of age will sign an assent form. All participants must be taking a stable medium or high dose ICS/LABA (see Table 8) for at least 4 weeks prior to Visit 1. Participants who have not withheld asthma medications prior to Visit 1 and failed spirometry testing per Inclusion #6 at Visit 1 should return to the clinic to repeat spirometry testing within two business days. If the repeat spirometry is failed per Inclusion #6, then the participant must be screen-failed. After meeting all eligibility criteria, participants will discontinue their medium or high dose ICS/LABA at Visit 1 and initiate run-in BFF MDI 320/9.6 µg taken BID until evening prior to Visit 5 (randomization) when the run-in BFF MDI will be discontinued. All participants will receive albuterol sulfate inhalation aerosol or salbutamol sulfate inhalation aerosol, hereinafter referred to as albuterol, at Visit 1 for rescue use during the study (see Section 6.5.1).

Participants will return for Visit 2 after adequate washout of prohibited asthma medications. There will be a minimum of 7 days between Visit 1 and Visit 2. Participants ≥18 years of age must demonstrate a pre-bronchodilator FEV_1 of <80% of predicted normal value at Visits 1, 2,

3, 4, and 5 (pre-randomization) and participants 12 to <18 years of age must demonstrate a pre-bronchodilator FEV_1 of <90% predicted normal value at Visits 1, 2, 3, 4, and 5 (pre-randomization). All participants must have an ACQ-7 total score of ≥1.5 at Visits 1, 3, and 5. All participants must be assessed for reversibility to albuterol at Visit 2 (and Visit 3 if reversibility is not demonstrated at Visit 2; see Section 5.1 and Section 8.1.1.3) to provide reversibility baseline data for characterization. However, participants who have historically documented reversibility within 12 months of Visit 1 can still be randomized to the study even if they fail reversibility testing at Visits 2 and 3.

Run-in BFF MDI during the Screening Period and study intervention during the Treatment Period must be taken in the evening 12 hours (±1 hour) prior to the expected in-clinic dosing time at the following morning visit. The morning dose must be withheld until after pre-dose spirometry assessments in the clinic. Albuterol must be withheld at least 6 hours prior to the start time of the morning visit. If both conditions above are not met, then the visit will need to be rescheduled (see Section 8.1.1). All pre-dose (trough) spirometry will be required to be conducted in the morning (0800 ±2 hours).

Participants should return to the clinic at approximately the same time of day (±1 hour) for all visits. All in-clinic dosing must occur prior to 1000 (+1-hour allowance) in the morning and visits must be planned accordingly. The participants will be required to remain at the clinic until completion of all protocol-defined assessments and procedures.

Participants will use an electronic diary (eDiary) twice-daily (morning and evening) to record asthma symptoms scores, albuterol use, PEFR and confirmation of inhalations of run-in BFF MDI during the Screening Period (see Section 8.1.3). Compliance of ≥70% during screening (defined as "eDiary 14-day compliance" by completing the daily eDiary for any 10 mornings, and any 10 evenings, and answering "Yes" to taking 2 puffs of run-in BFF MDI for any 10 mornings and 10 evenings in the last 14 days prior to randomization) must be demonstrated in order for a participant to be randomized to study intervention at Visit 5 (see Section 8.1.3.6).

If an asthma exacerbation occurs during the Screening Period, the Screening Period may be extended up to 10 weeks to accommodate treatment for up to 2 weeks with corticosteroids and a 4-week washout from this treatment prior to randomization (see Section 5.5.2).

Participants meeting randomization criteria at Visit 5 (see Section 5.3) will discontinue run-in BFF MDI and in previous versions of the protocol were randomized in a 1:1:1:1 scheme to 1 of 4 treatment groups (see Section 6.1). CCI [redacted]

CCI

Randomization will be assigned based on 2 cohorts: adults and adolescents. For adults, randomization will be stratified by country, baseline pre-bronchodilator percent predicted FEV_1 (≤55% vs. >55%), severe exacerbation history in the 12 months prior to Visit 1 (0, 1, ≥2), and ICS dose (medium vs. high). For adolescents, randomization will be stratified by country and baseline pre-bronchodilator percent predicted FEV_1 (≤75% vs. >75%).

Following randomization, participants will enter the Treatment Period and undergo 6 to 10 additional treatment visits. Participants will record daily asthma symptom scores, albuterol use, PEFR, and study intervention use as well as PRO questionnaire responses as described in the SoA (Table 1), Section 8.1.3, and Section 8.1.4.

All participants who discontinue randomized study intervention prior to the end of the study will be encouraged to remain in the study to complete all remaining study visits and procedures until the end of the planned study (see Section 7.1).

This study includes the following three sub-studies: 12-hour serial spirometry, Pharmacokinetic (PK) profile, and 24-hour Holter Monitor. Participants who discontinue randomized study intervention prior to Visit 8 (Week 12) and who are also participating in sub-studies, will not complete the sub-study assessments at Visit 8, but will be encouraged to remain in the study to complete the remaining visits.

12-hour Spirometry Sub-Study: Serial spirometry will be conducted over 12 hours in a subset of approximately CCI randomized adult and adolescent participants across the two studies D5982C00007 and D5982C00008 (approximately CCI participants from each treatment group) at Visit 5 (Day 1) and Visit 8 (Week 12). On the test day, additional serial spirometry will be obtained at 6-, 9-, and 12-hours post-dose (see Table 2 for details). Adult and adolescent participants will also complete a weekly 5-item onset of effect questionnaire (OEQ) at home as described in the SoA (Table 1) and an OEQ item in the clinic during Visits 5 and 8 as described in Table 2.

The 12-hour spirometry sub-study will be conducted at specific sites that have agreed to participate. Approximately CCI participants will be randomized at Visit 5 to have approximately CCI participants complete at Visit 8. Once the target number of participants has been met, no further enrollment will be allowed in the sub-study.

24-hour Holter Monitor Sub-Study: 24-hour Holter monitoring will be performed in a subset of approximately CCI randomized participants between Visit 4 and Visit 5 (Holter Monitor baseline) and at Visit 6 (Week 4) and Visit 11 (Week 24). Those participants who have clinically significant abnormal findings defined as (but not limited to) criteria in Section 5.5.1 during the baseline 24-hour Holter monitoring MUST be screen failed from the full

study. Participants unable to provide a minimum of 18 hours of acceptable quality recording in a 24-hour period after 2 attempts will not be eligible for the Holter monitoring sub-study but WILL NOT need to be screen failed from the full study.

12-hour Pharmacokinetic Sub-Study: PK assessments will be performed in a subset of adult and adolescent participants who have confirmed to have taken the last 6 inhalations (3 doses) of each study intervention device prior to Visit 8 (Week 12) in the daily eDiary. Approximately CCI participants with at least 6 participants per treatment group 12 to <18 years of age will be assessed at Visit 8 (Week 12) (see Section 8.5.1 for details). Approximately CCI participants will be randomized at Visit 5 to account for a dropout rate of around 10%. Once the target number of participants has been met, no further enrollment will be allowed in the PK sub-study.

See Sections 9.6 and 9.7 for information regarding the Data Monitoring Committee and Independent Adjudication Committee(s) (IAC), respectively.

4.2 Study Conduct Mitigation During Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis

The guidance given below supersedes instructions provided elsewhere in this Clinical Study Protocol and should be implemented only during cases of civil crisis, natural disaster, or public health crisis (eg, during quarantines and resulting site closures, regional travel restrictions, and considerations if site personnel or study participants become infected with SARS-CoV-2 virus or a similar pandemic infection) which would prevent the conduct of study-related activities at study sites, thereby compromising the study site staff or the participant's ability to conduct the study. The Investigator or designee should contact AstraZeneca to discuss whether the mitigation plans in the Study Disruption Mitigation Instructions should be implemented.

In the scenario of a civil crisis, natural disaster, or public health crisis, changes may be implemented to ensure the safety of study participants, maintain compliance with Good Clinical Practice (GCP) and minimize risks to trial integrity.

Where allowable by local health authorities, ethics committees, healthcare provider guidelines (eg, hospital policies), or local government, if study participants cannot attend the visits at the study site due to significant regional disruption, evolving global pandemic or similar natural disaster, telemedicine sessions (video conference or telephone call) will be implemented for all participants currently randomized in the study and study intervention supply maintained for the participant given this comprises their asthma controller medications. These sessions should include all SoA (Table 1) assessments which can be performed virtually, to collect safety information as a minimum requirement. Assessments in the SoA (Table 1) which cannot be performed virtually should be captured at the next opportunity for an in-clinic visit,

provided the Investigator assesses the participant to be safe to continue in the study. Alternatively, if the Investigator considers it appropriate for the participant to stop study intervention and have alternative asthma controller medications, arrangements for this will need to be made by the study staff, in accordance with local regulatory requirements and guidance. All participants who stop study intervention and are prescribed alternative asthma controller medications will need to be followed-up with a telephone call 2 weeks following the cessation of study intervention to assess safety.

Visits 1 through 5 must be conducted at the study site. If mitigation practices are implemented at a site, until agreed otherwise with AstraZeneca, no further participants can be enrolled and all participants who are currently in Screening (Visits 1 through 5), must be screen failed (see Section 5.5). See Section 5.5.2 for details about rescreening of participants.

4.3 Scientific Rationale for Study Design

The products being tested in this study, two doses of BGF MDI, are being compared with BFF MDI and Symbicort pMDI. Combination therapy with an ICS and LABA for asthma is well established in clinical practice and the inclusion of a LAMA has demonstrated additional benefit in managing patients with poorly controlled asthma [Kerstjens 2012, Virchow 2019]. The addition of a LAMA is expected to improve lung function and health related quality of life, reduce exacerbations, and reduce the need for increased ICS or systemic corticosteroid use in this population. The development of a triple combination product also provides the convenience of a single inhaler for patients, increasing the likelihood of adherence.

The variable treatment length in this study will allow long-term safety to be captured in the participants who complete Week 52 and provide adequate time to observe lung function changes after 24 weeks and collect asthma exacerbation data in participants up to 52 weeks. The study will end when the last remaining randomized participant completes 24 weeks and the two-week safety follow-up phone call, if still on randomized study intervention at Week 24.

4.3.1 Participant Input into Design

Obtaining coordinator and participant insight early has provided opportunities for informing study design, improving operational feasibility, reducing patient/site burden and retaining interest, enthusiasm, and engagement in a study.

4.3.1.1 Coordinator Input

Four face-to-face coordinator meetings involving 25 coordinators from 17 countries were conducted. Coordinator perspectives and insights were collected around consenting, eligibility, requesting medical records, screening, randomization, safety/efficacy measures, study intervention, technology, retention, data, and the 12-hour PK and spirometry sub-

studies. The following changes to the protocol were made based on coordinator input:

- Reduced the number of serial spirometry assessments
- Broadened the window for performing morning assessments
- Shortened the systemic corticosteroid washout period prior to Visit 1
- Added vaping to smoking history eligibility criteria
- Refined corticosteroid eligibility criteria to include oral and intravenous (IV) use

Explaining the "why" behind a study and activities in the Schedule of Activities (SoA; Table 1) and improving training materials to support geographical challenges will be incorporated into Investigator and site training.

4.3.1.2 Participant Input

Two virtual meetings were conducted with 7 asthma patients from four countries. Insights were collected around exacerbations and the ability to collect medical records to support eligibility and/or an on-study event, eDiary burden, 12-hour PK and spirometry sub-studies, and virtual study visits. Patients indicated that ensuring direct lines of communication with site staff, allowing "in-clinic" assessments to be done at home, utilizing a personal device to collect data, and explaining why PROs are needed and how PRO data will be used, is important to them. These insights will be considered and when possible, incorporated into the protocol, Investigator, site and PRO eDiary training.

4.4 Justification for Dose

The glycopyrronium (GP) doses of 14.4 µg and 28.8 µg administered as two puffs twice daily (total daily doses of 28.8 µg and 57.6 µg, respectively) are being evaluated as part of the fixed-dose triple combination (BGF MDI) in this study and are supported by Study PT001101 (a 14-day double-blind, placebo-controlled, dose-ranging, crossover study) and Study PT001102 (a 6-month double-blind, parallel group, dose-confirming, placebo-controlled study). In PT001101, a dose ordered response in peak change from baseline in FEV_1 was observed across GP doses with the GP MDI 28.8 µg dose demonstrating the greatest overall improvement in change from baseline in morning trough FEV_1 and change from baseline FEV_1 AUC_{0-3} versus the placebo MDI arm.

In PT001102, dose ordering across GP doses was not observed and the primary comparison of the GP MDI 28.8 µg arm versus the placebo MDI arm did not demonstrate a statistically significant treatment difference. Although both GP doses (14.4 µg and 28.8 µg) were comparable in the pre-specified analyses in PT001102, greater treatment effects were observed with the 28.8 µg dose in post-hoc analyses. There were no new safety concerns observed with any GP dose in PT001102. These findings support inclusion of both GP doses in Phase III studies. The efficacy and safety profile of the GP 14.4 µg dose, as part of

glycopyrronium and formoterol fumarate (GFF) MDI 14.4/9.6 µg and BGF MDI 320/14.4/9.6 µg, has been established in the Phase III COPD programs and is part of the approved doses of Bevespi Aerosphere and Breztri Aerosphere, or doses submitted globally. It is expected that the asthma Phase III program will further establish the efficacy and safety profile of both GP doses, while also providing an additional long-term safety database for BGF MDI 320/28.8/9.6 µg in adolescent and adult participants with asthma.

The budesonide (BD) dose of 320 µg administered as two puffs twice daily (total daily dose of 640 µg) is being evaluated as part of BGF MDI and meets the medium ICS dose per GINA Step 4 guidelines, which advocate the addition of a LAMA, in the form of tiotropium, as a step-up therapy to asthma patients who are inadequately controlled on a medium or a high dose ICS/LABA and who are known to have a plateau in clinical response to higher ICS doses with an increased risk of side effects [GINA 2020]. The efficacy and safety profile of BD, as part of BFF MDI 320/9.6 µg and BGF MDI 320/14.4/9.6 µg, has been established in the Phase III COPD program and is part of the approved BGF MDI dose or dose submitted globally. It is expected that the asthma Phase III program will further establish the efficacy and safety profile of the BD dose as part of BGF MDI 320/14.4/9.6 µg and BGF MDI 320/28.8/9.6 µg in adolescent and adult participants with asthma.

The formoterol fumarate dose of 9.6 µg administered as two puffs twice daily (total daily dose of 19.2 µg) is being evaluated as part of the BGF MDI in asthma. The efficacy and safety profile of formoterol fumarate, as part of GFF MDI 14.4/9.6 µg and BGF MDI 320/14.4/9.6 µg, has been established in the Phase III COPD programs and is part of the approved doses of Bevespi Aerosphere and Breztri Aerosphere, or doses submitted globally. In addition, the formoterol fumarate dose of 9 µg in Symbicort pMDI has a well-established safety and efficacy profile and is comparable to the formoterol fumarate dose of 9.6 µg in the BGF MDI and BFF MDI treatment arms proposed in the asthma Phase III program. It is expected that the asthma Phase III program will further establish the efficacy and safety profile of the formoterol fumarate dose as part of BGF MDI 320/14.4/9.6 µg and BGF MDI 320/28.8/9.6 µg in adolescent and adult participants with asthma.

The active comparator (Symbicort [320/9 µg BID]) is an approved or submitted dose globally for the treatment of asthma and is consistent with the recommended dose for patients who are inadequately controlled on a medium to high dose ICS/LABA [GINA 2020]. The budesonide dose in Symbicort also contains the same ICS and dose used in the BGF MDI and BFF MDI treatment arms in this study.

4.5 End of Study Definition

For the purpose of Clinical Trial Transparency, the definition of the end of the study differs

under FDA and EU regulatory requirements:

European Union requirements define study completion as the last visit of the last participant for any protocol related activity.

Food and Drug Administration requirements defines two completion dates:

Primary Completion Date – the date that the final participant is examined or receives an intervention for the purposes of final collection of data for the primary outcome measure, whether the clinical study concluded according to the pre-specified protocol or was terminated. In the case of clinical studies with more than one primary outcome measure with different completion dates, this term refers to the date on which data collection is completed for all of the primary outcomes.

Study Completion Date – the date the final participant is examined or receives an intervention for purposes of final collection of data for the primary and secondary outcome measures and AEs (for example, last participant's last visit), whether the clinical study concludes according to the pre-specified protocol or is terminated.

A participant is considered to have completed the study if they have completed all phases of the study including the last visit Study Intervention Discontinuation and/or Study Withdrawal Visit or 2 weeks (±2 days) after last dose Follow Up telephone call.

The study is variable in length, with a planned minimum of 24 weeks and a maximum of 52 weeks. The study will end when the last remaining participant completes his/her Week 24 Visit and subsequent 2-week follow-up phone call. If study intervention was discontinued prior to the Week 24 Visit, then study will end at the completion of the Week 24 Visit.

Once the last remaining participant is randomized, a projected study completion date will be communicated. The sites should plan the last visit date in advance for the participants who will still be in the study at the time of projected study completion. The procedures at the last visit should match the procedures for Study Intervention Discontinuation and/or Study Withdrawal Visits (Table 1) as applicable to each of the participants.

- For participants who have their Week 24 Visit completed prior to the projected study completion, their last visit should be a scheduled visit to occur before but closest to the projected study completion date.
- For participants who use longer visit windows that leads to their scheduled Week 24 Visit beyond the projected study completion date, these participants must complete their Week 24 visit.

- The BSSR may result in increases (but not decreases) to the sample size and/or duration, for example such that all participants complete a 52-week dosing period. Details to be provided in the SAP.

5 STUDY POPULATION

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

Each participant must meet all of the inclusion criteria, none of the exclusion criteria, and all of the inclusion criteria requiring additional confirmation prior to randomization (Section 5.3) at Visit 5 for this study in order to be randomized to study intervention. Under no circumstances can there be exceptions to this rule. Participants who do not meet the entry requirements are screen failures (see Section 5.5).

5.1 Inclusion Criteria

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

Age

1 Participant must be at least 12 to 80 years of age inclusive, at the time of signing the ICF.

Note: For participants from 12 to <18 years of age, their parents or legal guardians must give their signed written informed consent, as appropriate, and participants will sign an assent form.

Type of Participant and Disease Characteristics

2 Participants who have a documented history of physician-diagnosed asthma ≥1 year prior to Visit 1, according to GINA guidelines [GINA 2020]. Healthcare records for 1 year prior to Visit 1 must be provided for adolescent participants (12 to <18 years of age) to ensure consistent evaluation and follow-up of treatment in those participants.

3 Participants who have been regularly using a stable daily ICS/LABA regimen (including a stable ICS dose), with the ICS doses allowed in Table 8, for at least 4 weeks prior to Visit 1.

4 Inclusion criterion #4 was removed with version 3.0 of the CSP.

5 ACQ-7 total score ≥1.5 at Visits 1, 3, and 5 (pre-randomization).

6 Pre-bronchodilator FEV_1 (assessed as an average of the 60- and 30-minute pre-dose assessments) <80% predicted normal value at Visits 1, 2, 3, 4, and 5 (pre-randomization)

for participants ≥18 years of age OR <90% predicted normal value for participants 12 to <18 years of age.

Note: Participants who have not withheld asthma medications prior to Visit 1 and failed spirometry testing at Visit 1 should return to the clinic to repeat spirometry testing within two business days. If repeat spirometry failed, then participants must be screen-failed.

7 Reversibility to albuterol, defined as a post-albuterol increase in FEV_1 of ≥12% and ≥200 mL for participants ≥18 years of age OR a post-albuterol increase of FEV_1 of ≥12% for participants 12 to <18 years of age, either in the 12 months prior to Visit 1, or at Visit 2, or at Visit 3.

Note: Even if there is documented history of reversibility, all participants must be assessed for reversibility at Visit 2 (and Visit 3, if reversibility is not demonstrated at Visit 2) to provide reversibility baseline data for characterization.

8 Willing and, in the opinion of the Investigator, able to adjust current asthma therapy, as required by the protocol.

9 Demonstrate acceptable MDI/pMDI administration technique.

Note: Historical use of a spacer device within the 4 weeks prior to and/or during the Screening and Randomized Treatment Periods is not permitted.

Weight

10 Body mass index <40 kg/m^2.

Sex and Contraceptive/Barrier Requirements

11 Male and/or female.
Females must be not of childbearing potential or using a form of highly effective birth control as defined below:

- Female participants: Women not of childbearing potential are defined as women who are either permanently sterilized (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy), or who are postmenopausal. Women will be considered postmenopausal if they have been amenorrhoeic for 12 months prior to the planned date of randomization without an alternative medical cause. The following age-specific requirements apply:
  - Women <50 years old would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatment and follicle stimulating hormone levels in the postmenopausal range.
  - Women ≥50 years old would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of all exogenous hormonal treatment.
- Female participants of childbearing potential must use a highly effective form of birth control. A highly effective method of contraception is defined as one that can achieve a failure rate of less than 1% per year when used consistently and correctly. Women of

childbearing potential who are sexually active with a non-sterilized male partner must agree to use a highly effective method of birth control, as defined below, from enrollment throughout the study and until at least 16 weeks after last dose of study intervention. Cessation of contraception after this point should be discussed with a responsible physician. All women of childbearing potential must have a negative highly sensitive urine pregnancy test result from Visit 1. Adolescent participants should be counselled appropriately by the Investigator.

- Highly effective birth control methods are listed below.
  - Sexual abstinence defined as complete abstinence from intercourse when it is the preferred and usual lifestyle of the participant. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
  - Contraceptive subdermal implant
  - Intrauterine device or intrauterine system
  - Oral contraceptive (combined or progesterone)
  - Injectable progestogen [Hatcher 2011]
  - Contraceptive vaginal ring [Hatcher]
  - Percutaneous contraceptive patches [Hatcher 2011]
  - Male partner sterilization with documentation of azoospermia prior to the female participant's entry into the study, and this male is the sole partner for that participant [Hatcher 2011]. The documentation on male sterility can come from the site personnel's review of participant's medical records, medical examination and/or semen analysis or medical history interview provided by her or her partner.
  - Bilateral tubal ligation

12 Inclusion criterion #12 was removed with version 2.0 of the Clinical Study Protocol.

13 Inclusion criterion #13 was removed with version 2.0 of the Clinical Study Protocol.

Informed Consent

14 Capable of giving signed informed consent as described in Appendix A which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

Criteria to be Confirmed at Visit 5

15 Received no asthma medication other than run-in BFF MDI BID and albuterol as needed during screening, except for allowed medications as defined in Table 9 and systemic corticosteroid or ICS for the treatment of an asthma exacerbation (see Section 5.5.2 regarding Screening extension).

16 eDiary 14-day compliance ≥70% during screening (defined as completing the daily eDiary for any 10 mornings, and any 10 evenings, and answering "Yes" to taking 2 puffs

of run-in BFF MDI for any 10 mornings and 10 evenings in the last 14 days prior to randomization).

17 No respiratory infection in the 4 weeks prior to randomization, or asthma exacerbation treated with systemic corticosteroid and/or additional ICS treatment in the 4 weeks prior to randomization.

18 Provision of signed and dated written Optional Genetic Research Information informed consent prior to collection of samples for optional genetic research that supports Genomic Initiative.

Conditional Inclusion criterion

19 Inclusion criterion #19 was removed with version 3.0 of the CSP.

5.2 Exclusion Criteria

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

Medical Conditions

1 Life-threatening asthma defined as a history of significant asthma episode(s) requiring intubation associated with hypercapnia, respiratory arrest, hypoxic seizures, or asthma-related syncopal episode(s).

2 Completed treatment for respiratory infection or asthma exacerbation with systemic corticosteroids in the 4 weeks prior to Visit 1.

3 Participants where, in the opinion of the Investigator, treatment with biological therapy for asthma would be appropriate.

4 Hospitalization for asthma within 2 months of Visit 1.

5 Historical or current evidence of a clinically significant disease including, but not limited to: cardiovascular, hepatic, renal, hematological, neurological, endocrine, gastrointestinal, or pulmonary (eg, active tuberculosis, bronchiectasis, pulmonary eosinophilic syndromes, and COPD). Significant is defined as any disease that, in the opinion of the Investigator, would put the safety of the participant at risk through participation, or that could affect the efficacy or safety analysis if the disease/condition exacerbated during the study.

6 Known history of drug or alcohol abuse within 12 months of Visit 1.

7 Narrow angle glaucoma not adequately treated and/or change in vision that may be relevant, in the opinion of the Investigator, within 3 months of Visit 1.

Note: All medications approved for control of intraocular pressures are allowed, including topical ophthalmic non-selective beta-blockers.

8 Symptomatic prostatic hypertrophy or bladder neck obstruction/urinary retention that, in the opinion of the Investigator, is clinically significant.

Note: Participants with trans-urethral resection of prostate or full resection of the prostate within 6 months prior to Visit 1 are excluded from the study.

9 Unresectable cancer that has not been in complete remission for at least 5 years prior to Visit 1.

Note: Squamous cell and basal cell carcinomas of the skin are not exclusionary.

Prior/Concomitant Therapy

10 Oral and IV corticosteroid use (any dose) within 4 weeks of Visit 1. Use of systemic corticosteroids for any other reason except for the acute treatment of severe asthma exacerbation is prohibited for the duration of the study.

11 Depot corticosteroid use for any reason within 3 months of Visit 1.

12 Use of LAMA, either alone or as part of an inhaled combination therapy, in the 12 weeks prior to Visit 1.

13 Use of oral beta$_2$-agonist within 3 months of Visit 1.

14 Any marketed (eg, omalizumab, mepolizumab, benralizumab, reslizumab) or investigational biologic within 3 months or 5 half-lives of Visit 1, whichever is longer and must not be used during study duration.

15 Regular use of a nebulizer or a home nebulizer for receiving asthma medications.

Note: Acute use of a nebulizer for an asthma exacerbation during acute healthcare attendance is allowed as long as there is no occurrence within 4 weeks of Visit 1.

16 Use of any immunomodulators or immunosuppressive medication within 3 months or 5 half-lives, whichever is longer, and must not be used during study duration.

Note: Topical administration of immunosuppressive medication may be allowed at the discretion of the Investigator.

17 Unable to abstain from protocol-defined prohibited medications during Screening and Treatment Periods.

18 Participants with personalized treatment action plans at home who are not willing to contact the site prior to the start of prednisolone (or equivalent) for the treatment of an asthma exacerbation.

19 Using any herbal products by inhalation or nebulizer within 4 weeks of Visit 1 and does not agree to stop during the study duration.

Prior/Concurrent Clinical Study Experience

20 Participation in another clinical study with a study intervention administered in the last 30 days or 5 half-lives, whichever is longer. Any other study intervention that is not identified in this protocol is prohibited for use during study duration.

21 Participants with a known hypersensitivity to beta$_2$-agonists, corticosteroids, anticholinergics, or any component of the MDI or pMDI.

Diagnostic assessments

22 Participants with an estimated glomerular filtration rate (eGFR) ≤30 mL/minute/1.73m^2 using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula for participants 18 to 80 years of age and on repeat prior to Visit 5 OR using the Schwartz formula for participants 12 to <18 years of age and on repeat prior to Visit 5.

23 Any clinically relevant abnormal findings in physical examination, clinical chemistry, hematology, urinalysis, vital signs, or ECG, which in the opinion of the Investigator, may put the participant at risk because of his/her participation in the study.

Note: Participants with ECG QTcF interval (corrected for heart rate using Fridericia's formula [QTcF]) >480 msec will be excluded. Participants with high degree atrioventricular block II or III, or with sinus node dysfunction with clinically significant pauses who do not have a pacemaker will also be excluded.

Other Exclusions

24 Current smokers, former smokers with >10 pack-years history, or former smokers who stopped smoking <6 months prior to Visit 1 (including all forms of tobacco, e-cigarettes or other vaping devices, and marijuana).

25 Planned hospitalization during the study.

26 Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site).

27 Study Investigators, sub-Investigators, coordinators, and their employees or immediate family members.

28 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.

29 Previous or current randomization into studies within the AEROSPHERE program including KALOS, LOGOS, VATHOS, LITHOS, or any glycopyrronium studies (PT001).

30 For women only – currently pregnant (confirmed with positive highly sensitive pregnancy test), breast-feeding, or planned pregnancy during the study or not using acceptable contraception measures, as judged by the Investigator.

5.3 Inclusion Criteria Confirmation prior to Randomization

At Visit 5, the following inclusion criteria need to be confirmed for each participant prior to randomization:

- Inclusion # 5: ACQ-7 total score ≥1.5 from Visits 1, 3, and 5.

- Inclusion #6: Pre-dose FEV_1 <80% of predicted normal from Visits 1 to 5 for participants ≥18 years OR pre-dose FEV_1 <90% of predicted normal for participants 12 to <18 years of age.
- Inclusion #15: Received no asthma medication other than run-in BFF MDI BID and albuterol as needed during screening, except for allowed medications defined in Table 9 and systemic corticosteroid or ICS for the treatment of an asthma exacerbation.
- Inclusion #16: eDiary 14-day compliance ≥70% during screening (defined as completing the daily eDiary for any 10 mornings and any 10 evenings and answering "Yes" to taking 2 puffs of run-in BFF MDI for any 10 mornings and 10 evenings in the last 14 days prior to randomization).
- Inclusion #17: No respiratory infection in the 4 weeks prior to randomization, or asthma exacerbation treated with systemic corticosteroid and/or additional ICS treatment in the 4 weeks prior to randomization.
- Inclusion #19 was removed with version 3 of the CSP.
- For Holter Monitor sub-study only – no clinically significant findings in baseline 24-hour Holter Monitoring.

5.4 Lifestyle Considerations

5.4.1 Meals and Dietary Restrictions

Participants in the 12-hour PK sub-study are encouraged to refrain from consuming grapefruits or grapefruit juice between Visit 7 and Visit 8.

Participants should not eat or drink 1 hour prior to FeNO testing.

5.4.2 Caffeine, Alcohol, and Tobacco

Participants will abstain from ingesting caffeine- or xanthine-containing products (eg, coffee, tea, cola drinks, and chocolate) for 6 hours before and for the duration of each in-clinic study visit. Use of tobacco products or vaping will not be allowed from 6 months prior to Visit 1 until after the final follow-up visit.

5.4.3 Illicit Drugs or Drugs of Abuse

Illicit drugs or drugs of abuse will not be allowed from Visit 1 to the end of the follow-up telephone call or to whenever the participant withdraws from the study. If any illicit drugs or drugs of abuse are used by the participant during the study, the dates of use and the amount will be documented, and the participant will be discontinued from randomized study intervention and will be withdrawn from the study at the discretion of the Investigator.

5.5 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention. 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 publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any AEs.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Rescreened participants should be assigned the same participant number as for the initial screening.

If a participant is rescreened and fails for any reason other than pre-bronchodilator FEV_1 and ACQ score (see Section 5.5.2), another rescreening is allowed after a 3-month period. Details of potential rescreening due to failure of pre-bronchodilator FEV_1 and ACQ are also described in Section 5.5.2.

Participants are expected to return the investigational and rescue products together with eDiary to the site upon confirmation of screen failure. For all participants who are screen failures and received intervention, an AE assessment and highly sensitive urine pregnancy test (for women of childbearing potential) must be performed within 7 days of the screen failure date. Onsite visit required if pregnancy test and/or physical examination is required.

5.5.1 Holter Monitor Sub-Study Exclusion Criteria

Participants with clinically significant abnormal findings during the baseline Holter monitor recording defined as (but not limited to) any of the following will be excluded from the full study. Participants unable to provide a minimum of 18 hours of acceptable quality recording in a 24-hour period after 2 attempts will be excluded from the Holter Monitor sub-study but WILL NOT need to be excluded from the full study.

- Average HR ≤40 bpm for any 1 hour
- Second-degree atrioventricular block (Type 2) or third-degree atrioventricular block
- Sinus pause of 3.0 seconds duration during the daytime or nighttime
- Any episode of ventricular flutter and/or ventricular fibrillation
- Any episode of non-sustained ventricular tachycardia (NSVT) with symptoms of hypotension or syncope or asymptomatic NSVT >15 ventricular premature beats in a row
- Sustained ventricular tachycardia (>30 seconds in duration)
- 5 or more episodes of NSVT over 24 hours
- Greater than 1000 ventricular premature beats/24-hour period

5.5.2 Extension of Screen Period and Rescreening

In instances where an asthma exacerbation is treated with systemic corticosteroids or an additional ICS during the Screening Period, the Screening Period may be extended to a maximum of 10 weeks (to account for a short course of systemic corticosteroids or additional ICS of up to 2 weeks in duration and a 4-week washout period after the last dose of systemic corticosteroids or additional ICS).

Rescreening and/or up to a 14-day extension of the Screening Period is allowed, upon approval by the Study Physician, for screen failure reason(s) that are transient (including, but not limited to, not meeting pre-defined time period requirements, site closure due to study disruption, equipment/procedure failure [eg, problems with the eDiary impacting availability of data], required study documentation, or unforeseen personal reasons).

Each participant will have a maximum of 2 rescreening opportunities during the recruitment period.

Participants may not be rescreened due to failure to meet the study requirements of pre-bronchodilator FEV_1 and ACQ score during the Screening Period until at least 12 months after that screen failure. Rescreening would have to be approved based on a discussion between the Investigator and the Study Physician.

Rescreened participants will be assigned the same participant number as for the initial screening. Rescreened participants will re-sign the ICF. All procedures required for the screening/run-in periods should be repeated. Rescreening should be documented so that its effect on the study results, if any, can be assessed.

6 STUDY INTERVENTION

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

Study interventions are masked in a double dummy fashion, whereby participants randomized to BGF MDI or BFF MDI are given placebo pMDI to match Symbicort pMDI and participants randomized to Symbicort pMDI are given placebo MDI to match BGF/BFF MDI.

Placebo MDI and pMDI devices will be provided for training purposes. Run-in BFF MDI will be provided during the Screening Period.

6.1 Study Intervention(s) Administered

6.1.1 Investigational/Non-Investigational Products

Table 5 Investigational Products

	BGF MDI 320/28.8/9.6 µg	BGF MDI 320/14.4/9.6 µg	Run-in BFF/ Blinded BFF MDI 320/9.6 µg	Placebo MDI to match BGF/BFF MDI	Budesonide/ formoterol fumarate pMDI 320/9 µg	Placebo pMDI to match budesonide/ formoterol fumarate pMDI
Intervention Name	Budesonide, glycopyrronium, and formoterol fumarate pressurized inhalation suspension, CCI	Budesonide, glycopyrronium, and formoterol fumarate pressurized inhalation suspension, CCI	Budesonide and formoterol fumarate pressurized inhalation suspension, CCI	Placebo pressurized inhalation suspension, CCI	Symbicort®	Placebo to match Symbicort
Type	Combination Product (Drug + Device)	Combination Product (Drug + Device)	Combination Product (Drug + Device)	Combination Product (Drug + Device)	Combination Product (Drug + Device)	Combination Product (Drug + Device)
Dose Formulation	Inhaler	Inhaler	Inhaler	Inhaler	Inhaler	Inhaler
Unit Dose Strength (Delivered Dose)	160/14.4/4.8 µg per actuation	160/7.2/4.8 µg per actuation	160/4.8 µg per actuation	No active ingredient	160/4.5 µg per actuation	No active ingredient
Dosage Level(s)	2 inhalations BID	2 inhalations BID	2 inhalations BID	2 inhalations BID	2 inhalations BID	2 inhalations BID
Total Daily Dose	640/57.6/19.2 µg	640/28.8/19.2 µg	640/19.2 µg	No active ingredient	640/18 µg	No active ingredient
Route of Administration	Oral inhalation	Oral inhalation	Oral inhalation	Oral inhalation	Oral inhalation	Oral inhalation
Use	Experimental	Experimental	Experimental/ Comparator	Placebo	Comparator	Placebo
Sourcing	Provided centrally by AstraZeneca	Provided centrally by AstraZeneca	Provided centrally by AstraZeneca	Provided centrally by AstraZeneca	Provided centrally by AstraZeneca	Provided centrally by AstraZeneca

Table 5 Investigational Products

	BGF MDI 320/28.8/9.6 µg	BGF MDI 320/14.4/9.6 µg	Run-in BFF/ Blinded BFF MDI 320/9.6 µg	Placebo MDI to match BGF/BFF MDI	Budesonide/ formoterol fumarate pMDI 320/9 µg	Placebo pMDI to match budesonide/ formoterol fumarate pMDI
Packaging and Labelling	Study intervention will be provided in an MDI. Each MDI will be labelled as required per country requirement	Study intervention will be provided in an MDI. Each MDI will be labelled as required per country requirement	Study intervention will be provided in an MDI. Each MDI will be labelled as required per country requirement	Study intervention will be provided in an MDI. Each MDI will be labelled as required per country requirement	Study intervention will be provided in a pMDI. Each pMDI will be labelled as required per country requirement	Study intervention will be provided in a pMDI. Each pMDI will be labelled as required per country requirement

Instructions for use of Investigational Products will be provided.

Table 6 Non-Investigational Products

Intervention Name	Albuterol sulfate inhalation aerosol (CCI/Salbutamol sulfate inhalation aerosol (CCI/RoW)	Prednisolone or Equivalent (see Table 7)
Type	Combination Product (Drug + Device)	Drug
Dose Formulation	Inhaler	Tablet
Unit Dose Strength	90 µg per actuation (CCI 100 µg per actuation (CCI/RoW)	Variable
Dosage Level(s)	2 inhalations as-needed; as directed for reversibility testing at Visits 2 or 3	40 to 50 mg
Total Daily Dose	N/A	N/A
Route of Administration	Oral inhalation	Oral
Use	Rescue medication/ reversibility testing	Exacerbation treatment
Sourcing	Provided centrally by AstraZeneca or locally	Provided centrally by AstraZeneca or locally
Packaging and Labelling	If centrally supplied, the product will be provided in an MDI. Each MDI will be labelled as required per country requirement	If centrally supplied, the product will be provided in a bottle or a blister pack. Each pack will be labelled as required per country requirement

Metered doses: albuterol sulfate=108 µg. Albuterol sulfate inhalation aerosol will be sourced for the CCI Salbutamol sulfate inhalation aerosol will be sourced for CCI and Rest of World (RoW). Throughout the protocol, both will be referred to as albuterol.
CCI , RoW=Rest of World

6.1.2 Medical Devices Including Combination Products with a Device Constituent

1 The AstraZeneca manufactured combination product with a device constituent provided for use in this study are the Metered Dose Inhaler (Approved) and Pressurized Metered Dose Inhaler (Approved).

2 Instructions for combination products with a device constituent use are provided in the Investigator Brochure and Combination Products section of the Summary of Medical Product Characteristics.

3 All device constituent deficiencies (including malfunction, use error and inadequate labelling) shall be documented and reported by the investigator throughout the clinical investigation (see Section 8.3.11) and appropriately managed by AstraZeneca.

6.2 Preparation/Handling/Storage/Accountability of Interventions

All study intervention should be kept in a locked cabinet or room with limited access. The temperature of the site's storage area for study intervention must be monitored by site staff for temperature ranges consistent with those specified for each product label. Documentation of temperature monitoring should be maintained at the site and available for review.

The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received, and any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive study intervention and only authorized site staff may supply study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the Investigator and authorized site staff.

At Visit 8 for the 12-hour PK sub-study, specific precautions should be taken to prevent any contamination of collected PK samples by the particles of study intervention inhalations. All devices must be primed by study personnel before the first use in a separate area from where blood samples are drawn. Then, administration of study intervention will take place in a separate area from where priming and blood samples are drawn.

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

All handling instructions and further guidance and information for the final disposition of unused study intervention will be provided separately outside of the protocol.

6.3 Measures to Minimise Bias: Randomization and Blinding

All participants will be centrally assigned to one of CCI randomized study interventions using a Randomization and Trial Supply Management (RTSM). Before the study is initiated, the log-in information and directions for the RTSM will be provided to each site.

Study intervention will be dispensed at the study visits summarized in SoA (Table 1).

Returned study intervention should not be re-dispensed to the participants.

The RTSM will provide to the Investigators or pharmacists the kit identification number to be allocated to the participant at the dispensing visit.

Routines 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.

AstraZeneca retains the right to break the code for serious adverse events (SAEs) that are unexpected and are suspected to be causally related to a study intervention 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.

The bioanalytical laboratory must receive the randomization schemes to allow appropriate selection of samples for PK analysis.

6.3.1 Emergency Unblinding

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

The treatment code should not be broken except in medical emergencies when the appropriate management of the participant requires knowledge of the treatment allocation. Individual treatment codes, indicating the treatment allocation for each randomized participant, will be available to the Investigator(s) from the RTSM. Routines for unblinding will be described in the RTSM user manual that will be provided to each center. If the web based RTSM system is not working, unblinding remains possible via a telephone support helpdesk provided by the RTSM vendor, available 24 hours per day, 365 days per year. The telephone number for this helpdesk is found in the RTSM user manual.

The number of individuals at the study site who become aware of the treatment status should be kept to an absolute minimum, including keeping the participant blinded if possible. Treatment with study intervention should be continued, or re-initiated if interrupted, if considered appropriate.

6.4 Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the Investigator or designee, under medical supervision. The date, and time if applicable, of dose administered in the clinic will be recorded in the source documents and in the electronic Case

Report Form (eCRF). The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person providing the run-in BFF during screening or study intervention during the Treatment Period to participant.

When participants self-administer study intervention at home, compliance with study intervention will be assessed at each visit. Compliance will be assessed by reviewing the daily eDiary recording and the remaining doses of the dose counter during the site visits. The dose counter reading should be documented in the source documents.

Compliance requirements during the Screening Period and Treatment Period are located in Sections 5.3 and 8.1.3.6, respectively.

The number of MDIs and pMDIs dispensed to and taken by each participant will be recorded. Study intervention start and stop dates will also be recorded in the eCRF.

6.5 Concomitant Therapy

Any medication or vaccine (including over the counter or prescription medicines, vitamins, and/or herbal supplements or other specific categories of interest) that the participant is receiving from up to 12 months for asthma medications and up to 3 months for non-asthma medications prior to Visit 1 until the last study visit or 2-week safety follow-up phone call must be recorded in the eCRF along with:

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

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Sponsor-provided study intervention will not be captured on prior/concomitant eCRF pages, but on separate medication dispensing/return logs.

6.5.1 Rescue Medication

Albuterol for participants to use as rescue medication and for reversibility testing at Visits 2 and 3 (if needed) is not regarded as study intervention but will be provided/reimbursed by AstraZeneca according to local regulations in order to maintain appropriate oversight and access to this concomitant medication.

Although the use of albuterol is allowable at any time during the study, the use of rescue medications should be withheld, if possible, for at least 6 hours prior to the start and during

each clinic visit. If albuterol is used within 6 hours from the start of a clinic visit, then the visit will need to be re-scheduled within the allowed visit window. The number of puffs of rescue medication will be recorded by the participant daily in the eDiary.

6.5.2 Prednisolone or Equivalent for the Treatment of a Severe Exacerbation

Prednisolone tablets or equivalent for the treatment of severe exacerbations are not regarded as study intervention. As requested, prednisolone can be provided/reimbursed by AstraZeneca according to local regulations in order to maintain appropriate oversight and access to prednisolone.

The recommended treatment [GINA 2020] for a severe asthma exacerbation is prednisolone 1 to 2 mg/kg/day up to a total of 40 mg/day (or equivalent) for children and 40 to 50 mg/day (or equivalent) for adults once daily in the morning for 5 to 7 days. Either scenario may be considered appropriate for adolescents. Tapering the prednisolone dose is not needed if the treatment has been given for two weeks or less [GINA 2020]. A maximum duration for a short course of systemic corticosteroids is defined as 14 days. If a prednisolone equivalent is prescribed as treatment, Table 7 provides the estimated oral corticosteroid dose therapy equivalent to a dose of 40 mg of prednisolone.

Table 7 Estimated Oral Corticosteroid Dose Therapy Equivalence

Oral Corticosteroid	Equivalent to 40 mg of Prednisolone
Prednisone	40 mg
Prednisolone	40 mg
Cortisone	200 mg
Hydrocortisone	160 mg
Methylprednisolone	32 mg
Triamcinolone	32 mg
Betamethasone	4.8 mg
Dexamethasone	6 mg
Deflazacort	48 mg

6.5.3 Prior Medications

Participants eligible for this study are required to be on a stable regimen of an inhaled asthma maintenance therapy defined as an ICS/LABA for at least 4 weeks prior to Visit 1 per Inclusion #3. The required total daily ICS dosage to qualify for the study is defined in Table 8 [GINA 2020]. Any ICS not listed in the GINA 2020 guidelines or considerations outside of this list should be discussed with the Medical Monitor prior to entry of the participant.

Table 8 Required ICS Doses (in Combination with LABA) Prior to Visit 1[a]

Inhaled Corticosteroid	Medium Dose Total Daily Dose (µg/day)	High Dose Total Daily Dose (µg/day)
Beclomethasone dipropionate (pMDI, standard particle, HFA)	>500-1000	>1000
Beclomethasone dipropionate (pMDI, extrafine particle, HFA)	>200-400	>400
Budesonide (DPI or pMDI, standard particle, HFA)[b]	>400-800	>800
Ciclesonide (pMDI, extrafine particle, HFA)	>160-320	>320
Fluticasone furoate (DPI)	100	200
Fluticasone propionate (DPI)	>250-500	>500
Fluticasone propionate (pMDI, standard particle, HFA)	>250-500	>500
Mometasone furoate (DPI)	Due to complexity around dosing in different devices/formulations, please discuss with the Study Physician	
Mometasone furoate (pMDI, standard particle, HFA)	200-400	>400

[a] Daily doses in this table are shown as metered doses.
[b] The total daily dose of budesonide in Symbicort 160/4.5 µg pMDI, taken as two puffs twice daily, equals a total delivered dose of 640 µg, which is equivalent to 800 µg metered dose.
Use of ICS/Formoterol as reliever medication is prohibited for 8 weeks prior to Visit 1 and throughout the study.
HFA = Hydrofluoroalkane (propellant), DPI = Dry Powder Inhaler, pMDI = pressured metered-dose inhaler

6.5.4 Concomitant Medications

Any current ongoing medications, including over-the-counter medications, herbal supplements, and vaccinations, will be allowed provided they are not explicitly prohibited by the protocol. Participants should also be instructed to contact the Investigator if they develop any illnesses, especially those requiring medicinal interventions.

Medications meeting the stable dosing period prior to Visit 1 are allowed during the study and listed in Table 9.

Table 9 Allowed Medications With Defined Stable Dosing Period Prior to Visit 1

Medication	Minimum Stable Dosing Period Prior to Visit 1
Leukotriene antagonists/modifiers (eg, Zileuton®)	8 weeks
Selective serotonin reuptake inhibitors/serotonin and norepinephrine reuptake inhibitors[a]	4 weeks
Tricyclic antidepressants	2 weeks
Antipsychotics	4 weeks
Anticonvulsants	52 weeks for seizure disorders[b] 12 weeks for other conditions
Non-sedating long- and short-acting antihistamines	4 weeks
Intranasal corticosteroids	4 weeks
Intranasal ipratropium bromide[c]	4 weeks
Intranasal antihistamines or combination products of intranasal antihistamines/corticosteroids	4 weeks

[a] Must be on a stable dose for at least 4 weeks prior to Visit 1 and not altered during the Screening Period.
[a] Must be free of seizures for 1 year prior to Visit 1.
[b] Intranasal ipratropium bromide should be withheld for at least 6 hours prior to each visit.

6.5.4.1 Vaccinations

All participants should be vaccinated with annual influenza vaccine [GINA 2020] or any other inactive/killed vaccines per local policies, availability, and affordability. If a participant has egg intolerance or refuses to be vaccinated, the vaccination may be omitted. The annual influenza vaccine can be given at Visit 1 or at any other visit throughout the study at the discretion of the Investigator; however, administration should occur after obtaining all requisite spirometry assessments for that specific test day. There should be at least 7 days between vaccination and subsequent spirometry assessments.

If a participant is considering enrollment into the study and is also being considered for SARSCoV-2 vaccination, the participant must not be randomized until at least 7 days after receipt of the SARS-CoV-2 vaccination dose. If SARS-CoV-2 vaccination is in the best interest of the participant and the participant is vaccinated during the study, there should be at least 7 days between vaccination and subsequent spirometry assessments.

Live attenuated vaccines are not allowed within 30 days prior to Visit 1 or during the study.

6.5.5 Prohibited Medications

Participants requiring medications presented in Table 10 are prohibited from participating in this study. Participants who recently discontinued use of these medications may be considered for study enrollment provided they have met the minimum cessation period prior to Visit 1. These medications are prohibited throughout the course of the study. If participants require any of the prohibited medications listed in Table 10, the Investigator should discuss with the

Medical Monitor the suitability of the participant continuing study intervention.

Table 10 Prohibited Medications Throughout the Study and Required Cessation Period Prior to Visit 1

Medication	Minimum Cessation Period Prior to Visit 1
Long-acting beta$_2$-agonist as reliever (LABA)	8 weeks
Long-acting muscarinic antagonist (LAMA)	12 weeks
Theophylline	7 days
Oral and IV corticosteroids[a]	4 weeks
Injectable systemic corticosteroids (eg, depot formulation, intra-articular, intradermal, intramuscular)	3 months
Prophylactic antibiotics	4 weeks
Roflumilast	30 days
Any immunomodulators or immunosuppressives[b]	3 months or 5 half-lives, whichever is longer
Monoclonal antibodies (eg, anti-immunoglobulin E, anti-interleukin-5)	3 months or 5 half-lives, whichever is longer
Medications not currently licensed for use in the treatment of asthma and not part of current standard of care	30 days
Other investigational drugs	30 days or 5 half-lives, whichever is longer
Any drug with potential to significantly prolong the QT interval[c]	14 days or 5 half-lives, whichever is longer
Live attenuated vaccines	30 days
Non-selective non-ocular beta-blocking agents (except carvedilol)	7 days
Monoamine oxidase inhibitors	14 days
Systemic treatment with strong CYP3A4-inhibitors (eg, ketoconazole, itraconazole, and ritonavir)	30 days
Systemic anticholinergics[d]	7 days
Herbal remedies for the treatment of allergic, inflammatory, or respiratory diseases (eg, Chinese complementary and alternative bronchodilatory medicines)	10 days

[a] Use of systemic corticosteroids for any other reason except for the acute treatment of a severe asthma exacerbation is prohibited for the duration of the study.

[b] Topical administration of immunosuppressive medication maybe allowed at the discretion of the Investigator after discussion with the Study Physician.

[c] Participants who are on medications that have the potential to prolong the QTc interval may be enrolled provided the dose has remained stable for at least 3 months prior to Visit 1, the participant meets none of the ECG exclusion criteria, and if, in the opinion of the Investigator, there are not safety concerns for the participant to participate in the study.

[d] If systemic anticholinergics are used for the treatment of irritable bowel syndrome or overactive bladder and the treatment has been constant for at least 1 month, they are allowed.

Specific prohibited asthma and allergy medications and their required washout periods from Visit 1 prior to Visit 2 are displayed in Table 11.

Table 11 Prohibited Asthma and Allergy Medications From Visit 1 Onwards

Medication	Minimum Washout Period Prior to Visit 2
ICS[a]	7 days
ICS/LABA[b] other than sponsor-provided	7 days
Cromoglycate[c]	7 days
Nedocromil[c]	7 days
Ketotifen[c]	7 days
Short-acting muscarinic antagonists (SAMA) and/or short-acting beta$_2$-agonists (SABA) alone, loose, or fixed combination other than sponsor-provided albuterol[d]	7 days

[a] A short course of an ICS may be added for treatment of a moderate asthma exacerbation.
[b] Must be a minimum washout period of 7 days prior to Visit 2 for participants who failed spirometry.
[c] Cromoglycate, nedocromil, and ketotifen eye drops for allergic conjunctivitis are allowed; no washout period.
[d] Administration as fixed or loose combinations.

6.6 Dose Modification

Not applicable for this study.

6.7 Intervention after the End of the Study

At the end of the Randomized Treatment Period, the Investigator or treating physician of participant will prescribe alternative asthma therapy for the participant. There will be no provisions to supply BGF MDI, BFF MDI, or Symbicort pMDI after the end of the Treatment Period.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION

7.1 Discontinuation of Study Intervention

It may be necessary for a participant to permanently discontinue study intervention under certain circumstances. Discontinuation from study intervention does not indicate that the participant is withdrawn from the study. If study intervention is permanently discontinued, the participant should be encouraged to remain in the study and complete the remainder of the study visits and procedures.

See the SoA (Table 1) for procedures to be conducted at the time of study intervention discontinuation.

If a participant experiences any of the below, the study intervention MUST be discontinued:

- Development of exclusion criteria or other safety reasons as judged by the Investigator during the Treatment Period
- Pregnancy (see Section 8.3.9)

If a participant experiences the change of concern listed below, a repeat assessment should be obtained, and if confirmed, the study intervention MUST be discontinued:

- Calculated QTcF of >500 msec, OR
- a ≥60 msec change from pre-dose baseline value obtained at Visit 1

7.1.1 Procedures for Discontinuation of Study Intervention

The Investigator should instruct the participant to contact the site before or at the time of stopping study intervention. A participant who decides to discontinue study intervention prematurely will be encouraged to remain in the study to complete all remaining study visits.

All participants who discontinue study intervention and agree to continue study participation will complete a Study Intervention Discontinuation/Withdrawal Visit prior to transitioning back to regularly scheduled visits. Participants who discontinue study intervention will return to appropriate maintenance asthma medications, per the Investigator's or treating physician's discretion. The reason for discontinuation of study intervention must be recorded in the eCRF.

7.2 Participant Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioural, compliance, or administrative reasons. This is expected to be uncommon.
- A participant who considers withdrawing from the study must be informed by the investigator about modified follow-up options (eg, telephone contact, a contact with a relative or treating physician, or information from medical records).
- At the time of withdrawal from the study, if possible, an Early Study Intervention Discontinuation visit should be conducted, as shown in the SoA (Table 1). See SoA for data to be collected at the time of study withdrawal and follow-up for any further evaluations that need to be completed.
- If the participant withdraws consent for disclosure of future information, AstraZeneca may retain and continue to use any data collected before such a withdrawal of consent.

- If a participant withdraws from the study, it should be confirmed if he/she still agrees for existing samples to be used in line with the original consent. If he/she requests withdrawal of consent for use of samples, destruction of any samples taken and not tested should be carried in line with what was stated in the informed consent and local regulation. The Investigator must document the decision on use of existing samples in the site study records and inform the Global Study Team.

7.3 Lost to Follow up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required 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 mailing 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

- Study procedures and their timing are summarized in the SoA (Table 1). Protocol waivers or exemptions are not allowed.
- The suggested order of assessments is vital signs, AE/SAE assessment, 60 minutes pre-dose spirometry, PRO questionnaires, 30 minutes pre-dose spirometry, ECG, and blood draw, followed by study intervention administration. **Spirometry MUST be performed in accordance with the specified timing.**
- Immediate safety concerns should be discussed with AstraZeneca immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

- Adherence to the study design requirements, including those specified in the SoA (Table 1), is essential and required for study conduct. Protocol waivers or exemptions are not allowed.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- The maximum amount of blood collected from each participant over the duration of the study will not exceed 170 mL (this includes 110 mL maximum for samples taken for participants in the PK sub-study). Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Efficacy Assessments

8.1.1 Pulmonary Function Tests

8.1.1.1 Spirometry Standardization

All spirometry including FEV_1, FVC, and FEF_{25-75} as defined in American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines will be performed in accordance with ATS/ERS acceptability and repeatability criteria [Miller 2005] and will be assessed using a spirometer that meets or exceeds minimum performance recommendations. Calculated predicted spirometry results will be obtained using the Global Lung Initiative equations [Quanjer 2012].

To standardize spirometry, all sites will be provided with identical spirometry systems (MasterScope) with customized, study-specific software. Spirometry calibration and data quality checks (including monitoring of unexpectedly high variability of results) will be detailed in a separate spirometry procedures manual.

For an exact determination of lung volume, the sensor unit (pneumotach) must be calibrated at least once a day on the day spirometry measurements are performed. A calibration pump with a certified volume of 3 L is used for calibration. Calibration is carried out under Ambient Temperature Pressure conditions, ie, ambient conditions. Please refer to the Instruction for Use Manual for additional calibration details. The results will be printed and maintained in a calibration log, which will be monitored for compliance during the monitoring visits.

All study staff responsible for performing spirometry assessments will receive standardized training. All site personnel involved in spirometry assessments are required to pass an ERT® spirometry proficiency test to demonstrate proficiency in the use of the equipment and the ability to perform technically acceptable spirometry assessments (ATS criteria) prior to performing any spirometry assessments for the purpose of this study. After each test is performed, the spirometry software will provide immediate feedback to the technician

indicating whether the effort meets ATS acceptability and repeatability standards [Miller 2005]. The final assessment will be performed by a Central Overread Department. All spirometry assessments will be stored electronically, and a signed and dated copy of the printouts must be kept at study site for source data verification.

After completion of testing, the study staff will electronically transmit the spirometry measurements for centralized quality assurance review to ERT. Feedback on the quality of the measurements will be provided to the investigational site via alert report in case of any data changes and/or unacceptable data. Additionally, the reports can be viewed at any time by the site and AstraZeneca representative via the ERT Portal.

As spirometry results are primary and secondary efficacy endpoints for this study, it is important for the medication withholding conventions and timing of spirometry to be consistently managed throughout the study (see Section 8.1.1.2).

8.1.1.2 Spirometry Schedule

Spirometry collection is briefly outlined below. For exact spirometry collection and specifications, please refer to the SoA (Table 1) and Timing of Spirometry Measurements (Table 2).

Important requirements to support consistent spirometry assessments during study:

- All pre-dose (trough) spirometry should be conducted in the morning (0800 ±2 hours).
- During the Screening and Treatment Periods, sites should call 24 to 48 hours prior to each visit to remind participants that the evening dose of study intervention (run-in BFF MDI or study intervention) should be 12 ±1 hr prior to the expected dosing time at the next morning visit.

  Note: If the site morning dose time is going to be >13 hours from the prior evening dose time, then the visit should be re-scheduled within the allowed visit window.
- Participants will be required to return to the clinic at approximately the same time ±1 hr as Visit 1 throughout the study.
- All in-clinic dosing should occur prior to 1000 (+1-hour allowance) in the morning and visits must be planned accordingly. Participants will be dispensed and administered new study intervention at each clinic visit during the Treatment Period.
- The morning dose on the day of the clinic visit must be withheld until after all pre-dose assessments are completed at the clinic.

  Note: Albuterol must be withheld at least 6 hours prior to the start time of the morning visit. If these requirements are not met, then the visit will need to be rescheduled within visit windows.

- Participants will be required to remain at the clinic until completion of all protocol-defined assessments and procedures.
- During the Treatment Period, if a participant discontinues study intervention and agrees to continue in the study and complete all remaining study visits, the participant's asthma maintenance medication(s) will be administered for spirometry testing instead of study intervention.

Screening Period (Visit 1 to Visit 5):

- The average of the 2 pre-bronchodilator FEV_1 values (60- and 30-minutes pre-dose) will be assessed at every visit from 1 to 5 (pre-randomization).
- The average of the 2 pre-bronchodilator FEV_1 values (60- and 30-minutes pre-dose) will be calculated to determine if a participant meets the Inclusion criterion #6 at Visit 1 to 5. If a participant does not meet this criterion at any one of the screening visits, the participant will be screen-failed at that visit.
- Participants who have not withheld asthma medications eg, ICS/LABA (12 hours washout required for BID dosing or 24 hours washout required for once daily dosing) and SABA (6 hours washout required) prior to Visit 1 and failed to meet the FEV_1 inclusion requirements at Visit 1, should return to the clinic to repeat spirometry testing within two business days. If the repeat spirometry testing fails to meet the FEV_1 inclusion criterion, then participants must be screen-failed. For all visits after Visit 1, if study intervention has not been withheld for the specified timeframes then visits should be rescheduled and conducted within the specified visit windows.

  Note: Run-in BFF MDI and albuterol will only be dispensed to participants after meeting eligibility criteria at Visit 1 to proceed to Visit 2.

Visit 1:

- Spirometry will be conducted 60 and 30 minutes prior to run-in BFF MDI administration.

Visit 2:

- Spirometry will be conducted at 60 and 30 minutes prior to albuterol administration and 30 minutes post-albuterol (see Section 8.1.1.3).
- Albuterol reversibility testing should be conducted for all participants at Visit 2; participants who fail to meet the reversibility criterion at Visit 2 should still proceed to Visit 3 for further reversibility testing (including those with documented historical reversibility).
- If participants are not reversible to albuterol at 30 minutes post-dose, the post-dose spirometry can be repeated at 60 minutes post-dose.

- Administer run-in BFF MDI after completion of reversibility test.

Visit 3:

- For participants who did meet the albuterol reversibility criterion at Visit 2, spirometry will be conducted 60 and 30 minutes prior to run-in BFF MDI administration.
- For participants who did not meet albuterol reversibility criterion at Visit 2 (including those with documented historical reversibility to albuterol within 12 months prior to Visit 1), albuterol reversibility testing must be repeated at Visit 3. The albuterol reversibility testing at Visit 2 (and Visit 3 if reversibility is not demonstrated at Visit 2) is required to provide reversibility baseline data for characterization.
- Participants who fail to meet the albuterol reversibility criterion at both Visit 2 or Visit 3 can still proceed to Visit 4 if they meet all other study criteria, **provided** they have a documented history of reversibility in the 12 months prior to Visit 1.
- Participants who have not met historical reversibility in the 12 months prior to Visit 1 and do not meet the reversibility criterion at Visit 2 or Visit 3 will be screen failed.
- Administer run-in BFF MDI after completion of reversibility test.

Visit 4:

- Spirometry will be conducted 60 and 30 minutes prior to run-in BFF MDI administration.

Visit 5 (Randomization):

- Serial spirometry will be conducted 60 minutes and 30 minutes prior to the first dose of study intervention and **5**, 15, and 30 minutes, and 1-, 2-, and 3-hours post-dose.
- For 12-hour serial spirometry sub-study participants only, additional serial spirometry will be conducted at 6-, 9-, and 12-hours post-dose.

Visits 6, 8, 11, 15/Final or Treatment Discontinuation/Study Withdrawal Visit:

- Serial spirometry will be conducted 60 minutes and 30 minutes prior to study intervention administration and 15 and 30 minutes, and 1-, 2-, and 3-hours post-dose.
- At Visit 8, for 12-hour serial spirometry sub-study participants only, additional serial spirometry at 6-, 9-, and 12-hours post-dose.

Visits 7, 9, 10, 12, 13, and 14:

- Spirometry will be conducted 60 minutes and 30 minutes prior to study intervention administration.

8.1.1.3 Reversibility to Albuterol

Reversibility to albuterol will be evaluated for participant qualification purposes and baseline data characterization. For participants without historically documented reversibility, the reversibility criterion must be met at Visit 2 or Visit 3 (see Section 5.1), otherwise, the participant will be screen failed. For participants who meet reversibility criterion at Visit 2, reversibility testing will not be repeated at Visit 3. Participants with historically documented reversibility criterion who fail to meet reversibility at Visit 2 and Visit 3 can still proceed to Visit 4 if they meet all other criteria.

All participants must demonstrate reversibility either through historically documented reversibility in the 12 months prior to Visit 1 or through demonstrating reversibility at Visit 2 or Visit 3.

The procedure for testing reversibility to albuterol is as follows:

1 Confirm run-in BFF MDI was taken the prior evening 12 hours (±1 hour) prior to the expected dosing time at the next morning visit. The morning dose must not have been taken and albuterol withheld at least 6 hours prior to the start time of the visit.
2 Perform pre-bronchodilator spirometry at 60 and 30 minutes prior to administration of bronchodilator.
3 Administer 4 puffs of albuterol.
4 Perform post-bronchodilator spirometry 30 minutes after the administration of albuterol. If participants are not reversible to albuterol at 30 minutes, the post-dose spirometry can be repeated at 60 minutes post-dose.

Reversibility will be a comparison of the average best FEV_1 effort obtained at 60- and 30minutes pre-bronchodilator to the best FEV_1 effort obtained at 30 minutes (or up to 60 minutes, if repeated) post-bronchodilator following administration of albuterol. A participant ≥18 years of age is considered reversible if the improvement in FEV_1 at 30 minutes (or at 60 minutes) post-dose is ≥12% and ≥200 mL. A participant 12 to <18 years of age is considered reversible if the improvement in FEV_1 at 30 minutes (or at 60 minutes) post-dose is ≥12%.

Administer run-in BFF MDI after completion of reversibility test.

8.1.2 Asthma Exacerbations

An asthma exacerbation is defined as worsening of asthma that requires a medical intervention as described in Section 8.1.2.3.

Worsening of asthma is defined as (at least 1 of the following 3 elements of worsening listed

below must be fulfilled for at least 2 consecutive days) (see Section 8.1.3.5 for eDiary alerts):

- worsening of asthma signs/symptoms (see Section 8.1.2.1)
- increased use of 'as-needed' rescue/reliever medication (see Section 8.1.3.2)
- deterioration of lung function (ie, PEFR, FEV_1) (see Section 8.1.3.3)

8.1.2.1 Definition of Worsening of Asthma Signs/Symptoms

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

- asthma symptoms (eg, shortness of breath, wheezing, chest tightness, cough)
- night-time awakening due to asthma
- physical exam finding consistent with deterioration of asthma

8.1.2.2 Investigator Justified Asthma Exacerbations

The majority of asthma exacerbations should be associated with worsening of asthma signs/symptoms described in Section 8.1.2.1. However, clinical presentations may vary among participants and the associated asthma worsening signs/symptoms and/or duration may not meet the definition of a moderate or severe exacerbation. For moderate and severe exacerbations without an eDiary alert date recorded in the eCRF, the Investigator will record the worsening signs/symptoms with duration and provide the justification(s) for diagnosing the exacerbation (eg, rapid onset and/or severity of worsening asthma) in the eCRF. If an exacerbation is recorded in the setting of treatment with additional corticosteroids for less than 3 days (Section 8.1.2.3), the Investigator will record whether it is considered severe or moderate and the justification(s) for diagnosis and treatment duration (eg, single administration of IV corticosteroid without an oral corticosteroid prescribed) in the eCRF.

8.1.2.3 Severity of Asthma Exacerbation

All protocol defined asthma exacerbations will be classified as severe or moderate based on the following treatment criteria [Reddel 2009].

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

- A short course of systemic corticosteroids for at least 3 consecutive days to treat symptoms of asthma worsening.
- An ER 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 treatment with systemic corticosteroids
- An in-patient hospitalization (defined as admission to an in-patient facility and/or evaluation and treatment in a healthcare facility for ≥24 hours) due to asthma

- Death related to asthma

A moderate asthma exacerbation is defined as a worsening of asthma symptoms (defined in Section 8.1.2.1) that results in an additional ICS for at least 3 days.

8.1.2.4 Treatment for Asthma Exacerbations

Asthma exacerbations should be treated at the discretion of the Investigator. If a participant experiences an asthma exacerbation, they should continue dosing with study intervention if Investigator or treating physician assess it is safe do so.

In the instance a participant is hospitalized for a severe asthma exacerbation and study intervention is interrupted, the participant may be able to restart study intervention upon stopping the asthma medications.

The recommended treatment [GINA 2020] for a **severe** asthma exacerbation is prednisolone 1 to 2 mg/kg/day up to a total of 40 mg/day (or equivalent; see Table 7) for children and 40 to 50 mg/day (or equivalent) for adults once daily in the morning for 5 to 7 days. Either regimen may be considered appropriate in adolescents. Tapering the prednisolone dose is not needed if the treatment has been given for less than two weeks [GINA 2020]. A maximum duration for a short course of systemic corticosteroids is defined as 14 days.

Use of depot corticosteroids in the treatment of asthma exacerbations is prohibited.

The recommended treatment for a **moderate** asthma exacerbation is a short course of an additional ICS for 5 to 7 days to help avoid progression to a severe asthma exacerbation. If a participant has not adequately improved at the end of 2 weeks of treatment with an additional ICS, a short course of systemic corticosteroids should be given, and the asthma exacerbation will be considered as a severe asthma exacerbation.

8.1.2.5 Onset and Duration of Asthma Exacerbations

For **moderate** or **severe** asthma exacerbations, the duration is defined by the **prescribed treatment**. For severe asthma exacerbations, the duration of hospitalization or ER visit could replace the duration of prescribed systemic corticosteroids as described below.

For **severe** asthma exacerbations:

- The start date will be defined as the start date of prescribed treatment with a systemic corticosteroid, the hospital/ER admission date, or the date of death (if the exacerbation resulted in death), whichever is earlier.

  Note: The start date could be the start date of an additional ICS when treatment is switched to at least 3 days of systemic corticosteroids as described in Section 8.1.2.4.

- The stop date is defined as the last day of prescribed systemic corticosteroids, hospital/ER discharge date or the date of death (from the exacerbation), whichever is later.
- 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 systemic corticosteroid treatment, hospitalization admission/discharge dates will be used as start/stop dates as described in Section 8.1.2.3.

For **moderate** asthma exacerbations:

- The start date is defined as the first day of the additional dose of ICS treatment.
- The end date is defined as the last day of the above treatment.

In order to ensure that the same event is not counted twice, consecutive exacerbations with start and stop days ≤7 days apart will be considered the same event of the highest severity. If there is a >7 day time period between ICS or systemic corticosteroid treatments, then separate exacerbations should be recorded in the eCRF.

8.1.2.6 Approach for Capturing Asthma Exacerbations

A copy of the medical records should be obtained for exacerbations evaluated and treated at a non-study center (eg, by the primary care Health Care Provider or at an emergency department/hospital) and details entered in the exacerbation eCRF in a timely fashion. Changes in concomitant medication due to the exacerbation must be recorded in the appropriate module of the eCRF.

All moderate or severe asthma exacerbations (including Investigator justified asthma exacerbations) following Visit 1 must be captured using the Asthma Exacerbation eCRF.

If there were eDiary alerts within the window of -7 to +1 days of the initiation of exacerbation treatment, the exacerbation will be considered an eDiary supported exacerbation. One of the eDiary alert dates within the defined window should be captured on the exacerbation eCRF. If an exacerbation is not supported by an eDiary alert date in the defined window, then Investigators will provide justifications and record in the eCRF.

If an asthma exacerbation meets the definition of an SAE, the exacerbation will be reported as an SAE as well as on the Asthma Exacerbation eCRF.

Any symptoms of asthma or an asthma exacerbation of any severity will be considered the disease under study and will not be reported as AEs unless meeting the definition of an SAE or leads to discontinuation of study intervention.

8.1.2.7 CCI

CCI [redacted]

8.1.3 Participant's eDiary Data Collection at Home

Participants will be supplied with a hand-held electronic device at Visit 1 to take home to enter data electronically on a daily basis at home. Prior to issuing the eDiary to the participant, site personnel will receive eDiary training. The site staff are responsible for setting up the eDiary for each participant's use and for ensuring each participant is trained to complete the following in the morning and evening:

- Daily asthma symptoms and night-time awakening questions (Section 8.1.3.1)
- Number of puffs of albuterol (Section 8.1.3.2)
- Ensure collection of PEFR (Section (8.1.3.3)
- Daily use of inhaled asthma maintenance treatment including run-in BFF MDI and study interventions (Section 8.1.3.4)
- Respond to eDiary alerts, as applicable (Section 8.1.3.5)
- Compliance alerts (Section 8.1.3.6)

The eDiary will be completed by participants each morning and each evening for the duration of the study. The eDiary will alert the participant with an alarm when it is time to fill out the questions. The eDiary will also prompt the participant to collect PEFR. Reporting via the eDiary will occur before administration of run-in BFF MDI during the Screening Period and study intervention/or asthma maintenance medication during the Randomized Treatment Period.

In addition, the eDiary will be used to complete the SGRQ (Section 8.1.3.7), which is a health-related-quality of life (HRQoL) questionnaire.

Important reminders regarding eDiary use prior to clinic visits:

- On the evening prior to the clinic visit, participants will complete their eDiary before dosing. Dosing should be 12 hours (±1 hour) prior to the expected dosing time at the next morning visit.
- On the evening prior to clinic Visits 5, 6, and 11, participants will complete the SGRQ HRQoL before dosing.

- On the morning of the clinic visit, participants **will not** complete their eDiary at home, but will instead bring their eDiary to the visit to complete at the clinic.

8.1.3.1 Daily Asthma Symptoms Scoring

The participant will record their symptoms in the eDiary each morning (reflecting nighttime symptoms) and each evening (reflecting daytime symptoms) before dosing.

The daily eDiary questions will ask participants about severity of nighttime and daytime symptoms of asthma; limitations on activities, albuterol use, and prompt the participant to electronically record PEFR. Daytime is defined as the time period between the morning peak flow/lung function assessment (upon rising in the morning) and the evening peak flow/lung function assessment. Night-time is defined as the time period between the evening peak flow/lung function assessment (at bedtime) and the morning peak flow/lung function assessment.

Nocturnal awakenings due to asthma symptoms will be recorded by the participant in the daily eDiary each morning by answering the questions whether he/she woke up during the night due to asthma symptoms by a "yes" or "no" response.

8.1.3.2 Rescue Medication Use

Use of rescue medication (albuterol) will be recorded in the eDiary each morning (reflecting night-time albuterol use) and each evening (reflecting daytime albuterol use). The participant will record the total number of "puffs" of albuterol used over the time period. For example, when rescue medication is required, and 2 actuations are inhaled, this should be recorded as 2 "puffs". If the participant requires 4 actuations, this should be recorded as 4 "puffs".

8.1.3.3 Peak Expiratory Flow Rate

The PEFR is to be assessed using the sponsor provided PEFR meter that is linked to the eDiary device. Participants will be dispensed and trained on the device at Visit 1. The eDiary will prompt the participant to obtain their peak flow every morning and every evening. Once the participant has completed the peak flow assessment, the data will be automatically transmitted from the PEFR to the eDiary. The best (highest) of 3 PEFR efforts will be captured in the eDiary twice daily.

Participants will complete the PEFR maneuver at home in the morning and in the evening after recording asthma symptoms and before dosing with run-in BFF MDI during the Screening Period or study intervention during the Treatment Period. In addition, PEFR will be measured before use of rescue albuterol.

At Visit 5, a PEFR baseline will be calculated to define a stability limit. The stability limit is defined as the average of the available morning PEFR eDiary recordings during the last 7 days

before Visit 5 (ie, the baseline PEFR), multiplied by 0.8. The PEFR stability limit will be used as a threshold for an eDiary alert.

8.1.3.4 Inhaled Asthma Maintenance Use

Inhaled asthma maintenance use includes run-in BFF MDI, study intervention or asthma maintenance medication (for participants who discontinue study intervention). The eDiary will ask participants about daily inhaled asthma maintenance use each morning and each evening. For participants receiving study intervention, the question will refer to taking two puffs from both inhalers and the response will be "yes" or "no" to the question. Participants will record the prior evening dose in the morning eDiary entry, and the morning dose will be recorded in the evening eDiary entry.

Rescue inhaler use will be collected in a separate eDiary question.

8.1.3.5 Symptom Worsening Assessment and eDiary Alert System

The eDiary will be programmed to alert both the participant and study site if any of the thresholds listed below are met on at least 2 consecutive days:

- PEFR: a decrease in morning PEFR ≥20% as compared with baseline average, and/or
- Rescue albuterol use: an increase of ≥4 inhalations compared with baseline average use, and/or
- Nighttime awakening: an increase of 2 or more nights with awakenings due to asthma requiring rescue medication use over a 7-day period compared with the average baseline and/or ≥6 out of the previous 7 nights with awakenings due to asthma requiring rescue medication, and/or
- Asthma symptoms: an increase of total asthma symptom score (the sum of daytime plus nighttime) of at least 2 units above the average baseline or the highest possible score (daily score of 6)

An eDiary alert is not an asthma exacerbation per se. Although the eDiary alert should initiate contact between the participant and the investigational site, the Investigator or designee will always assess the participant's symptoms and determine whether to treat the participant for an asthma exacerbation.

8.1.3.6 eDiary Compliance Requirement

Compliance with eDiary is required throughout the study on a daily basis. Participants must have an eDiary 14-day compliance of ≥70% during screening to be eligible for randomization (defined as completing the daily eDiary for any 10 mornings, and any 10 evenings, and answering "Yes" to taking 2 puffs of run-in BFF MDI for any 10 mornings and any 10 evenings in the last 14 days prior to Visit 5). During the Treatment Period, daily eDiary compliance is critical for capturing worsening symptoms and use of study interventions. The

Investigator/authorized delegate will check the participant's adherence to the daily eDiary at each visit during the study. An alert will be generated when a participant is not consistently completing the eDiary and/or confirming on the eDiary that they have taken their study intervention.

8.1.3.7 St. George's Respiratory Questionnaire (SGRQ)

The SGRQ is a 50-item PRO instrument developed to measure the health status of patients with respiratory diseases [Jones 1991]. The questionnaire is divided into two parts: part 1 consists of 8 items pertaining to the severity of respiratory symptoms in the preceding 4 weeks; part 2 consists of 42 items related to the daily activity and psychosocial impacts of the individual's respiratory condition. The SGRQ yields a total score (range 0 to 100) and three domain scores (symptoms, activity, and impacts). The total score indicates the impact of disease on overall health status. This total score is expressed as a percentage of overall impairment, in which higher scores indicate worse health. Likewise, the domain scores range from 0 to 100, with higher scores indicative of greater impairment. St. George's Respiratory Questionnaire score changes of 4 points on the total score and in each domain are considered clinically meaningful. Specific details on the scoring algorithms are provided by the developer in a user manual [Jones 2009].

The SGRQ will be administered and completed on the eDiary by the participant on the evening before specific site visits throughout the Treatment Period. The SGRQ is estimated to take approximately 15 to 25 minutes to complete on the evening prior to a clinic visit per the SoA (Table 1).

The Investigator/authorized delegate will check participant's adherence to the SGRQ at each specified visit.

8.1.3.8 Weekly 5-Item Onset of Effect Questionnaire

To capture onset of effect in this study, a weekly 5-item OEQ PRO [Leidy 2007, Leidy 2009, Kaiser 2008, Mathias 2007] will be completed at home by participants in the 12-hour spirometry sub-study **only** according to the SoA (Table 1).

The weekly 5-item OEQ at home is used to assess participant perception of feeling medication begin to work right away. There are 5 items that ask participants to think about the past week. Participants are asked to respond to each item on the following scale: strongly agree, somewhat agree, neither agree nor disagree, somewhat disagree, or strongly disagree.

The five items are:

1 During the past week, you could tell your study medication was working
2 During the past week, you could feel your study medication begin to work right away

3 During the past week, you felt physical sensations shortly after taking your study medication that reassured you that it was working

4 During the past week, your study medication worked as quickly as albuterol

5 During the past week, you were satisfied with how quickly you felt your study medication begin to work

Although the five items are referred to as the "OEQ", this is for efficiency and is not intended to reflect a single concept or a unidimensional instrument. There is no total score. Each of the five items comprising the OEQ are scored and interpreted separately.

The responses for each item are transformed to a dichotomous (yes/no) variable to classify a 'responder'. Thus, participants choosing "strongly agree" and "somewhat agree" are classified as "yes" on that item, while those who respond, "neither agree nor disagree," "somewhat disagree," and "strongly disagree" are classified as "no". In addition, mean values for each item can be presented (strongly agree = 1; somewhat agree= 2; neither agree nor disagree = 3; somewhat disagree = 4, and strongly disagree = 5).

The response to Item 2 is used to classify participants in terms of whether or not they perceived a medication begin to work right away for testing treatment effects. Thus, participants responding, "strongly agree" and "somewhat agree" are classified as perceivers, while those who respond, "neither agree nor disagree," "somewhat disagree," and "strongly disagree" are assigned to the "no" perception group. The Likert-type scaling permits participants to evaluate the perception along a continuum, with the scoring conservatively placing participants who are uncertain in the "no" group (did not perceive) to minimize overestimation of effect.

8.1.4 Participant's eDiary Data Collection at the Site Visit

Participants will fill out PRO questionnaires electronically on the eDiary at each clinic visit. Participants will bring their eDiary device to every clinic visit after Visit 1.

On the morning of a clinic visit day, participants will wait until the clinic visit before filling out the eDiary. Participants will complete all required eDiary questionnaires prior to dosing at the clinic, except for the OEQ-item included in the PFT sub-study, which is required to be completed post-dosing. After each study visit, participants will return to the normal schedule of completing the daily eDiary at home.

Table 12 describes the number of items and time to complete the PROs administered at clinic visits. However, not every questionnaire is administered at every visit. The eDiary device will be programmed to administer the appropriate questionnaires in the right order that correspond with the site-selected visit.

The estimated timeframe for completion of all the PROs during a clinic visit is about 15 minutes. The time to complete will vary depending on the specific PROs administered at each visit.

Table 12 Patient Reported Outcomes Administered at the Clinic Visit

	Number of Questions	Estimated Minutes to Complete
ACQ (pre-dose)	6	2
AQLQ(s)+12 (pre-dose)	32	8
EQ-5D (pre-dose)	6	2
PGIC (pre-dose)	1	1
eDiary – morning (pre-dose)	10	3
OEQ 1-item (post-dose)	5	2

Asthma Control Questionnaire (ACQ), Asthma Quality of Life Questionnaire 12 Years of Age and Older (AQLQ(s)+12), European Quality-of-Life-5 Dimensions (EQ-5D-5L), Patient Global Impression of Change (PGIC), Onset of Effect Questionnaire (OEQ) 1-item

8.1.4.1 Asthma Control Questionnaire

The ACQ [Juniper 1999a] was developed to measure asthma control and has been fully validated for use in adults (18 years and older) and children 6 to 17 years of age. International guidelines for the treatment of asthma have identified that the primary clinical goal of asthma management is to optimize asthma control (minimization of symptoms, activity limitation, bronchoconstriction, and rescue bronchodilator use) and thus reduce the risk of life-threatening exacerbations and long-term morbidity. The ACQ was developed to meet these criteria by measuring both the adequacy of asthma control and change in asthma control, which occurs either spontaneously or as a result of treatment.

There are three versions of the ACQ that are being analyzed in this study, ACQ-5, ACQ-6, and ACQ-7 (the ACQ-6 and ACQ-7 building on the components of the ACQ-5). Each version supports different endpoint calculations for this study. The ACQ-5 and ACQ-6 are patient-reported, and the ACQ-7 includes one additional item of pre-bronchodilator FEV_1 percent predicted normal.

In the ACQ, participants are asked to recall how their asthma has been during the previous week by responding to 1 bronchodilator use question and 5 symptom questions. Questions are weighted equally and scored from 0 (totally controlled) to 6 (severely uncontrolled). The mean ACQ score is the mean of the responses. Mean scores of ≤ 0.75 indicate well-controlled asthma, scores between 0.75 and <1.5 indicate partly controlled asthma, and a score ≥ 1.5 indicates not well-controlled asthma [Juniper 2006]. Individual changes of at least 0.5 are considered clinically meaningful.

The Investigator/authorized delegate will check participant's adherence to the ACQ at each visit per the SoA (Table 1).

8.1.4.2 Asthma Quality of Life Questionnaire 12 Years of Age and Older

The AQLQ(s)+12 is a 32-item validated questionnaire that measures health-related quality of life experienced by patients with asthma who are 12 years or older in age [Juniper 2005, Juniper 1999b, Juniper 1994, Juniper 1993, Juniper 1992].

The AQLQ(s)+12 comprises 4 separate domains (symptoms, activity limitation, emotional function, and environmental stimuli) and a global score.

Participants are asked to recall the previous 2 weeks and score each of the questions on a 7-point scale ranging from 7 (no impairment) to 1 (severe impairment). The overall score is calculated as the mean response to all questions. The individual domain scores (symptoms, activity limitation, emotional function, and environmental stimuli) are the means of the responses to the questions in each of the domains. Individual AQLQ(s)+12 total or domain score changes $\geq$0.5 are considered clinically meaningful.

The questionnaire will be completed at each visit, starting at randomization.

The Investigator/authorized delegate will check participant adherence to the AQLQ(s)+12 at each visit per the SoA (Table 1).

8.1.4.3 European Quality-of-Life-5 Dimensions

The EQ-5D [EuroQol Group 2020] is a standardized instrument for use as a measure of health outcome. Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status. The EQ-5D data will be collected using EQ-5D-Y for the participants age between 12 and 15 years old at randomization and EQ-5D-5L for the participants age 16 years and older [EQ-5D User Guides: EQ-5D-Y 2014, EQ-5D-5L 2019]. The participants will complete same questionnaire used at randomization throughout the study. The EQ-5D-5L consists of 2 assessments, a descriptive system, and a VAS. The descriptive system comprises 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. The EQ-5D-Y consists of 2 assessments, a descriptive system, and a VAS. The descriptive system comprises the same 5 dimensions as the EQ-5D-5L, but using a child-friendly wording (mobility, looking after myself, doing usual activities, having pain or discomfort, feeling worried, sad, or unhappy). Each dimension has 3 levels: no problems, some problems, a lot of problems.

EQ-5D-5L and EQ-5D-Y index score can be calculated based upon participants' responses to the 5 dimensions and using an appropriate value set [EQ-5D User Guides: EQ-5D-5L 2019,

EQ-5D-Y 2014]. A value set provides values (weights) for each health state description according to the preferences of the general population of a country/region.

The VAS records the respondent's self-rated health on a 20 cm, 0 to 100 vertical scale with endpoints labelled "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 will be completed on the eDiary by the participant at 11 site visits throughout the Treatment Period per the SoA (Table 1). The Investigator/authorized delegate will check participant's adherence to the EQ-5D at each visit.

8.1.4.4 Patient Global Impression of Change

The PGIC captures the participant's overall evaluation of response to treatment. The participant is asked to report the degree to which they have changed since entering the Treatment Period using a 7-point scale ('Much Better', to 'About the same', to 'Much worse').

The PGIC will be completed on the eDiary by the participant at 2 site visits throughout the Treatment Period and at the final visit. The Investigator/authorized delegate will check participant's adherence to the PGIC at each visit per the SoA (Table 1).

8.1.4.5 Onset of Effect 1-Item in the Clinic

To capture immediate onset of effect [Leidy 2007, Leidy 2009, Kaiser 2008, Mathias 2007] in this study, participants in the 12-hour spirometry sub-study **only** will be asked if they can feel the study medication working after administration. It is one question that asks about whether or not the participants can feel the medication working. Participants respond with either 'yes' or 'no'.

The repeat OEQ item is:

- Can you feel your study medication working?

The repeat OEQ item will be administered to participants in the 12-hour spirometry sub-study **only** at specific timepoints following the study intervention dosing at specified clinic visits per Table 2.

8.1.5 Fractional Exhaled Nitric Oxide

Planned timepoints for fractional exhaled nitric oxide (FeNO) measurements are provided in the SoA (Table 1).

Airway inflammation will be evaluated using a standardized single-breath FeNO test in

accordance with the SoA (Table 1). A single exhalation technique recommended by the manufacturer will be followed [Alving 2017].

The FeNO measurements will not be performed within 2 weeks of a respiratory infection. The FeNO test will be performed prior to spirometry. Participants should not eat or drink 1 hour prior to having the FeNO test. Participants should not use their rescue SABA medication (eg, albuterol/salbutamol) within 6 hours of the measurement. Inhaled bronchodilators (including ICS/LABA) should be withheld for the effect duration specific to the bronchodilator as described in the spirometry section. If not, the assessment will be postponed till after the required time has passed since the meal or drink or the visit must be rescheduled within the allowed visit window.

8.2 Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA (Table 1).

8.2.1 Medical/Surgical History

Medical/surgical history will be collected at Visit 1 and during the study period, if necessary.

8.2.1.1 Respiratory Medical History

Medical history related to asthma will be recorded on a separate respiratory medical history eCRF page.

The number of asthma exacerbations (at least 3 days of systemic corticosteroids **and** an associated physician visit, hospitalization, or ER visit due to an asthma exacerbation within 3 days of the corticosteroid use) in the 12 months prior to screening will be collected at Visit 1 or Visit 2, if all documentation is not available at Visit 1.

Participant verbal reports are not acceptable. Appropriate documentation includes physician notes or records from hospitalization or ER visit or letter from treating physician (if physician is not involved in the study).

8.2.2 Physical Exam

A brief physical examination will be performed at Visits 1, 5, 11, and 15/Final Visit or Study Intervention Discontinuation Visit/Study Withdrawal Visit. The brief physical examination will include the following:

- General appearance, respiratory, cardiovascular, and abdomen

8.2.3 Height and Weight

Height and weight will be measured at Visit 1 only for participants ≥18 years of age. Height and weight will be measured at Visits 1, 11, and 15/Final Visit or Study Intervention

Discontinuation Visit/Study Withdrawal Visit for participants 12 to <18 years of age.

8.2.4 Vital Signs

Vital signs will be performed at timelines as specified in the SoA (Table 1).

Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in either a supine or seated position in a quiet setting without distractions (eg, television, cell phones).

For participants who discontinue study intervention or withdraw consent, a single measurement of vital signs will be obtained at the Study Intervention Discontinuation Visit or Study Withdrawal Visit, respectively.

8.2.5 Electrocardiograms

An ECG will be performed at visits as specified in the SoA (Table 1).

The 12-lead ECG will be taken in supine position after 10 minutes of rest. The Investigator or authorized delegate will be responsible for the overall interpretation and determination of clinical significance of any potential ECG findings. In case of discrepancy between the Investigator's interpretation and that provided by the ECG machine (if applicable), the Investigator's interpretation will take precedence and should be noted on the printout and recorded in the eCRF. A copy of the ECG will be produced, and quality checked and kept in case of further need for re-evaluation.

For participants who discontinue study intervention or withdraw consent, a single ECG will be obtained at the Study Intervention Discontinuation Visit or Study Withdrawal Visit, respectively.

For participants in the Holter Monitor sub-study, at Visit 5 (randomization) 6 ECG readings will be taken pre-dose and triplicate ECG readings will be taken 30 minutes and 4 hours post-dose (see Table 2). Triplicate ECG readings will be taken pre-dose at all other visits as specified in the SoA (Table 1) as well as triplicate ECG readings at Visit 8 (Week 12) 15 minutes post-dose. The triplicate ECG readings should be performed within 5 minutes of starting the first reading. For the 6 ECG readings at baseline, the first set of triplicate readings should be performed within 5 minutes of starting the first reading, a 10-minute period of rest should occur and then the second set of triplicate readings should again be performed within 5 minutes.

The ECG parameters to be assessed include heart rate, PR interval, QRS interval, and QT/QTcF interval. The QT intervals and calculated QTcF intervals will be reviewed and checked for gross inaccuracies by the Investigator or designated ECG reviewer. Participants who experience a change from their baseline ECG may need to discontinue study intervention

per criteria specified in Section 7.1.

8.2.6 Holter Monitoring: 24-Hour Continuous Electrocardiography

The following information applies only to those participants in the 24-hour Holter Monitor sub-study.

Continuous Holter Monitoring will be conducted over 24 hours between Visit 4 and Visit 5 and at Visit 6 and Visit 11. Holter Monitor recordings are to be initiated at approximately the same time (±2 hours) for these visits.

Continuous Holter Monitor recordings will be collected for 24 hours. Holter Monitor recordings must contain a minimum of 18 hours of acceptable quality recording in a 24-hour period to be deemed a successful Holter Monitor assessment.

All Holter Monitor recordings will be assessed for cardiac arrhythmias by an independent cardiologist.

8.2.6.1 Baseline Holter Monitoring Procedures (Between Visit 4 and Visit 5)

Baseline Holter Monitoring will be initiated. Participants will be instructed to return to the clinic the following day for removal of the Holter Monitor.

When the participant returns to the clinic the following day, the quality of the Holter Monitor recordings will be assessed at the site. If the first Holter Monitoring attempt is not successful (ie, <18 hours of acceptable quality recording), the Holter Monitor will be reconnected for another 24 hours. The participant will be instructed to continue his/her medications as per the study protocol. The participant will return the following day for removal of the Holter Monitor. This second attempt should be scheduled so that the Holter Monitoring will be completed at least 24 hours before administration of the morning dose of study intervention at Visit 5.

If the Holter Monitoring recording remains inadequate on the second attempt, the participant will not be eligible to participate in the Holter Monitoring sub-study but WILL NOT need to be excluded from the full study. If clinically significant findings (as defined in Section 5.5.1) are noted on any of the Holter Monitor recordings, there will be no further attempts; the participant will be considered a screen failure and will not be eligible to enroll in the full study.

8.2.6.2 Visit 6 and Visit 11 Holter Monitoring Procedures

At Visit 6 and Visit 11, Holter Monitoring will be initiated at approximately the same time (±2 hours) as Visit 4. Participants will be instructed to return to the clinic the following day for removal of the Holter Monitor.

When the participant returns to the clinic the following day, the quality of the Holter Monitor recordings will be assessed at the site. If the first Holter Monitoring attempt is not successful (ie, <18 hours of acceptable quality recording), the Holter Monitor will be reconnected for another 24 hours. The participant will be instructed to continue his/her medications as per study protocol. The participant will return the following day for removal of the Holter Monitor.

If the Holter Monitoring recording remains inadequate on the second attempt, there will be no further attempts.

8.2.7 Clinical Safety Laboratory Assessments

Blood and urine samples for determination of clinical chemistry and hematology will be taken pre-dose prior to 1000 +1 hour at the visits indicated in the SoA (Table 1).

Clinical safety laboratory tests will be analyzed by a central laboratory according to standardized, validated assays with the exception of highly sensitive urine pregnancy tests. The laboratory will supply detailed procedures for the preparation and collection of blood and urine samples along with all containers needed for their collection. Urine pregnancy tests will be performed at the clinical site using a highly sensitive test product provided to the site.

The Investigator should assess the available results with regard to clinically relevant abnormalities. The laboratory results will be signed and dated and retained at the center as source data for laboratory variables.

Additional safety samples may be collected if clinically indicated at the discretion of the Investigator at unscheduled visits. The date of collection will be recorded on the appropriate eCRF.

For information on how AEs based on laboratory tests should be recorded and reported, see Section 8.3.6.

The following laboratory variables will be measured (Table 13):

Table 13 Laboratory Variables

Hematology (whole blood)	Clinical Chemistry (serum or plasma)
Hemoglobin	Creatinine
Leukocyte count (including differential count)	Bilirubin, total
Eosinophil count	Alkaline phosphatase
Platelet count	Aspartate transaminase
	Alanine transaminase
Other Tests	Albumin
Pregnancy test for women of childbearing potential (Urine)	Potassium
eGFR[a]	Calcium, total
	Sodium
	Glucose
	Cortisol

[a] Estimated by the CKD-EPI formula [Levey 2009] for participants 18 to 80 years of age or the Schwartz formula for participants 12 to <18 year of age [Schwartz 1987].

8.2.8 Other Safety Assessments

8.2.8.1 Paradoxical Bronchospasm

Monitoring for paradoxical bronchospasm will occur at each in-clinic visit in which there are post-dose spirometry assessment during the Treatment Period (Visits 5, 6, 8, 11, 15/Final or Treatment Discontinuation/Study Withdrawal Visit) at 15- and 30-minutes post-dose. In this study, paradoxical bronchospasm is defined as a reduction in FEV_1 of >20% from baseline (ie, the mean FEV_1 values obtained 60 and 30 minutes prior to study intervention administration) that occurs within 30 minutes post-dosing with associated symptoms of wheezing, shortness of breath, or cough. If an event meets both the spirometry and the symptoms for a paradoxical bronchospasm, then it will be reported as an AE.

8.3 Adverse Events and Serious Adverse Events

The Principal 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.

AE 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.

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

Adverse events will be collected from first intake of study intervention after Visit 1, during screening and throughout the Treatment Period and including the follow-up period.

All SAEs will be recorded from the time of signing of informed consent form.

If the Investigator becomes aware of an 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, without undue delay, report the SAE to AstraZeneca.

8.3.2 Follow-up of AEs and SAEs

Any AEs that are unresolved at the participant's last AE assessment or other assessment/visit in the study are followed up by the Investigator for as long as medically indicated, but without further recording in the eCRF. AstraZeneca 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 study intervention(s) (yes or no)
- Action taken with regard to study intervention(s)
- Outcome.

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

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- AE is serious due to
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death

- Autopsy performed
- Causality assessment in relation to study procedure(s)
- Causality assessment to other medication

8.3.3 Causality Collection

The Investigator should assess causal relationship between study intervention 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 study intervention?'

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.

8.3.4 Adverse Events Based on Signs and Symptoms

All AEs spontaneously reported by the participant 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.

8.3.5 Adverse Events Associated with Use of ICS, LAMAs, and LABAs

Certain AEs have been identified as associated to the class of drugs being studied. Known effects of LAMAs and LABAs include cardiovascular effects, ocular disorders, urinary retention, gastrointestinal disorders, and anticholinergic effects for LAMAs and cardiovascular and tremor effects for LABAs. Local corticosteroid effects include oral candidiasis, oropharyngeal candidiasis, dysphonia, and throat irritation. These AEs will be captured as described in Section 8.3.4 and presented as summary tabulation in the Clinical Study Report (CSR).

Participants with changes in vision, captured as described in Section 8.3.4, will be referred by the Investigator for a local ophthalmological assessment for evaluation; any diagnosis including cataract or glaucoma, the type, and location (left eye, right eye, or both) will be determined. Any subsequent ophthalmological diagnosis will be captured in Medical History, if identified at Screening, or as an AE, if identified during run-in or after randomization to study intervention. A follow-up evaluation will be recorded up until discontinuation of study intervention.

Participants who are diagnosed with new or worsening narrow angle glaucoma will be discontinued from study intervention but will be encouraged to remain in the study.

8.3.6 Adverse Events Based on Examinations and Tests

The results from the Clinical Study Protocol mandated laboratory tests and vital signs will be summarized in the CSR.

Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs, or ECGs should therefore only be reported as AEs if they fulfil any of the SAE criteria, are the reason for discontinuation of study intervention or are considered to be clinically relevant as judged by the Investigator (which may include but not limited to consideration as to whether treatment or non-planned visits were required or other action was taken with the study intervention, eg, dose adjustment or drug interruption).

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

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE unless unequivocally related to the disease under study.

8.3.7 Disease Under Study

Symptoms of disease under study are those which might be expected to occur as a direct result of asthma and are captured in the eDiary. Events which are unequivocally due to disease under study should not be reported as an AE during the study unless they meet SAE criteria or lead to discontinuation of the study intervention or the sign or symptom is new to the participant or not consistent with the participant's pre-existing asthma history.

Moderate and severe asthma exacerbations will be considered study efficacy endpoints and will not be reported as AEs unless considered an SAE or lead to discontinuation of study intervention.

Associated symptoms of asthma are considered as symptoms of disease under study and will not be recorded as AEs unless considered an SAE or lead to discontinuation of study intervention.

Serious adverse events will be reported as per standard reporting guidance.

8.3.8 Reporting of Serious Adverse Events

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

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

The designated AstraZeneca representative works with the Investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within 1 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 is undertaken immediately. Investigators or other site personnel inform AstraZeneca 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 eCRF, an automated email alert is sent to the designated AstraZeneca representative.

If the eCRF is not available, then the Investigator or other study site staff reports an SAE to the appropriate AstraZeneca representative by telephone.

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

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

The reference document for definition of expectedness/listedness is the Investigator Brochures for AstraZeneca drugs and for the comparator products (including any AstraZeneca comparator).

8.3.9 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca from Visit 1, except for:

If the pregnancy is discovered before the study participant has received any study intervention.

8.3.9.1 Maternal Exposure

If a participant becomes pregnant during the course of the study, study intervention should be

discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the study intervention 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) 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 informs the appropriate AstraZeneca representatives within 1 day (ie, immediately but **no later than 24 hours**) of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 calendar days for SAEs (see Section 8.3.8) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

The PREGREP module in the eCRF is used to report the pregnancy and the paper based PREGOUT module is used to report the outcome of the pregnancy.

8.3.10 Medication Error, Drug Abuse, and Drug Misuse

8.3.10.1 Timelines

If an event of medication error, drug abuse, **or** drug misuse occurs during the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within **1 calendar day** (ie, immediately but **no later than 24 hours**) of when they become aware of it.

The designated AstraZeneca representative works 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, drug abuse, or misuse (see Section 8.3.8) and **within 30 days** for all other events.

8.3.10.2 Medication Error

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

The full definition and examples of medication error can be found in Appendix B 4.

8.3.10.3 Drug Abuse

Drug abuse is the persistent or sporadic **intentional**, non-therapeutic excessive use of Investigation Medicinal Product (IMP) or AstraZeneca Non-Investigational Medicinal Product (NIMP) for a perceived reward or desired non-therapeutic effect.

The full definition and examples of drug abuse can be found in Appendix B 4.

8.3.10.4 Drug Misuse

Drug misuse is the **intentional** and inappropriate use (by a study participant) of IMP or AstraZeneca NIMP for medicinal purposes outside of the authorized product information, or for unauthorized IMPs or AstraZeneca NIMPs, outside the intended use as specified in the protocol and includes deliberate administration of the product by the wrong route.

The full definition and examples of drug misuse can be found in Appendix B 4.

8.3.11 Device Constituent Deficiencies

Combination products with a device constituent are being provided for use in this study. In order to fulfil regulatory reporting obligations worldwide, the Investigator is responsible for the detection and documentation of events meeting the definition of a device constituent deficiency that occur during the study with the device constituent of the combination products in this study.

Device constituent deficiencies from this study will be collected and monitored to ensure the safety of participants and improve the safety and performance of the device.

Device constituent deficiencies will not be presented in the CSR, but where required by local regulations, deficiencies will be summarized in the relevant periodic report.

The definition of a device constituent deficiency is an inadequacy of a device constituent with respect to its identity, quality, durability, reliability, safety, or performance. Device constituent deficiencies include malfunctions, use errors, and information supplied by the manufacturer.

NOTE: Deficiencies fulfilling the definition of an AE/SAE will also follow the processes outlined in Appendix F.

The AstraZeneca Device Constituent Report Form and/or Product Complaint Intake Form will be used to collect the deficiency.

8.3.11.1 Time Period for Detecting Device Constituent Deficiencies

Device constituent incidents or malfunctions will be detected, documented, and reported during all periods of the study in which the device constituent is used.

If the Investigator learns of any device constituent deficiency at any time after a participant

has been discharged from the study, and such incident is considered reasonably related to a device constituent provided for the study, the Investigator will promptly notify AstraZeneca.

The method of documenting Device Constituent Deficiency is provided in Appendix F.

8.3.11.2 Follow-up of Device Constituent Deficiencies

Follow-up applies to all participants, including those who discontinue study intervention. The Investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the deficiency. New or updated information will be recorded on the originally completed form with all changes signed and dated by the Investigator.

8.3.11.3 Prompt Reporting of Device Constituent Deficiencies to AstraZeneca

Device constituent deficiencies will be reported to AstraZeneca within 24 hours after the Investigator determines that the event meets the protocol definition of a device constituent deficiency.

The AstraZeneca Device Constituent Deficiency Report Form and/or Product Complaint Intake Form will be sent to AstraZeneca by email to the AstraZeneca Data Entry Site. If paper is unavailable, then Investigator or other study site staff reports an SAE to the appropriate AstraZeneca representative by telephone. AstraZeneca will be the contact for the receipt of device constituent deficiency reports.

8.3.11.4 Regulatory Reporting Requirements for Device Deficiencies

The Investigator will promptly report all device constituent deficiencies occurring with any medical device provided for use in the study in order for AstraZeneca to fulfil the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

The Investigator, or responsible person according to local requirements (eg, the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of medical device deficiencies to the IRB/IEC.

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

8.3.12 Major Adverse Cardiovascular Events

Major adverse cardiovascular events (MACE) will be evaluated by an Independent Adjudication Committee (IAC) according to criteria as described in an IAC Charter/Manual of Operations.

The IAC Charter/Manual of Operations will be established to govern these processes as described in Section 9.7 and Appendix A 5.

8.4 Overdose

For this study, any dose greater than 2 administrations of each study intervention twice daily (or 4 inhalations of each study intervention) or greater than BFF MDI 320/9.6 µg twice daily during Screening will be considered an overdose.

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

If an overdose on an AstraZeneca study intervention occurs in the course of the study, the Investigator or other site personnel inform appropriate AstraZeneca representatives immediately, but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within 1 or 5 calendar days** for overdoses associated with an SAE (see Section 8.3.8) and **within 30 days** for all other overdoses.

8.5 Human Biological Samples

Instructions for the collection and handling of biological samples will be provided in the study specific laboratory manual. Samples should be stored in a secure storage space with adequate measures to protect confidentiality. For further details on Handling of Human Biological Sample see Appendix C.

Samples will be stored for a maximum of 15 years from the date of the issue of the CSR in line with consent and local requirements, after which they will be destroyed/repatriated.

- Pharmacokinetic (PK) samples will be disposed of after the Bioanalytical Report finalization or six months after issuance of the draft Bioanalytical Report (whichever is earlier), unless consented for future analyses.
  - Pharmacokinetic samples may be disposed of or anonymized by pooling. Additional analyses may be conducted on the anonymized, pooled, or individual pharmacokinetic samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR.

8.5.1 Pharmacokinetics

- Plasma samples will be collected for measurement of plasma concentrations of budesonide, glycopyrronium, and formoterol as specified in the SoA (Table 1) and Section 4.1. In a subset of participants randomized to each study intervention arm at

Visit 8 (Week 12) and who have confirmation of the last 3 doses (6 inhalations) of study intervention taken prior to Visit 8, approximately 10 mL of whole blood will be collected within 30 minutes before administration of study intervention and at 2, 5, 20, and 40 minutes, and 1, 2, 4, 8, 10, and 12 hours post-dose.

- Plasma samples will be used to analyse the PK of budesonide, glycopyrronium, and formoterol. Samples collected for analyses of budesonide, glycopyrronium, and formoterol plasma concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.
- Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual.
- If spirometry and PK assessments are to be performed at the same timepoint, PK samples should be drawn first followed by spirometry measurements.

8.5.1.1 Determination of Drug Concentration

Samples for determination of drug concentration in plasma will be assayed by bioanalytical test sites operated by or on behalf of AstraZeneca, using an appropriately validated bioanalytical method. Plasma samples will be analyzed only for the relevant components of the administered study intervention (ie, glycopyrronium will not be reported in treatments that do not contain glycopyrronium). Full details of the analytical method used will be described in a separate bioanalytical report.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation, if performed, will be reported in a separate Bioanalytical Report.

8.5.2 Immunogenicity Assessments

Immunogenicity assessments are not evaluated in this study.

8.5.3 Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.6 Human Biological Sample Biomarkers

Blood samples for exploratory biomarker research will be collected from all participants in this study as specified in the SoA (Table 1). These blood samples will be saved to be tested for biomarkers for characterization and understanding of this patient population.

8.7 Optional Genomics Initiative Sample

Collection of optional samples for genomics initiative research is also part of this study as specified in the SoA and is subject to agreement in the ICF addendum.

Blood sample for DNA isolation will be collected from participants who have consented to participate in the genetic analysis component of the study. Participation is optional. Participants who do not wish to participate in the genetic research may still participate in the study.

For storage and destruction of genetic samples see Appendix D.

8.8 Healthcare Resource Utilization Data

Healthcare resource utilization (HCRU) data, associated with medical encounters, will be collected in the eCRF by the Investigator and study-site personnel for all participants throughout the study. During screening at Visit 4, HCRU information will be collected with a 'one year' recall period. All the subsequent visits after Visit 5, will collect HCRU information with a recall period of 'since the last scheduled visit'. The data may be used as input to health economic analyses (ie, cost utility analysis or cost effectiveness analysis). Protocol-mandated procedures, tests, and encounters are excluded. Any results from such analyses may be reported separately from the CSR.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

Budesonide, Glycopyrronium, and Formoterol Fumarate metered-dose inhaler (BGF MDI) is being fully developed for use in the treatment of asthma. The primary objective of this study is to assess the effect of BGF MDI relative to BFF MDI and Symbicort pMDI on lung function in participants with inadequately controlled asthma. For the efficacy comparisons, the null hypothesis for each pair-wise comparison will be that the mean treatment difference is zero (mean treatment effects are equal). The alternative hypothesis is that the mean treatment difference is not zero (mean treatment effects are not equal). All p-values will be reported as 2-sided.

To support CCI of CCI MDI in CCI an additional objective of this study is to assess the effect of BFF MDI relative to Symbicort pMDI on lung function and severe exacerbations. For these comparisons, the null hypothesis for each pair-wise comparison will be that the mean treatment difference is in excess of the non-inferiority (NI) margin (see Section 9.1.1 for the NI margins relevant to each endpoint). The alternative hypothesis is that the mean treatment difference is within the NI margin. All confidence intervals will be 2-sided with 95% confidence and p-values will reflect the test for NI.

9.1.1 Analysis Methods for Estimands

The primary estimand strategy for ICEs will be utilized for superiority analyses of the primary, secondary, and selected tertiary endpoints. Other estimand strategies for ICEs of interest include the While on Treatment strategy, supportive Composite strategy, and Principal

Stratum strategy (for NI analyses).

Analyses utilizing the primary estimand strategy for ICEs answer the clinical question of what the effect of randomized treatment at the end of the planned Treatment Period is regardless of the occurrence of any ICEs unless asthma medication is initiated in conjunction with premature discontinuation of therapy (which will be considered an unfavorable outcome). For participants with such an ICE, a Composite strategy will be utilized, where the participant will be imputed as having a treatment failure from the start of the relevant ICE until the planned last visit date in the planned Treatment Period. Treatment failure for analyses of lung function endpoints will impute the worst FEV_1 value of a 12% decrease from participant's baseline value or the participant's worst observed value post baseline during the study. For binary outcome variables, the occurrence of an ICE utilizing the Composite strategy is taken to be a component of the variable resulting in a non-responder status, ie, the ICE is integrated with one or more other measures of clinical outcome as the variable of interest. For analysis of 'rate of' or 'time to' severe or moderate/severe exacerbations, if there is sufficient time during the planned Treatment Period, a severe exacerbation will be imputed midway between the start date + 2 days of this ICE and the planned last visit date during the Treatment Period (any other observed exacerbation during that period will be ignored for the analysis). For further imputation details on other endpoints and handling of special cases, refer to the SAP.

Analyses utilizing the While on Treatment estimand strategy for ICEs answer the clinical question of what the effect of the randomized treatments is assuming continuation of randomized treatments for the duration of the planned Treatment Period regardless of actual compliance and will use data obtained prior to participants experiencing certain ICEs. For further information on individual data points included in analyses for each endpoint, refer to the SAP.

For analyses utilizing the supportive Composite estimand strategy for ICEs, the occurrence of the ICE is taken to be a component of the variable resulting in a non-responder status, ie, the ICE is integrated with one or more other measures of clinical outcome as the variable of interest. However, data following study intervention discontinuation for reasons related to global/country situation will be considered missing and will not be imputed. For further details on the supportive Composite estimand, refer to the SAP.

Analysis of the PK endpoints and Holter Monitoring sub-study endpoints will use a While on Treatment estimand strategy for ICEs in the respective analysis populations.

The following efficacy comparisons will be made for CCI and CCI approaches, in the following order in accordance with the strategy for controlling the Type I error described in Section 9.1.2:

- Superiority of BGF MDI 320/28.8/9.6 µg versus BFF MDI 320/9.6 µg

- Superiority of BGF MDI 320/14.4/9.6 µg versus BFF MDI 320/9.6 µg

The following efficacy comparisons will be made for the CCI approach, in the following order in accordance with the strategy for controlling the Type I error described in Section 9.1.2:

- Superiority of BGF MDI 320/28.8/9.6 µg versus Symbicort pMDI 320/9 µg
- Superiority of BGF MDI 320/14.4/9.6 µg versus Symbicort pMDI 320/9 µg

The following efficacy comparisons will be made for the CCI approach, in the following order in accordance with the strategy for controlling the Type I error described in Section 9.1.2:

- Superiority of BGF MDI 320/28.8/9.6 µg versus ICS/LABA (pooled BFF MDI 320/9.6 µg and Symbicort pMDI 320/9 µg)
- Superiority of BGF MDI 320/14.4/9.6 µg versus ICS/LABA (pooled BFF MDI 320/9.6 µg and Symbicort pMDI 320/9 µg)

In addition, NI comparisons of BFF versus Symbicort will be conducted in order to support CCI of CCI in CCI The Principal Stratum estimand strategy for ICEs will be the primary estimand strategy for the NI comparison. This estimand strategy answers the question of what the treatment effect is on participants who have no IPDs impacting efficacy at randomization under any treatment assignment, in the absence of ICEs (as data obtained after any IPD impacting efficacy or ICE will be excluded). The NI assessment for FEV_1 AUC_{0-3} will apply an NI margin of CCI mL, and the NI assessment for morning pre-dose trough FEV_1 will use an NI margin of CCI mL. These margins are consistent with CCI he NI margin for the pooled assessment of the severe exacerbation rate will be set at CCI as this margin preserves more than 50% of the observed severe rate reduction when comparing a medium daily dose of budesonide versus a low daily dose of budesonide with or without formoterol CCI CCI

9.1.2 Type I Error Control

The change from baseline in FEV_1 AUC_{0-3} will be the primary endpoint for CCI and a key secondary endpoint for CCI and CCI The change from baseline in morning pre-dose trough FEV_1 will be the primary endpoint for CCI and the key secondary endpoint for CCI Each region has a specific approach, which refers to the submission to their Health Authorities. Lung function parameters will be evaluated in studies D5982C00007 and D5982C00008 to provide replicate results for regions requiring this approach.

Data from the 2 studies will be combined to analyze the rate of severe exacerbations. In the multiple testing procedure, the Type I error for the analysis of the primary and secondary endpoints will be strongly controlled and will include the pooled analysis. As such, both studies D5982C00007 and D5982C00008 are included in the description of the procedure.

Due to variation in the CCI requirements, the multiple testing procedure will be different depending on the region.

9.1.2.1 CCI Approach

The Type I error control procedure for CCI will apply a sequential testing method.

The procedure starts by comparing BGF MDI CCI µg versus BFF MDI 320/9.6 µg, testing the primary endpoint, change from baseline in FEV_1 AUC_{0-3}, within each of the two studies (Study D5982C00007 and Study D5982C00008). If these results are statistically significant (alpha = 0.05, 2-sided) within a study, change from baseline in trough FEV_1 will be tested at 2-sided alpha of 0.05 for that study. If these results are statistically significant within a study, the onset of action on Day 1 (within-group superiority test for the BGF MDI CCI µg arm) will be tested at alpha = 0.025 (1-sided) for that study. If the test for onset of action on Day 1 is statistically significant in at least one study, the pooled severe exacerbation rate will be tested at alpha = 0.05 (2-sided).

If the test for the pooled severe exacerbation rate is statistically significant for BGF MDI CCI µg versus BFF 320/9.6 µg, the change from baseline in FEV_1 AUC_{0-3}, change from baseline in trough FEV_1, and onset of action on Day 1 (within-group 1-sided superiority test) and pooled severe exacerbation rate will be tested comparing BGF MDI CCI µg versus BFF MDI 320/9.6 µg, in the same manner as described above at alpha = 0.05 (2-sided).

If the test for pooled severe exacerbation rate comparing BGF MDI CCI µg versus BFF MDI 320/9.6 µg is statistically significant, the secondary endpoints (percentage of responders in ACQ-7, ACQ-5, AQLQ(s)+12, and SGRQ) will be simultaneously tested by study (alpha=0.05, 2-sided) with a Hochberg procedure [Gou 2014] comparing BGF MDI CCI µg versus BFF MDI 320/9.6 µg. If all the tests for those secondary endpoints are statistically significant by study, the same Hochberg approach will be applied for those endpoints comparing BGF MDI CCI µg versus BFF MDI 320/9.6 µg in the respective study.

If all the tests for the secondary endpoints in the Hochberg procedure are statistically significant in at least one of the studies, the pooled severe exacerbation rate for participants with baseline percent predicted $FEV_1 \leq 55\%$ will be tested at alpha = 0.05 (2-sided) comparing BGF MDI CCI µg versus BFF MDI 320/9.6 µg. In case of a statistically significant result, the same test will be performed comparing BGF MDI CCI µg versus BFF MDI 320/9.6 µg. If the test in the subgroup is statistically significant, the pooled

severe exacerbation rate for participants with ≥ 1 severe exacerbation in the 12 months prior to Visit 1 will be tested at alpha = 0.05 comparing BGF MDI CCI µg versus BFF MDI 320/9.6 µg. In case of a statistically significant result, the same test will be performed comparing BGF MDI CCI µg versus BFF MDI 320/9.6 µg.

Endpoints evaluated at individual study level (ie, any endpoint other than severe exacerbation rate) will only be tested if the tests for all preceding endpoints performed within the respective study were statistically significant.

9.1.2.2 CCI Approach

The Type I error control procedure for CCI starts by comparing BGF MDI CCI µg versus ICS/LABA, testing the primary endpoint, change from baseline in trough FEV_1, within each of the two studies (Study D5982C00007 and Study D5982C00008). If these results are statistically significant (alpha = 0.05, 2-sided) within a study, the alpha is further split with 0.04 allocated to the test of the pooled severe exacerbation rate and 0.01 allocated to the test of change from baseline in FEV_1 AUC_{0-3} within the respective study.

Two-way recycling will be implemented between the tests of the pooled severe exacerbation rate and FEV_1 AUC_{0-3}. If the test for the pooled severe exacerbation rate is significant, the 4% alpha may be recycled back to the respective study such that FEV_1 AUC_{0-3} is tested with alpha = 0.05 (2-sided). Conversely, if the p-value for FEV_1 AUC_{0-3} is less than 0.01, the 1% alpha may be recycled to the test of pooled severe exacerbation rate such that up to the full 5% alpha (2-sided) may be used.

If the tests for the pooled severe exacerbation rate and FEV_1 AUC_{0-3} are both statistically significant, the onset of action on Day 1 (within-group test for BGF MDI CCI µg) will be tested at alpha = 0.025 (1-sided).

If the test for onset of action is then statistically significant, change from baseline in trough FEV_1 and change from baseline in FEV_1 AUC_{0-3}, pooled severe exacerbation rate comparing BGF MDI CCI µg versus ICS/LABA, and onset of action Day 1 (within-group 1-sided superiority test for the BGF MDI CCI µg), will be tested in the same manner as described above.

If the test for onset of action is then statistically significant within a study, the secondary endpoints (severe exacerbation rate in the individual studies and percentage responders in ACQ-7, ACQ-5, AQLQ(s)+12, and SGRQ) will be simultaneously tested (alpha = 0.05, 2-sided) for the respective study with a Hochberg procedure [Gou 2014] comparing BGF MDI CCI µg versus ICS/LABA. If all the tests for those secondary endpoints are statistically significant within a study, the same Hochberg approach will be applied for those endpoints comparing BGF MDI CCI µg versus ICS/LABA in the respective study.

If all the tests for the secondary endpoints in the Hochberg procedure are statistically significant in at least one of the studies, the pooled severe exacerbation rate for participants with percent predicted $FEV_1 \leq 55\%$ will be tested at alpha = 0.05 (2-sided) comparing BGF MDI CCI µg versus ICS/LABA. In case of a statistically significant result, the same test will be performed comparing BGF MDI CCI µg versus ICS/LABA. If the test in this subgroup is statistically significant, the pooled severe exacerbation rate for participants with ≥ 1 severe exacerbation in the 12 months prior to Visit 1 will be tested at alpha = 0.05 comparing BGF MDI CCI µg versus ICS/LABA. In case of a statistically significant result, the same test will be performed comparing BGF CCI µg versus ICS/LABA.

Endpoints evaluated at individual study level (ie, any endpoint other than severe exacerbation rate) will only be tested if the tests for all preceding endpoints performed within the respective study were statistically significant.

9.1.2.3 CCI Approach

The Type I error control procedure for CCI will apply a sequential testing method.

The procedure starts by comparing BGF MDI CCI µg versus Symbicort pMDI 320/9.6 µg, testing the primary endpoint, change from baseline in trough FEV_1, within each of the two studies (Study D5982C00007 and Study D5982C00008). If these results are statistically significant (alpha = 0.05, 2-sided) within a study, change from baseline in FEV_1 AUC_{0-3} will be tested (alpha = 0.05, 2-sided) for that study. If these results are statistically significant within a study, the onset of action on Day 1 (within-group superiority test for the BGF MDI CCI µg arm) will be tested at alpha = 0.025 (1-sided) for that study. If the test for onset of action on Day 1 is statistically significant in at least one study, the pooled severe exacerbation rate will be tested at alpha = 0.05 (2-sided).

If the test for the pooled severe exacerbation rate is statistically significant, change from baseline in trough FEV_1, change from baseline in FEV_1 AUC_{0-3}, and onset of action on Day 1 (within-group 1-sided superiority test for the BGF MDI CCI µg) and pooled severe exacerbation rate will be tested comparing BGF MDI CCI µg versus Symbicort pMDI 320/9.6 µg, in the same manner as described above at alpha = 0.05 (2-sided).

If the test for the pooled severe exacerbation rate comparing BGF MDI CCI µg versus Symbicort pMDI 320/9.6 µg is statistically significant, the secondary endpoints (percentage of responders in ACQ-7, ACQ-5, AQLQ(s)+12, and SGRQ) will be simultaneously tested for each study (alpha = 0.05, 2-sided) with a Hochberg procedure [Gou 2014] comparing BGF MDI CCI µg versus Symbicort pMDI 320/9.6 µg. If all the tests for those secondary endpoints are statistically significant within a study, the same Hochberg approach will be applied for those endpoints comparing BGF MDI CCI µg versus Symbicort pMDI 320/9.6 µg in the respective study.

If all the tests for the secondary endpoints in the Hochberg procedure are statistically significant in at least one of the studies, the pooled severe exacerbation rate for participants with percent predicted $FEV_1 \leq 55\%$ will be tested at alpha = 0.05 (2-sided) comparing BGF MDI [redacted] µg versus Symbicort pMDI 320/9.6 µg. In case of a statistically significant result, the same test will be performed comparing BGF MDI [redacted] µg versus Symbicort pMDI 320/9.6 µg. If the test in this subgroup is statistically significant, the pooled severe exacerbation rate for participants with ≥ 1 severe exacerbation in the 12 months prior to Visit 1 will be tested at alpha = 0.05 comparing BGF MDI [redacted] µg versus Symbicort pMDI 320/9.6 µg. In case of a statistically significant result, the same test will be performed comparing BGF MDI [redacted] µg versus Symbicort pMDI 320/9.6 µg.

Endpoints evaluated at individual study level (ie, any endpoint other than severe exacerbation rate) will only be tested if the tests for all preceding endpoints performed within the respective study were statistically significant.

Additionally, NI tests of BFF MDI vs Symbicort pMDI will be conducted to support potential [redacted] of [redacted] MDI in [redacted] (see Section 9.1.1).

The NI tests of BFF MDI vs Symbicort pMDI will be conducted in the following sequential order within that study: change from baseline in trough FEV_1 and change from baseline in FEV_1 AUC_{0-3}. A test for a given endpoint will not be interpreted inferentially unless the prior endpoint in the sequence was declared as NI within the respective study (alpha = 0.025, 1-sided). If NI is declared for those endpoints within a study, the within-group test for onset of action on Day 1 for BFF MDI will be conducted at alpha = 0.025 (1-sided). If the test for onset of action on Day 1 is statistically significant in at least one of the 2 studies, the pooled severe exacerbation rate will be tested at alpha = 0.025 (1-sided). If the test for the pooled rate of severe exacerbation demonstrates NI, the remaining secondary endpoints (percentage of responders in ACQ-7, ACQ-5, AQLQ(s)+12, and SGRQ) will be simultaneously tested for NI (alpha = 0.025, 1-sided) with a Hochberg procedure [Gou 2014]. All the lung function endpoints for the testing will use the "over 24 Weeks" endpoints.

9.1.2.4 [redacted] Approach

The Type I error control procedure for [redacted] will apply a sequential testing method.

The procedure starts by comparing BGF MDI [redacted] µg versus BFF MDI 320/9.6 µg, testing the primary endpoint, change from baseline in trough FEV_1. If this result is statistically significant (alpha = 0.05, 2-sided), change from baseline in FEV_1 AUC_{0-3} will be tested (alpha = 0.05, 2-sided). If this result is statistically significant, the onset of action on Day 1 (within-group superiority test for the BGF MDI [redacted] µg arm) will be tested at alpha = 0.025 (1-sided). If the test for onset of action on Day 1 is statistically significant, the pooled (Study D5982C00007 and Study D5982C00008) severe exacerbation rate will be tested at alpha = 0.05 (2-sided).

If the test for the pooled severe exacerbation rate is statistically significant, change from baseline in trough FEV_1, change from baseline in FEV_1 AUC_{0-3}, and onset of action on Day 1 (within-group test for the BGF MDI CCI µg) and pooled severe exacerbation rate will be tested comparing BGF MDI CCI µg versus BFF MDI 320/9.6 µg, in the same manner as described above at alpha = 0.05 (2-sided).

If the test for the pooled severe exacerbation rate comparing BGF MDI CCI µg versus BFF MDI 320/9.6 µg is statistically significant, the secondary endpoints (percentage of responders in ACQ-7, ACQ-5, AQLQ(s)+12, and SGRQ) will be simultaneously tested (alpha = 0.05, 2-sided) with a Hochberg procedure [Gou 2014] comparing BGF MDI CCI µg versus BFF MDI 320/9.6 µg. If all the tests for those secondary endpoints are statistically significant, the same Hochberg approach will be applied for those endpoints comparing BGF MDI CCI µg versus BFF MDI 320/9.6 µg.

If all the tests for the secondary endpoints in the Hochberg procedure are statistically significant, the pooled severe exacerbation rate for participants with percent predicted $FEV_1 \leq 55\%$ will be tested at alpha = 0.05 (2-sided) comparing BGF MDI CCI µg versus BFF MDI 320/9.6 µg. In case of a statistically significant result, the same test will be performed comparing BGF MDI CCI µg versus BFF MDI 320/9.6 µg. If the test in this subgroup is statistically significant, the pooled severe exacerbation rate for participants with ≥ 1 severe exacerbation in the 12 months prior to Visit 1 will be tested at alpha=0.05 comparing BGF MDI CCI µg versus BFF MDI 320/9.6 µg. In case of a statistically significant result, the same test will be performed comparing BGF MDI CCI µg versus BFF MDI 320/9.6 µg.

Endpoints evaluated at individual study level (ie, any endpoint other than severe exacerbation rate) will only be tested if the tests for all preceding endpoints were statistically significant.

9.2 Sample Size Determination

A sample size of 2200 participants (approximately 550 participants per treatment group) will provide probabilities of over 99% to detect a CCI mL difference at Week 24, over 12 to 24 Weeks, and over 24 Weeks between BGF MDI CCI µg versus BFF MDI 320/9.6 µg or BGF MDI CCI µg versus Symbicort pMDI 320/9 µg in the analysis of change from baseline in FEV_1 AUC_{0-3}. The assumed standard deviation (SD) is CCI mL at each visit based on an internal CCI months Phase II/III dose-ranging study of CCI MDI. The effective SD of CCI mL for over 12 to 24 Weeks assumes 2 visits and that the correlation among visits is CCI The effective SD of CCI mL for over 24 Weeks assumes 3 visits over the interval and that the correlation among visits is CCI. The 2-sided alpha for each pairwise comparison is CCI per the procedure to control Type I error across comparisons for the two BGF MDI dose levels. This sample size assumes that approximately CCI % of randomized participants will have discontinued study intervention prior to Week 4, CCI % prior to Week 12, and CCI % at Week 24.

A sample size of 2200 participants (approximately 550 participants per treatment group) will provide power of 93%, 99%, and 99% to detect a [redacted] mL difference at Week 24, over 12 to 24 Weeks, and over 24 Weeks, respectively, between BGF MDI [redacted] µg versus BFF MDI 320/9.6 µg or BGF MDI [redacted] µg versus Symbicort pMDI 320/9 µg in the analysis of change from baseline in morning pre-dose trough FEV_1. The assumed SD is [redacted] mL at each visit based on an internal [redacted] months Phase II/III dose-ranging study of [redacted] MDI. For the at Week 24 endpoint, the SD is estimated as [redacted] mL and assumes [redacted] % of randomized participants will have discontinued treatment by Week 24. The effective SD of [redacted] mL for over 12 to 24 Weeks assumes [redacted] % of randomized participants will have discontinued treatment by Week 12, the remaining participants will complete 3 visits in the interval on average, and that the correlation among visits is [redacted] For the interval of over 24 Weeks, the effective SD is estimated as [redacted] mL assuming [redacted] % of randomized participants will have discontinued treatment by Week 4, the remaining participants will complete 4 visits on average, and a correlation of [redacted] between visits. The 2-sided alpha for each pairwise comparison is [redacted] per the procedure to control Type I error across comparisons for the two BGF MDI dose levels.

Pooled Analyses: The data from studies D5982C00007 and D5982C00008 will be pooled and analyzed for severe asthma exacerbations. A sample size of 1100 participants per arm will also provide 80% probability to detect a [redacted] % reduction in the rate of severe asthma exacerbations for BGF MDI [redacted] µg versus BFF MDI 320/9.6 µg or BGF MDI [redacted] µg versus Symbicort pMDI 320/9 µg. The assumed 2-sided alpha for each pairwise comparison is [redacted] per the Type I error control procedure. This calculation assumes a dispersion parameter of [redacted] and an annualized event rate for BFF MDI 320/9.6 µg or Symbicort pMDI 320/9 µg of [redacted] [Virchow 2019, Kerstjens 2020, Lee 2021]. An average exposure time of [redacted] years is also assumed.

Approximately 6300 participants will be screened to achieve 2200 randomly assigned to study intervention and 1760 evaluable participants per study.

The [redacted] cohort will consist of all participants randomized in sites located in [redacted] It is targeted that approximately [redacted] participants will be randomized in this study, with [redacted] participants per treatment group. This sub-population will enable standalone safety and efficacy analyses, which will be the basis for developing a [redacted] -specific CSR to support [redacted] regulatory requirements. Participants from [redacted] will also be included in the global study analyses. [redacted] cohort analyses have not been powered a priori to detect the expected treatment difference; therefore, they will be considered exploratory and p-values nominal.

A BSSR may be conducted approximately three months prior to last-participant-in in the earlier completing of the two replicate studies. The primary/key secondary lung function endpoints (FEV_1 AUC_{0-3} and morning pre-dose trough FEV_1) will be analyzed. In addition, the

underlying rate of severe asthma exacerbations and negative binomial shape parameter will be predicted and the sample size potentially increased (but not decreased) using information from both studies. The increase in sample size will be capped at CCI participants per arm for the 2 combined studies, such that the total number of randomized participants will not exceed CCI for the 2 combined studies. The study duration may also be amended such that all participants complete 52 weeks of treatment. The operating characteristics of the BSSR will be fully detailed in the BSSR SAP, if it is decided to conduct a BSSR.

9.3 Populations for Analyses

The following populations are defined:

Table 14 Populations for Analysis

Analysis Set	Description
Enrolled	All participants who sign the ICF.
Randomized	All participants who are randomized to study intervention
Efficacy	All participants who are randomized to study intervention and receive any amount of study intervention. Participants will be analyzed according to the study intervention assigned at randomization, regardless of the actual study intervention received.
Safety	All participants who are randomized to study intervention and receive any amount of randomized study intervention. Participants will be analyzed according to the actual study intervention received rather than randomized.
Per Protocol (PP)	All participants in the Efficacy Analysis Set without an IPD impacting efficacy at the date of randomization. Furthermore, data obtained after any IPD impacting efficacy or ICE will be excluded. Since receiving the wrong treatment will be an IPD, participants in the PP analysis population will be analyzed as randomized (which for this analysis population is identical to analysis by the actual treatment received).
Pharmacokinetic (PK)	All participants in the Efficacy Analysis Set who enrolled in the PK sub-study, who have at least one post-dose PK measurement and who have correctly self-administered the last 3 doses of study intervention (6 inhalations) in order to have achieved steady state by Visit 8. Participants will be analyzed according to the actual treatment received rather than randomized.
PFT Sub-Study	All participants in the Efficacy Analysis Set who are randomized to PFT study and have at least one post-baseline spirometry assessment (after the first dose of study medication).
Holter Monitoring Sub-Study	All participants in the Safety Analysis Set who enrolled in the Holter Monitoring sub-study, had no IPD impacting the data prior to receiving study intervention, and had at least 18 hours of acceptable quality Holter monitoring data at both Visit 4 (Holter baseline) and at least one of Visit 6 (Week 4) and Visit 11 (Week 24). Data judged to be impacted by IPDs will

Table 14 Populations for Analysis

Analysis Set	Description
	be determined prior to database lock and excluded per the statistical protocol deviation plan.

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 secondary endpoints. Additional analyses assessing the impact of SARS-CoV-2 pandemic or any other natural event may be included in the SAP.

9.4.1 General Considerations

9.4.1.1 Demographic and Baseline Characteristics

Demographic and baseline characteristics data will be summarized by treatment for the Efficacy and Safety Analysis Sets.

9.4.1.2 Visit Windows

For post-randomization visit-based analyses, the variables are summarized based on data from scheduled or repeat visits (including premature study intervention discontinuation visits) by mapping the visit date to an adjusted analysis-defined visit window irrespective of the visit's label numbering. The adjusted analysis-defined windows will be specified in the SAP. For spirometry endpoints by timepoint pre- and post-dosing, the assessments will be allocated to derived nominal collection time windows of minutes from study intervention dosing. These will be specified in the SAP. Actual time will be used for the AUC calculations.

9.4.1.3 Baseline

For FEV_1, baseline is defined as the average of all pre-bronchodilator/pre-dose measurements at Visit 4 and Visit 5. For onset of action on Day 1, baseline is defined as the mean of the pre-dose FEV_1 assessments on Visit 5 (Day 1). For the asthma PROs, baseline is defined as the last non-missing value before randomization. For daily eDiary metrics (rescue medication, awakenings, PEFR, and asthma symptoms scores), baseline is defined as the average of eDiary metrics measured during last 7 days before randomization. Baseline reversibility will use Visit 2 for its baseline value (or Visit 3 in case Visit 2 is missing). For further details, refer to the SAP.

9.4.2 Efficacy

All superiority efficacy analyses will use the Efficacy Analysis Set.

9.4.2.1 Primary Endpoints

The primary analysis will be conducted using the Primary estimand strategy for ICEs. Supportive analyses will be conducted applying the While on Treatment strategy for all ICEs.

Change from Baseline in FEV_1 AUC_{0-3} (CCI Primary Endpoint)

Change from baseline in FEV_1 AUC_{0-3} will be analyzed using a repeated measures analysis of covariance model. The model will include treatment, visit, prior ICS dose (medium vs. high), and treatment-by-visit interaction as categorical covariates and baseline trough FEV_1 and percent reversibility as continuous covariates. An unstructured matrix will be used to model the variance-covariance structure. If this model fails to converge, an alternative structure will be employed as pre-specified in the SAP. Contrasts will be used to obtain estimates of the treatment differences at Week 24. Two-sided p-values and point estimates with 2-sided 95% confidence intervals (CIs) will be produced for each treatment difference. The model-based statistics for other visits, over 24 Weeks or over 12 to 24 Weeks will also be reported.

The FEV_1 AUC_{0-3} will be calculated for the changes from baseline using the trapezoidal rule and will be normalized by dividing by the time (in hours) from dosing to the last measurement included (typically 3 hours). Only 1 non-missing, post-dose value is required for the calculation of FEV_1 AUC_{0-3}. Actual time from dosing will be used in the calculation if available; otherwise, scheduled time will be used.

Change from Baseline in Morning Pre-dose Trough FEV_1 (CCI , and CCI Primary Endpoint)

Change from baseline in morning pre-dose trough FEV_1 will be analyzed using a repeated measures analysis of covariance model. The model will be similar to the one used for FEV_1 AUC_{0-3}. Contrasts will be used to obtain estimates of the treatment differences over 24 Weeks for CCI and CCI and over 12 to 24 Weeks for CCI Two-sided p-values and point estimates with 2-sided 95% CIs will be produced for each treatment difference. The model-based statistics for the at Week 24 and other visits will also be reported.

9.4.2.2 Secondary Endpoints

The analysis of the secondary endpoints will be conducted using the Primary strategy for ICEs. Supportive analyses will be conducted for the key secondary endpoints utilizing the While on Treatment strategy for all ICEs. Analysis of percentage of responders for PRO and symptom endpoints will also use the supportive Composite estimand strategy for ICEs; see Table 3 for details.

Change from baseline in morning pre-dose trough FEV_1 is the key secondary endpoint for the CCI For CCI and CCI the key secondary endpoint is change from baseline in FEV_1 AUC_{0-3}. Their analyses are similar as described in the previous section.

Percentage of Responders in ACQ-7 (≥ 0.5 decrease equals response) and ACQ-5 (≥ 0.5 decrease equals response)

Responder analyses will be performed for ACQ-7 and ACQ-5 at Week 24, over 24 Weeks or over 12 to 24 Weeks. Responders are defined as participants with an improvement of ≥ 0.5 points decrease over baseline.

Logistic regression will be used to compare the treatment groups with treatment and prior ICS dose (medium vs. high) as categorical covariates and baseline instrument score, baseline trough FEV_1, and percent reversibility as continuous covariates. P-values and odds ratios with 95% CIs will be produced for each treatment comparison.

Percentage of Responders in the Asthma Quality of Life Questionnaire for 12 Years and Older (AQLQ(s)+12) (≥ 0.5 increase equals response)

Responder analyses will be performed for AQLQ(s)+12 at Week 24, over 24 Weeks or over 12 to 24 Weeks for participants 12 years and older. Responders are defined as participants with an improvement of ≥ 0.5 points increase over baseline.

Logistic regression will be used to compare the treatment groups, similar to the one used for percentage of responders in ACQ-5. P-values and odds ratios with 95% CIs will be produced for each treatment comparison.

Percentage of Responders in the St. George's Respiratory Questionnaire (SGRQ) (≥ 4.0 unit decrease equals response)

Responder analyses will be performed for SGRQ at Week 24 or over 24 Weeks. Responders are defined as participants with an improvement (≥ 4.0 points decrease) over baseline. For over 24 Weeks, if the participant responds for at least 50% visits over that period, the participant will be considered responder over that period. Otherwise, the participant will be considered as non-responder.

Logistic regression will be used to compare the treatment groups, similar to the one used for percentage of responders in ACQ-5. P-values and odds ratios with 95% CIs will be produced for each treatment comparison.

Onset of Action on Day 1

All spirometry attempts at Visit 5 (Day 1) that meet ATS/ERS acceptability criteria will be recorded along with the actual time.

The onset of action on Day 1 will be defined as absolute change from baseline in FEV_1 at 5 minutes post-dose on Day 1. Descriptive statistics will be presented by treatment group. A within-group T-test to demonstrate that the mean change from baseline in FEV_1 at 5 minutes post-dose is statistically greater than 100 mL will also be provided with corresponding p-value and 95% CI.

Rate of Severe Asthma Exacerbation

For [CCI] approach only, the rate of severe asthma exacerbations will be analyzed in a manner similar to the analysis of the rate of severe asthma exacerbations in the primary pooled analysis.

9.4.2.3 Tertiary/Exploratory Endpoints

Unless otherwise specified, tertiary/exploratory endpoint efficacy analyses will be conducted using the While on Treatment estimand strategy for all ICEs; see Table 3 for details.

Change from Baseline in the Mean Number of Puffs of Rescue Medication Use (puffs/day)

The mean daily number of puffs of rescue medication use will be calculated overall and for each of the 4-week intervals during the Treatment Period. For every period of time for which the mean number of puffs of rescue medication will be calculated, missing values will be ignored in both the numerator and denominator. As such, the denominator will be adjusted based on the number of days (including half days) with non-missing values. A repeated measures analysis of covariance model will be used to analyze change from baseline in average daily rescue albuterol use. The model will include treatment, the number of the relevant 4-week interval (interval 1 to 13), baseline severe asthma exacerbation history (0, 1, ≥ 2), prior ICS dose (medium vs. high), and the treatment-by-4-week interval interaction as categorical covariates and baseline daily rescue albuterol use, baseline trough FEV_1, and percent reversibility as continuous covariates.

An unstructured variance-covariance matrix will be fit. If this model fails to converge, an alternative structure will be employed as pre-specified in the SAP. Contrasts will be used to obtain estimates of the treatment differences over 24 weeks or over 12 to 24 Weeks. Two-sided p-values and point estimates with 2-sided 95% CIs will be produced for each treatment difference.

Percentage of Rescue-Free and Symptom-Free Days

The percentages of rescue-free days and symptom-free days will each be analyzed over 24 Weeks and over 12 to 24 Weeks. Additionally, analyses will be conducted over each 4-week interval in the study. A repeated measures analysis of covariance model will be used with treatment, the number of the relevant 4-week interval (interval 1 to 13), baseline severe asthma exacerbation history (0, 1, ≥ 2), prior ICS dose (medium vs. high), and the treatment-by-4-week interval interaction as categorical covariates. Baseline percentage of endpoint days (where endpoint is rescue free, or symptom free), baseline trough FEV_1, and percent reversibility will be continuous covariates.

Peak Change from Baseline in FEV_1

Peak change from baseline in FEV_1 will be analyzed over 24 Weeks, 12 to 24 Weeks, and by visit for measures assessed at clinic visits using a repeated measures analysis of covariance

model. The model will be similar as the one used for the primary analyses.

Time to Peak FEV_1 on Day 1

Time to peak FEV_1 on Day 1 will be analyzed with analysis of covariance model to compare the treatment groups, adjusted for prior ICS dose (medium vs. high) baseline trough FEV_1, and percent reversibility. The time to peak will be based on the actual rather than nominal assessment time.

Change from Baseline in FVC, PEFR, and FEF_{25-75} Evaluated Using AUC_{0-3}

Change from baseline in FVC, PEFR, and FEF_{25-75} evaluated using AUC_{0-3} will be analyzed over 24 Weeks, 12 to 24 Weeks, and by visit for measures assessed at clinic visits using a repeated measures analysis of covariance model. The model will be similar to the one used for the primary analyses except that the covariate baseline trough FEV_1 will be replaced with the relevant baseline value for the respective parameter.

Change from Baseline in Morning Pre-Dose Trough PEFR

Change from baseline in morning pre-dose trough PEFR will be analyzed using a repeated measures analysis of covariance model. The model will include treatment, 4-week interval (interval 1 to 13), prior ICS dose (medium vs. high), and treatment by 4-week interval interaction as categorical covariates and baseline morning pre-dose trough PEFR and percent reversibility as continuous covariates. An unstructured matrix will be used to model the variance-covariance structure. If this model fails to converge, an alternative structure will be employed as pre-specified in the SAP. Contrasts will be used to obtain estimates of the treatment differences over 24 weeks or over 12 to 24 Weeks.

Two-sided p-values and point estimates with 2-sided 95% CIs will be produced for each treatment difference.

Change from Baseline in Evening Pre-Dose PEFR

Change from baseline in evening pre-dose PEFR will be analyzed over 24 Weeks, over 12 to 24 Weeks, and over each 4-week interval using a repeated measures analysis of covariance model. The model will be similar to the one used for the change from baseline in morning pre-dose PEFR with the respective baseline covariate.

Percentage of Responders in ACQ-6 (≥0.5 decrease equals response)

Responder analyses will be performed for ACQ-6 at Week 24, over 24 Weeks or over 12 to 24 Weeks. Responders are defined as participants with an improvement (decrease of ≥ 0.5 points) over baseline. The Primary strategy for ICEs will be utilized for this analysis.

Logistic regression will be used to compare the treatment groups, similar to the one used for percentage of responders in ACQ-5. P-values and odds ratios with 95% CIs will be produced for each treatment comparison.

Change from Baseline in ACQ-5, ACQ-6, ACQ-7, and AQLQ(s)+12

Change from baseline in ACQ-5, ACQ-6, ACQ-7, and AQLQ(s)+12 will each be analyzed using a repeated measures analysis of covariance model utilizing the Primary strategy for ICEs. The model will include treatment, visit, prior ICS dose (medium vs. high), and treatment-by-visit interaction as categorical covariates and baseline trough FEV_1, percent reversibility, and baseline score for the patient-reported outcome instrument as continuous covariates. Contrasts will be used to obtain estimates of the treatment differences by visit for measures assessed at clinic visits, over 24 Weeks, 12 to 24 Weeks, and over each 4-week interval. Two-sided p-values and point estimates with 2-sided 95% CIs will be produced for each treatment difference.

Change from baseline in SGRQ

Change from baseline in SGRQ will be analyzed using a repeated measures analysis of covariance model utilizing the Primary strategy for ICEs. The model will be similar as the one used for the analysis of change from baseline in ACQ-5. Contrasts will be used to obtain estimates of the treatment differences at Week 24 and over 24 Weeks. Two-sided p-values and point estimates with 2-sided 95% CIs will be produced for treatment difference.

Time to First Clinically Important Deterioration (CID)

A CID is a composite endpoint defined as at least one of the following:

- 12% decrease from baseline in pre-bronchodilator FEV_1
- AQLQ(s)+12 decrease of $\geq$0.5 from baseline
- ACQ-5 increase of $\geq$0.5 from baseline
- One severe or moderate asthma exacerbation
- Use of antibiotics for respiratory conditions

Time to first CID will be analyzed with a Cox regression model to compare the treatment groups, adjusted for baseline severe asthma exacerbation history (0, 1, $\geq$ 2), prior ICS dose (medium vs. high), region, baseline trough FEV_1, and percent reversibility.

CCI [redacted]

There will be two analyses for CCI [redacted]. First analysis will include only data up to and including Visit 8 (Week 12). Participants who did not have an event by then would be censored at their Week 12 visit. The second analysis will include all observed data with censoring at the last visit.

Both analyses will be analyzed in a manner similar to the analysis of time to first CID.

CCI [redacted]
CCI [redacted] events will be analyzed in a manner similar to the pooled analysis of

severe exacerbations utilizing the While on Treatment strategy for all ICEs.

Time to First Intercurrent Event

Time to first ICE will be analyzed in a manner similar to the analysis of time to first CID.

Time to First Intercurrent Event of Initiation of New Asthma Therapy or Prohibited Medications Thought to Impact Efficacy in Conjunction with Premature Discontinuation from Study Intervention

Time to first ICE will be analyzed in a manner similar to the analysis of time to CID utilizing the Primary strategy for ICEs.

Patient Global Impression of Change (PGIC)

The number and percentage of participants defined as responders will be presented by treatment group and visit. A responder is defined as a participant with any responses categorized as: "Much better", "Moderately better", or "A little better".

European Quality-of-Life-5 Dimensions (EQ-5D) and Visual Analogue Scale (VAS) Questionnaires Scored at Each Post-Randomization Visit and End of Study Visit

The EQ-5D data will be scored to calculate an index score based upon participants' responses to the 5 dimensions. The visual analogue scale will be scored from 0 (worst imaginable health state) through 100 (best imaginable health state) to represent the participant's self-report concerning how bad or how good their health was during that day.

The percentage of participant's categorical responses to each of the 5-dimensions will be summarized for the EQ-5D-Y and EQ-5D-5L questionnaires, respectively. Descriptive statistics for the index score and VAS will be presented by treatment group and type of questionnaire. The VAS scores at each post-randomization visit and end of study visit may be analyzed using repeated measures analysis of covariance model with age and baseline score as continuous covariates and region, gender, treatment, visit and treatment-by-visit as categorical covariates.

Fractional Exhaled Nitric Oxide (FeNO)

At Visit 1 and Visit 5, the percentage of participants with FeNO less than 25 ppb, between 25 ppb and less than 50 ppb, and at least 50 ppb will be summarized descriptively by treatment.

Percentage of Peak FEV_1 Improvement Achieved at 5 Minutes on Day of Randomization

Descriptive statistics will be presented by treatment group for the percentage of peak FEV_1 improvement achieved at 5 minutes on the day of randomization.

9.4.2.4 Health Care Resource Utilization

All Health Care Resource Utilization endpoints will be summarized for mean annualized rate

or percentage by treatment group.

9.4.3 Safety

All safety summaries will be performed on the Safety population. Participants will be analyzed according to the actual treatment received.

9.4.3.1 Primary Endpoints

Adverse events (AEs)

Adverse events during the Treatment Period will be summarized by the number of participants experiencing an event. Adverse events will be tabulated at the level of the Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term. The version of MedDRA current at the time of database lock will be used in the tabulations and listings. Tabulations will be broken down by intensity, seriousness, AEs leading to discontinuation, and by relationship to study intervention. No hypothesis tests will be performed; however, treatment groups will be compared as detailed in the SAP.

Adverse events associated with use of ICS, LAMAs, and LABAs will be presented in summary tabulations in the CSR. The selection of MedDRA terms proposed to be used in the assessment of these AEs will be described in the SAP.

Vital signs

Summary statistics (mean, median, SD, and range) of change from baseline will be tabulated by vital sign parameter and treatment for each scheduled assessment time. For vital signs, baseline will be defined as the last available value prior to dosing on the day of randomization. In addition, potentially clinically significant values will be identified and summarized.

Clinical laboratory values

Summary statistics (mean, median, SD, and range) of change from baseline values will be tabulated for each treatment and each assessment time. For clinical laboratory measurements, baseline will be defined as the last available value prior to randomization. Potentially clinically significant values will be identified and summarized.

ECGs

Summary statistics (mean, median, SD, and range) for absolute values and change from baseline will be tabulated by ECG parameter and treatment for each scheduled assessment time. For ECG parameters, baseline values will be defined as the last value obtained prior to randomization. In addition, potentially clinically significant values will be identified and summarized.

For Holter sub-study participants as well as for the Safety population, summary statistics (mean, median, SD, and range) for raw values and changes from baseline in QTcF intervals will be calculated where baseline is defined as the mean of the pre-dose measurements taken

prior to the start of treatment at Randomization (Visit 5). Number of cases and percentages will be summarized for the following categories: QTcF ≥ 450 msec, QTcF ≥ 480 msec, and QTcF ≥ 500 msec; change from baseline ≥ 30 msec and ≥ 60 msec; value > 500 msec or change from baseline ≥ 60 msec. These assessments will be tabulated for each treatment and assessment time. No hypothesis tests will be performed.

24-Hour Holter Monitoring

Change from baseline in the ventricular and supraventricular variables will be analyzed with nonparametric methods. The Wilcoxon Rank Sum Test will be used to produce p-values for the pairwise comparison of treatments. The median treatment differences will be presented with 95% CIs based on the Hodges-Lehmann approach. The number of participants experiencing a ventricular couplet, ventricular run, supraventricular couplet, and supraventricular run at Week 4 and Week 24 will be analyzed with a logistic regression model. Alternative analysis methods may be employed if found to be appropriate and will be pre-specified in the SAP.

Additionally, for the endpoints that involve incidences and proportions of events, those values will be summarized by treatment.

9.4.3.2 Other Safety Endpoints

Not applicable.

9.4.4 Pooled Analyses

The primary pooled analysis will be conducted using the Primary strategy for ICEs. Supportive pooled analyses will be conducted for the While on Treatment estimand strategy for all ICEs.

The primary analysis of NI endpoints will be performed for the Principal Stratum estimand strategy with the PP Analysis Set. Supplementary analyses of the rate of severe asthma exacerbations will be performed for the Primary and While on Treatment estimand strategies for ICEs. Details for the analysis of NI endpoints will be specified in SAP.

9.4.4.1 Primary Pooled Analyses

For the primary comparisons, the null hypothesis for each pair-wise comparison will be that the mean treatment difference is zero (mean treatment effects are equal). The alternative hypothesis is that the mean treatment difference is not zero (mean treatment effects are not equal). All p-values will be reported as 2-sided.

Rate of Severe Asthma Exacerbations

The rates of severe asthma exacerbations will be analyzed with negative binomial regression. Asthma exacerbations will be considered separate events if more than 7 days are between the recorded stop date of the earlier event and start date of the later event. Time at risk of

experiencing a severe exacerbation will be used as an offset variable in the model. Time during a severe exacerbation or in the 7 days following a severe exacerbation will not be included in the calculation of exposure. Treatments will be compared adjusting for baseline trough FEV_1, percent reversibility, baseline severe asthma exacerbation history (0, 1, $\geq$ 2), prior ICS dose (medium vs. high), region, and study.

The number and percentage of participants with severe exacerbations in each treatment group will be tabulated for individual study and pooled studies.

The same analysis will be repeated for the participants with percent predicted $FEV_1 \leq 55\%$ as well as for the participants with ≥ 1 severe exacerbation in the 12 months prior to Visit 1 as secondary evaluation of this endpoint.

9.4.4.2 Secondary Pooled Analyses

Similar to the primary pooled efficacy analysis, the secondary pooled efficacy analyses will be conducted for the Primary and While on Treatment strategies for ICEs. Analyses of difference in percentage of responders in responder endpoints will be conducted utilizing the Primary and supportive Composite strategies for ICEs.

Time to First Severe Asthma Exacerbation or Time to First Moderate/Severe Asthma Exacerbation

Time to first severe asthma exacerbation is the time from the first dose of study medication to the time of onset of the first severe asthma exacerbation. Time to first moderate/severe asthma exacerbation is defined similarly.

Time to first severe asthma exacerbation will be analyzed up to the Week 52 visit with a Cox regression model to compare the treatment groups, adjusted for baseline severe asthma exacerbation history (0, 1, $\geq$2), prior ICS dose (medium vs. high), region, study, baseline trough FEV1, and percent reversibility. Participants not having any severe asthma exacerbation will be censored at the date of their latest follow-up or end of study visit. Additionally, under the While on Treatment estimand strategy, participants experiencing 1 or more ICEs will be censored on the day of their first ICE.

Time to first moderate/severe asthma exacerbation will be analyzed in a manner similar to the analysis of time to first severe asthma exacerbation.

Rate of Moderate/Severe Asthma Exacerbations

Rate of moderate/severe asthma exacerbations will be analyzed in a manner similar to the analysis of the rate of severe asthma exacerbations in the primary pooled analysis.

Percentage of Responders in ACQ-7 (≥0.5 decrease equals response) and ACQ-5 (≥0.5 decrease equals response)

Responder analyses will be performed for ACQ-7 and ACQ-5 at Week 24, over 24 Weeks or over 12 to 24 Weeks. Responders are defined as participants with an improvement of ≥0.5 points decrease over baseline.

Percentage of responders in ACQ-7 and ACQ-5 will be analyzed in a manner similar to the analysis of percentage of responders in ACQ-7 and ACQ-5 for the individual study.

Percentage of Responders in the Asthma Quality of Life Questionnaire for 12 Years and Older (AQLQ(s)+12) (≥0.5 increase equals response)

Responder analyses will be performed for AQLQ(s)+12 at Week 24 and over 24 Weeks for participants 12 years and older. Responders are defined as participants with an improvement of ≥0.5 points increase over baseline.

Percentage of responders in AQLQ(s)+12 will be analyzed in a manner similar to the analysis of percentage of responders in AQLQ(s)+12 for the individual study.

9.4.4.3 Tertiary/Exploratory Pooled Analyses

Unless stated otherwise, tertiary/exploratory endpoints pooled efficacy analyses will be conducted for the While on Treatment estimand strategy for all ICEs only.

Time to First Hospitalization for Asthma Exacerbation

Time to first hospitalization for asthma exacerbation will be analyzed in a manner similar to the analysis of time to first severe asthma exacerbation in the secondary pooled analysis.

Rate of Hospitalization for Asthma Exacerbations

Rate of hospitalization for asthma exacerbations will be analyzed in a manner similar to the analysis of the rate of severe asthma exacerbations in the primary pooled analysis.

Rate of severe Asthma Exacerbations Resulting in A Temporary Course of Systemic Corticosteroids for at Least 3 Consecutive Days

Rate of severe asthma exacerbations resulting in a temporary course of systemic corticosteroids will be analyzed in a manner similar to the analysis of the rate of severe asthma exacerbations in the primary pooled analysis.

Time to CID

Time to CID will be analyzed in a manner similar to the analysis of time to first severe asthma exacerbation in the secondary pooled analysis.

CCI [redacted]

There will be two analyses for time to CCI [redacted]. First analysis will include only data up to and including Visit 8 (Week 12). Participants who did not have an event by then would be

censored at the minimum of (their Week 12 visit date, date of last dose + 1 day). The second analysis will include all observed data with censoring at the participant's date of last dose + 1 day.

Both analyses will be analyzed in a manner similar to the analysis of time to first severe asthma exacerbation in the secondary pooled analysis.

CCI
CCI events will be analyzed in a manner similar to the analysis of rate of severe asthma exacerbations in the primary pooled analysis.

Time to First Intercurrent Event

Time to first intercurrent event will be analyzed in a manner similar to the analysis of time to first severe asthma exacerbation in the secondary pooled analysis.

Time to First ICE of Initiation of New Asthma Therapy or Prohibited Medications Thought to Impact Efficacy in Conjunction with Discontinuation from Study Intervention

Time to first such ICE will be analyzed in a manner similar to the analysis of time to first severe asthma exacerbation in the secondary pooled analysis utilizing the Primary strategy for ICEs.

Percentage of Participants Who Permanently Discontinued Study Intervention Due to Asthma Exacerbation

Percentage of participants who permanently discontinued study intervention due to asthma exacerbation will be summarized by treatment group.

Total Number of Days on Systemic Corticosteroids to Treat Asthma Exacerbations

Total number of days on systemic corticosteroids to treat asthma exacerbations will be summarized by treatment group.

Rate of Severe Asthma Exacerbations Treated With Systemic Corticosteroids Only

Rate of severe asthma exacerbations treated with systemic corticosteroids only will be analyzed in a manner similar to the analysis of the rate of severe asthma exacerbations in the primary pooled analysis.

Rate of Asthma Deteriorations Treated With ICS and/or Antibiotics

Rate of asthma deteriorations treated with ICS and/or antibiotics will be analyzed in a manner similar to the analysis of the rate of severe asthma exacerbations in the primary pooled analysis.

Rate of Asthma Deteriorations Treated With Antibiotics

Rate of asthma deteriorations treated with antibiotics will be analyzed in a manner similar to

the analysis of the rate of severe asthma exacerbations in the primary pooled analysis.

Time to First Severe Asthma Exacerbation Treated With Systemic Corticosteroids Only

Time to first severe asthma exacerbation treated with systemic corticosteroids only will be analyzed in a manner similar to the analysis of time to first severe asthma exacerbation in the secondary pooled analysis.

Time to First Asthma Deterioration Treated With ICS and/or Antibiotics

Time to first asthma deterioration treated with ICS and/or antibiotics will be analyzed in a manner similar to the analysis of time to first severe asthma exacerbation in the secondary pooled analysis.

Time to First Asthma Deterioration Treated With Antibiotics

Time to first asthma deterioration treated with antibiotics will be analyzed in a manner similar to the analysis of time to first severe asthma exacerbation in the secondary pooled analysis.

9.4.4.4 12-Hour PFT Pooled Sub-Study Analyses

Serial PFTs will be conducted over 12 hours in a subset of participants at Visit 5 (Day 1) and Visit 8 (Week 12). Data from the 2 studies will be combined for the 12-hour PFT sub-study analyses. Unless stated otherwise, 12-hour PFT sub-study analyses will be conducted for the While on Treatment estimand strategy for all ICEs.

FEV_1 AUC_{0-12} at Day 1 and Week 12

The FEV_1 AUC_{0-12} will be calculated using the trapezoidal rule and transformed into a weighted average by dividing by the time in hours from dosing of the last measurement included (typically 12 hours). Only one non-missing post-dose value is required for the calculation of AUC. Actual time from dosing will be used if available; otherwise, scheduled time will be used. The differences between treatment groups in FEV_1 AUC_{0-12} at Day 1 and Week 12 will be evaluated utilizing the Primary strategy for handling ICEs and the While on Treatment strategy for all ICEs as a supportive approach using a repeated measures analysis of covariance model with baseline trough FEV_1 and percent reversibility as continuous covariates and study, treatment, visit, treatment by visit interaction, and prior ICS dose (medium vs. high) as categorical covariates. Two-sided p-values and point estimates with 2-sided 95% CIs will be produced for each treatment difference.

Change from Baseline in FEV_1 at Each Timepoint at Day 1 and Week 12

The differences between treatment groups in change from baseline in FEV_1 at each timepoint at Day 1 and at Week 12 will be evaluated using a repeated measures analysis of covariance model with baseline trough FEV_1 and percent reversibility as continuous covariates and study, treatment, post-dose timepoint, treatment by post-dose timepoint interaction, prior ICS dose (medium vs. high) as categorical covariates. Two-sided p-values and point estimates with 2-sided 95% CIs will be produced for each treatment difference.

Serial Spirometry Parameters Including FEV_1 AUC_{0-6}, FEV_1 AUC_{6-12}, and Peak FEV_1

FEV_1 AUC_{0-6}, and FEV_1 AUC_{6-12}, will be analyzed in a manner similar to the analysis of FEV_1 AUC_{0-12}.

Peak FEV_1 will be analyzed using a repeated measures analysis of covariance model with baseline trough FEV_1 and percent reversibility as continuous covariates and study, treatment, visit, treatment by visit interaction, prior ICS dose (medium vs. high) as categorical covariates.

FVC, PEFR, and FEF_{25-75} evaluated using AUC_{0-12}

FVC, PEFR, and FEF_{25-75} evaluated using AUC_{0-12} will be analyzed in a manner similar to the analysis of FEV_1 AUC_{0-12}, except that the covariate baseline trough FEV_1 will be replaced with the relevant baseline value for the respective parameter.

Weekly 5-Item OEQ at Home

For each item of the weekly 5-Item OEQ at home, the percentage of perceivers (participants responding, "strongly agree" or "somewhat agree") and percentage of non-perceivers (participants responding, "neither agree nor disagree," "somewhat disagree," or "strongly disagree") will be summarized for each treatment arm. Pearson chi-square test will be used to compare among pairs of treatment groups. The summary and comparison will be for each Week 1, 2, 3, 4, and 12.

The weekly 5-item OEQ will be completed at home on the eDiary weekly at Weeks 1, 2, 3, 4, and 12 after randomization. One OEQ item will be administered during site Visit 5 and Visit 8 at the scheduled timepoints (see Table 2).

One Item OEQ in Clinic

For the one item OEQ in the clinic, participants will be asked if they can feel the study medication working after administration.

The percentage of perceivers (participants responding 'yes') and percentage of non-perceivers (participants responding 'no') will be summarized for each treatment arm. Pearson chi-square test will be used to compare among pairs of treatment groups. The summary and comparison will be for Visit 5 and Visit 8 and at each of scheduled timepoints.

Time to first that participant feel the medication working will be analyzed in a manner similar to the analysis of time to first severe asthma exacerbation in the secondary pooled analysis.

9.4.5 12-Hour Pharmacokinetic Analyses

Pharmacokinetic statistical analysis will be performed using the PK analysis population. Plasma concentrations of budesonide, glycopyrronium, and formoterol will be summarized using descriptive statistics by treatment and nominal time for the PK analysis population.

Individual plasma concentration at each nominal and actual timepoint for each treatment will be listed by participant using the PK analysis population. The individual and mean plasma concentration will also be plotted as appropriate.

The PK parameters will be estimated for budesonide, glycopyrronium, and formoterol, as appropriate for each treatment, using plasma concentration-time data from Visit 8. Pharmacokinetic parameters calculated using pre-defined post-dose serial blood draws over 12 hours on at visit 8 will include the following: C_{max}, AUC_{0-12}, AUC_{last}, C_{trough}, C_{avg}, t_{max}. Additional PK parameters may be calculated, as appropriate. All budesonide, glycopyrronium, and formoterol PK parameters will be listed and summarized by treatment using appropriate descriptive statistics.

Non-compartmental parameter estimates for budesonide and formoterol C_{max}, AUC_{0-12}, AUC_{last}, C_{trough} and C_{avg} will be natural log transformed and analyzed using analysis of variance models in order to estimate the relative bioavailability of BGF MDI versus BFF MDI or Symbicort pMDI. Separate analysis of covariance models with fixed effects for treatment and relevant demographic characteristics will be fit for each analyte.

9.4.6 Subgroup 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.

Regional (CCI consistency analyses will follow the same analysis approach for the respective endpoints using individual study data or pooled data from studies D5982C00007 and D5982C00008. No adjustment for multiplicity will be made and the sequential testing procedure will not be followed.

9.5 Interim Analyses

Not applicable.

9.6 Data Monitoring Committee

An independent, external DMC will be set up to review the safety of the participants in the trial including all SAEs, discontinuations, fatal events, and pre-defined cardiovascular events. Members of the DMC will review data generated externally and independently from AstraZeneca in a semi-blinded or blinded manner at pre-determined intervals. If significant safety issues arise in between scheduled meetings, ad-hoc meetings will be scheduled to review the data. Based on the safety implications of the data, the DMC may recommend modification or termination of the study.

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 AstraZeneca will remain blinded to these analyses and will have no knowledge of the results presented to the DMC.

For details on DMC, refer to Appendix A 5.

9.7 Independent Adjudication Committee(s)

Adjudication committee(s) will be established for this study. The committee(s) will consist of independent experts who are not involved in the study conduct. Committee members will be blinded with respect to the participant's study medication. At regular intervals, the Committee(s) will review narratives, discharge summaries, and medical records, as available.

These committee(s) will review:

- Non-fatal Cardio- and Cerebro-vascular (CCV) events and classification of MACE.
- The cause of deaths for cardiovascular and respiratory related events. Determine if the fatal cardiovascular events meet MACE criteria.
- Serious events of cardiac arrhythmias within the Cardiovascular System Organ Class.
- Cases of ER or urgent care visits and hospitalizations related to respiratory conditions to evaluate whether any such events are related to a worsening of asthma and hence, diagnostic of a severe asthma exacerbation.

Further details are provided in the IAC Charter(s).

For details on IACs, refer to Appendix A 5.

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) GCP Guidelines
  - Applicable laws and regulations
- The protocol, revised protocol, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any revised protocol will require IRB/IEC and applicable Regulatory Authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- AstraZeneca will be responsible for obtaining the required authorizations to conduct the study from the concerned Regulatory Authority. This responsibility may be delegated to a Contract Research Organization but the accountability remains with AstraZeneca.
- The investigator will be responsible for providing oversight of the conduct of the study at the site and adherence to requirements of 21 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 AstraZeneca of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- AstraZeneca has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. AstraZeneca will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/ IEC, and Investigators.
- In the European Union, the Sponsor will comply with safety reporting requirements and procedures as described in the European Clinical Trials Regulation (EU) No 536/2014. All SUSARs to IMP will be reported to the EudraVigilance database within the required regulatory timelines.

- 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 an SAE or other specific safety information (eg, summary or listing of SAEs) from AstraZeneca will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

Regulatory Reporting Requirements for Serious Breaches

- Prompt notification by the Investigator to AstraZeneca of any (potential) serious breach of the protocol or regulations is essential so that legal and ethical obligations are met.
  - A 'serious breach' means a breach likely to affect to a significant degree the safety and rights of a participant or the reliability and robustness of the data generated in the clinical study.
- If any (potential) serious breach occurs in the course of the study, Investigators or other site personnel will inform the appropriate AstraZeneca representatives immediately after he or she becomes aware of it.
- In certain regions/countries, AstraZeneca has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about such breaches.
  - AstraZeneca will comply with country-specific regulatory requirements relating to serious breach reporting to the regulatory authority IRB/IEC, and Investigators. If EU Clinical Trials Regulation 536/2014 applies, AstraZeneca is required to enter details of serious breaches into the European Medicines Agency Clinical Trial Information System. It is important to note that redacted versions of serious breach reports will be available to the public via Clinical Trial Information System.
- The Investigator should have a process in place to ensure that:
  - The site staff or service providers delegated by the Investigator/Institution are able to identify the occurrence of a (potential) serious breach.
- A (potential) serious breach is promptly reported to AstraZeneca or delegated party, through the contacts (email address or telephone number) provided by AstraZeneca.

A 2 Financial Disclosure

Investigators and sub-Investigators will provide AstraZeneca with sufficient, accurate financial information as requested to allow AstraZeneca 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

- 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 at any time and for any reason during the study. Participants or their legally authorized representative will be required to sign a statement of informed consent 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 centre.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

A 4 Data Protection

- Participants will be assigned a unique identifier by AstraZeneca. Any participant records or datasets that are transferred to AstraZeneca 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 AstraZeneca 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 informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by AstraZeneca, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

A 5 Committees Structure

The safety of all AstraZeneca clinical studies is closely monitored on an on-going basis by

AstraZeneca Representatives, in consultation with Subject Safety and relevant adjudication and monitoring committees. Issues identified will be addressed; for instance, this could involve amendment to the Clinical Study Protocol and letters to the Investigator.

A 6 Dissemination of Clinical Study Data

Any results, both technical and lay summaries for this trial, will be submitted to EU Clinical Trial Information System within 6 months from global End of Trial Date in all participating countries, due to scientific reasons, as otherwise statistical analysis is not relevant.

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

A 7 Data Quality Assurance

- All participant data relating to the study will be recorded on eCRF unless transmitted to AstraZeneca or designee electronically (eg, laboratory 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 (source data) 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 source data documents.
- Quality tolerance limits (QTLs) will be predefined in the Integrated Quality Risk Management Plan (IQRMP) to identify systematic issues that can impact participant safety and/or reliability of study results. These predefined parameters will be monitored during the study.
- Monitoring details describing strategy, including definition of study-critical data items and processes (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- AstraZeneca or designee is responsible for medical oversight throughout the conduct of the study which includes clinical reviews of study data in accordance with the currently approved protocol. Monitoring details describing clinical reviews of study data from a medical perspective are included in more detail in the Monitoring Plan.

- AstraZeneca or designee is responsible for the data management of this study including quality checking of the data.
- AstraZeneca assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).
- Study monitors will perform ongoing source data verification as per the Monitoring Plan to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source 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 signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for a minimum of 25 years after study archiving or as required by local regulations, according to the AstraZeneca Global Retention and Disposal Schedule. No records may be destroyed during the retention period without the written approval of AstraZeneca. No records may be transferred to another location or party without written notification to AstraZeneca.

A 8 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data reported on the eCRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the monitoring plan.

A 9 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 AstraZeneca designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of AstraZeneca. Study sites will be closed upon study completion. 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 AstraZeneca 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, AstraZeneca's procedures, or GCP guidelines
- Inadequate recruitment of participants by the Investigator
- Discontinuation of further study intervention development

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

If the study is prematurely terminated or suspended, AstraZeneca shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(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.

A 10 Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to AstraZeneca before submission. This allows AstraZeneca to protect proprietary information and to provide comments.
- AstraZeneca will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, AstraZeneca will generally support publication of multicentre studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

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

B 1 Definition of Adverse Events

An AE is the development of any untoward medical occurrence in a participant 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 unfavourable 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 it's 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 intervention has been administered.

B 2 Definitions of Serious Adverse Event

A serious adverse event is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfils 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 abnormality or birth defect
- Is an important medical event that may jeopardise the participant or may require medical treatment to prevent one of the outcomes listed above.

Adverse Events (AEs) for **malignant tumours** 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 judgement on an individual event basis should be applied to clarify that the malignant tumour event should be assessed and reported as a **non-serious AE**. For example, if the tumour is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumour, the AE may not fulfil the attributes for being assessed as serious, although reporting of the progression of the malignant tumour as an AE is valid and should occur. Also, some types of malignant tumours, 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 ER is not in itself a serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). 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 judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalization, disability, or incapacity but may jeopardize the 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 judgement must be used.

Important medical events:

- 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 an 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 an 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 aetiology 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? AstraZeneca 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 disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

B 4 Medication Error, Drug Abuse, and Drug Misuse

Medication Error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an IMP or AstraZeneca NIMP 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 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, eg, 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 refrigerator when it should be at room temperature
- Wrong participant received the medication (excluding RTSM errors)
- Wrong drug administered to participant (excluding RTSM errors)

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

- Errors related to or resulting from 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

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

Drug Abuse

For the purpose of this study, drug abuse is defined as the persistent or sporadic intentional, non-therapeutic excessive use of IMP or AstraZeneca NIMP for a perceived reward or desired non-therapeutic effect.

Any events of drug abuse, with or without associated AEs, are to be captured and forward to the Data Entry Site using the Drug Abuse Report Form. This form should be used both in the drug abuse happened in a study participant or if the drug abuse involves a person not enrolled in the study (such as a relative of the study participant).

Examples of drug abuse include, but are not limited to:

- The drug is used with the intent of getting a perceived reward (by the study participant or a person not enrolled in the study)
- The drug in the form of a table is crushed and injected or snorted with the intent of getting high.

Drug Misuse

Drug misuse is the intentional and inappropriate use (by a study participant) of IMP or AstraZeneca NIMP for medicinal purposes outside of the authorized product information, or for unauthorized IMPs or AstraZeneca NIMPs, outside the intended use as specified in the protocol and includes deliberate administration of the product by the wrong route.

Events of drug misuse, with or without associated AEs, are to be captured and forwarded to the Data Entry Site using the Drug Misuse Report Form. This form should be used both if the drug misuse happened in a study participant or if the drug misuse regards a person not enrolled in the study (such as a relative of the study participant).

Examples of drug misuse include, but are not limited to:

- The drug is used with the intention to cause an effect in another person
- The drug is sold to other people for recreational purposes
- The drug is used to facilitate assault in another person

- The drug is deliberately administered by the wrong route
- The drug is split in half because it is easier to swallow, when it is stated in the protocol that it must be swallowed whole
- Only half the dose is taken because the study participant feels that he/she is feeling better when not taking the whole dose
- Someone who is not enrolled in the study intentionally takes the drug

Appendix C Handling of Human Biological Samples

C 1 Chain of custody

A full chain of custody is maintained for all samples throughout their lifecycle.

The Investigator keeps full traceability of collected biological samples from the participants while in storage at the centre until shipment or disposal (where appropriate) and records relevant processing information related to the samples whilst at site.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps record of receipt of arrival and onward shipment or disposal.

AstraZeneca or delegated representatives will keep oversight of the entire life cycle through internal procedures, monitoring of study sites, auditing or process checks, and contractual requirements of external laboratory providers

Samples retained for further use will be stored in the AstraZeneca-assigned biobanks or other sample archive facilities and will be tracked by the appropriate AstraZeneca Team during for the remainder of the sample life cycle.

If required, AstraZeneca will ensure that remaining biological samples are returned to the site according to local regulations or at the end of the retention period, whichever is the sooner.

C 2 Withdrawal of Informed Consent for donated biological samples

If a participant withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed/repatriated, and the action documented. If samples are already analyzed, AstraZeneca is not obliged to destroy the results of this research.

Following withdrawal of consent for biological samples, further study participation should be considered in relation to the withdrawal processes outlined in the informed consent.

The Investigator:

- Ensures participant's withdrawal of informed consent to the use of donated samples is highlighted immediately to AstraZeneca or delegate.
- Ensures that relevant human biological samples from that participant, if stored at the study site, are immediately identified, disposed of as appropriate, and the action documented
- Ensures that the participant and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the organization(s) holding the samples is/are informed about the

withdrawn consent immediately and that samples are disposed of or repatriated as appropriate, and the action documented, and study site notified.

C 3 International Airline Transportation Association (IATA) 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation Association (IATA) (**https://www.iata.org/whatwedo/cargo/dgr/Pages/download.aspx**) classifies infectious substances into 3 categories: Category A, Category B or Exempt

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals.

Category A pathogens are eg, Ebola, Lassa fever virus. Infectious substances meeting these criteria which cause disease in humans or both in humans and animals must be assigned to UN 2814. Infectious substances which cause disease only in animals must be assigned to UN 2900:

Category B Infectious Substances are infectious Substances that do not meet the criteria for inclusion in Category A. Category B pathogens are eg, Hepatitis A, C, D, and E viruses. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN3373 and IATA 650

Exempt – Substances which do not contain infectious substances or substances which are unlikely to cause disease in humans or animals are not subject to these Regulations unless they meet the criteria for inclusion in another class.

- Clinical study samples will fall into Category B or exempt under IATA regulations
- Clinical study samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging (https://www.iata.org/whatwedo/cargo/dgr/Documents/DGR-60-EN-PI650.pdf).
- Biological samples transported in dry-ice require additional dangerous goods specification for the dry-ice content

Appendix D Optional Genomics Initiative Sample

D 1 Use/analysis of DNA

- AstraZeneca intends to collect and store DNA for genetic research to explore how genetic variations may affect clinical parameters, risk and prognosis of diseases, and the response to medications. This genetic research may lead to better understanding of diseases, better diagnosis of diseases or other improvements in health care and to the discovery of new diagnostics, treatments, or medications. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting participants.
- This optional genetic research may consist of the analysis of the structure of the participant´s DNA, ie, the entire genome.
- The results of genetic analyses may be reported in a separate study summary.
- AstraZeneca will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on BGF MDI continues but no longer than 15 years or other period as per local requirements.

D 2 Genetic research plan and procedures

Selection of genetic research population

- All participants will be asked to participate in this genetic research. Participation is voluntary and if a participant declines to participate there will be no penalty or loss of benefit. The participant will not be excluded from any aspect of the main study.

Inclusion criteria

- For inclusion in this genetic research, participants must fulfil all of the inclusion criteria described in the main body of the Clinical Study Protocol and provide informed consent for the Genomics Initiative sampling and analyses.

Exclusion criteria

- Exclusion from this genetic research may be for any of the exclusion criteria specified in the main study or any of the following:
  - Previous allogeneic bone marrow transplant
  - Non-leukocyte depleted whole blood transfusion in 120 days of genetic sample collection
  - Adolescent participant (12 to <18 years of age) samples will not be collected for Genomics Initiative.

Withdrawal of consent for genetic research:

- Participants may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary withdrawal will not prejudice further treatment. Procedures for withdrawal are outlined in Section 7.2.

Collection of samples for genetic research

- The blood sample for this genetic research will be obtained from the participants at Visit 5 (Randomization). If for any reason the sample is not drawn at Visit 5, it may be taken at any visit until the last study visit. Only one sample should be collected per participant for genetics during the study.

Coding and storage of DNA samples

- The processes adopted for the coding and storage of samples for genetic analysis are important to maintain participant confidentiality. Samples will be stored for a maximum of 15 years, from the date of last participant last visit, after which they will be destroyed. DNA is a finite resource that is used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.
- An additional second code will be assigned to the sample either before or at the time of DNA extraction replacing the information on the sample tube. Thereafter, the sample will be identifiable only by the second, unique number. This number is used to identify the sample and corresponding data at the AstraZeneca genetics laboratories, or at the designated organization. No personal details identifying the individual will be available to any person (AstraZeneca employee or designated organizations working with the DNA).
- The link between the participant enrolment/randomization code and the second number will be maintained and stored in a secure environment, with restricted access at AstraZeneca or designated organizations. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit, and permit tracing of samples for destruction in the case of withdrawal of consent.

Ethical and regulatory requirements

- The principles for ethical and regulatory requirements for the study, including this genetics research component, are outlined in Appendix A.

Informed consent

- The genetic component of this study is optional, and the participant may participate in other components of the main study without participating in this genetic component. To participate in the genetic component of the study the participant must sign and date both the consent form for the main study and the addendum for the Genomics Initiative component of the study. Copies of both signed and dated consent forms must be given to the participant and the original filed at the study centre. The Principal Investigator(s) is responsible for ensuring that consent is given freely, and that the participant understands that they may freely withdrawal from the genetic aspect of the study at any time.

Participant data protection

- AstraZeneca will not provide individual genotype results to participants, any insurance company, any employer, their family members, general physician unless required to do so by law.
- Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the participant. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a participant. For example, in the case of a medical emergency, an AstraZeneca Physician or an Investigator might know a participant's identity and also have access to his or her genetic data. Regulatory authorities may require access to the relevant files, though the participant's medical information and the genetic files would remain physically separate.

Data management

- Any genetic data generated in this study will be stored at a secure system at AstraZeneca and/or designated organizations to analyse the samples.
- AstraZeneca and its designated organizations may share summary results (such as genetic differences from groups of individuals with a disease) from this genetic research with other researchers, such as hospitals, academic organizations, or health insurance companies. This can be done by placing the results in scientific databases, where they can be combined with the results of similar studies to learn even more about health and disease. The researchers can only use this information for health-related research purposes. Researchers may see summary results, but they will not be able to see individual participant data or any personal identifiers.
- Some or all of the clinical datasets from the main study may be merged with the genetic data in a suitable secure environment separate from the clinical database.

Appendix E Abbreviations

Abbreviation or special term	Explanation
ACQ	Asthma Control Questionnaire
ADE	Adverse Device Effect
AE	Adverse Event
AQLQ(s)+12	Asthma Quality of Life Questionnaire for 12 years and older
ATS	American Thoracic Society
AUC_{0-3}	Area Under the Curve 0 to 3 hours
AUC_{0-12}	Area Under the Curve 0 to 12 hours
AUC_{last}	Area Under the Curve from Time 0 to the Last Quantifiable Concentration
BD	Budesonide
BFF	Budesonide and Formoterol Fumarate
BGF	Budesonide, Glycopyrronium, and Formoterol Fumarate
BID	Twice Daily
BSSR	Blinded Sample Size Reassessment
C_{avg}	Average Concentration Over A Dosing Interval
C_{max}	Maximum Observed Concentration
CCV	Cardio- and Cerebro-vascular
CCU	Coronary Care Units
CFR	Code of Federal Regulations
CI	Confidence Interval
CID	Clinically Important Deterioration
CIOMS	Council for International Organizations of Medical Sciences
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
C_{max}	Steady-state Maximum (or Peak) Observed Plasma Concentration
CCI	[redacted]
COPD	Chronic Obstructive Pulmonary Disease
CSP	Clinical Study Protocol
CSR	Clinical Study Report
C_{trough}	Pre-dose PK Value
CCI	[redacted]
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic Acid
DPI	Dry Powder Inhaler
EAIR	Exposure adjusted incidence rate

Abbreviation or special term	Explanation
ECG	Electrocardiogram
eCRF	electronic Case Report Form
eDiary	electronic Diary
eGFR	estimated glomerular filtration rate
EQ-5D	European Quality-of-Life-5 Dimensions Questionnaire
ER	Emergency Room
ERS	European Respiratory Society
ERT	eResearchTechnology, Inc
EU	Europe
EU-CT	EU Clinical Trial
FDA	Food and Drug Administration
FEF_{25-75}	Forced Expiratory Flow at 25-75%
FeNO	Fractional Exhaled Nitric Oxide
FEV_1	Forced Expiratory Volume in 1 second
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GFF	Glycopyrronium and Formoterol Fumarate
GINA	Global Initiative for Asthma
GP	Glycopyrronium
HCRU	Healthcare Resource Utilization
HFA	Hydrofluoroalkane
HIPAA	Health Insurance Portability and Accountability Act
HR	Heart rate
HRQoL	Health-Related-Quality of Life
IAC	Independent Adjudication Committee
IATA	International Airline Transportation Association
ICE	Intercurrent event
ICF	Informed Consent Form
ICH	International Council for Harmonisation
ICS	Inhaled Corticosteroid
ICU	Intensive Care Unit
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IPD	Important protocol deviation
IQRMP	Integrated Quality Risk Management Plan

Abbreviation or special term	Explanation
IRB	Institutional Review Board
IV	Intravenous
IVRS	Interactive Voice/Web Response System
LABA	Long-Acting β_2-Agonist
LAMA	Long-Acting Muscarinic Antagonist
LTRA	Leukotriene Receptor Antagonist
MACE	Major Adverse Cardiovascular Events
MDI	Metered-Dose Inhaler
MDR	Medical Device Regulations
MedDRA	Medical Dictionary for Regulatory Activities
NI	Non-Inferiority
NIMP	Non-Investigational Medicinal Product
NSVT	Non-sustained ventricular tachycardia
OEQ	Onset of Effect Questionnaire
PCP	Primary Care Physician
PEFR	Peak Expiratory Flow Rate
PFT	Pulmonary Function Test
PGIC	Patient Global Impression of Change
PK	Pharmacokinetic
pMDI	pressurized Metered-Dose Inhaler
PP	Per Protocol
PRO	Patient Reported Outcome
PVC	Premature ventricular contractions
QTcF	QT interval corrected by Fridericia formula
QTL	Quality Tolerance Limits
RAU	Rescue Albuterol User
RoW	Rest of World
RTSM	Randomization and Trial Supply Management
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SD	Standard Deviation
SGRQ	St. George's Respiratory Questionnaire
SoA	Schedule of Activities

Abbreviation or special term	Explanation
SUSAR	Suspected Unexpected Serious Adverse Reactions
T_{max}	Time to reach C_{max}
US	United States of America
USADE	Unanticipated Serious Adverse Device Effect
VAS	Visual Analogue Scale

Appendix F Medical Device AEs, ADEs, SAEs, SADEs, USADEs and Medical Device Deficiencies: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting in Medical Device Studies

- The definitions and procedures detailed in this appendix are in accordance with International Organization for Standardization 14155 and European MDR 2017/745 for clinical device research (if applicable).
- Both the Investigator and AstraZeneca will comply with all local reporting requirements for medical devices.
- The detection and documentation procedures described in this protocol apply to all sponsor medical devices provided for use in the study. See Section 6.1.2 for the list of sponsor medical devices.

F 1 Definition of Medical Device AE and ADE

Medical Device AE and ADE Definition

- An AE is any untoward medical occurrence in a clinical study participant, users, or other persons, temporally associated with the use of study intervention, whether or not considered related to the investigational medical device. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of an investigational medical device. This definition includes events related to the investigational medical device or comparator and events related to the procedures involved.
- An adverse device effect (ADE) is defined as an AE related to the use of an investigational medical device. This definition includes any AE resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device as well as any event resulting from use error or from intentional misuse of the investigational medical device.

F 2 Definition of Medical Device SAE, SADE and USADE

A Medical Device SAE is an any serious adverse event that:

(a) Led to death

(b) Led to serious deterioration in the health of the participant, that either resulted in:

- A life-threatening illness or injury. The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death if it were more severe.

- A permanent impairment of a body structure or a body function.
- Inpatient or prolonged hospitalization. Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE.
- Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.
- Chronic disease (MDR 2017/745).

(c) Led to fetal distress, fetal death, or a congenital anomaly or birth defect

SADE definition

- A SADE is defined as an adverse medical device effect that has resulted in any of the consequences characteristic of an SAE.
- Any medical device deficiency that might have led to an SAE if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate.

Unanticipated SADE (USADE) definition

- An USADE (also identified as UADE in United States Regulations 21 CFR 813.3), is defined as a serious adverse medical device effect that by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report (see Section 2.3).

F 3 Definition of Medical Device Deficiency

Medical Device Deficiency Definition

- A medical device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Medical device deficiencies include malfunctions, use errors, and information supplied by the manufacturer.

F 4 Recording and Follow-up of AE and/or SAE and Medical Device Deficiencies

AE, SAE, and Medical Device Deficiency Recording

- When an AE/SAE/medical device deficiency occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.

- The Investigator will then record all relevant AE/SAE/medical device deficiency information in the participant's medical records, in accordance with the Investigator's normal clinical practice and on the appropriate form.
- It is **not** acceptable for the Investigator to send photocopies of the participant's medical records in lieu of completion of the AE/SAE/medical device deficiency form.
- There may be instances when copies of medical records for certain cases are requested by the AstraZeneca Data Entry Site. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the AstraZeneca Data Entry Site.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
- For medical device deficiencies, it is very important that the Investigator describes any corrective or remedial actions taken to prevent recurrence of the deficiency.
  - A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of a medical device deficiency. This includes any amendment to the medical device design to prevent recurrence.

Assessment of Intensity

The Investigator will make an assessment of intensity for each AE/SAE/medical device deficiency reported during the study and assign it to one of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. "Severe" is a category used for rating the intensity of an event; both AEs and SAEs can be assessed as severe.
- An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, **not** when it is rated as severe.

Assessment of Causality

- The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE/medical device deficiency.

- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship, cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The Investigator will also consult the Investigator's Brochure (IB) in his/her assessment.
- For each AE/SAE/medical device deficiency, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE/medical device deficiency and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to the AstraZeneca Data Entry Site. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the AstraZeneca Data Entry Site.
- The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

MDCG 2020 Guidance

For the purpose of harmonizing reports, each SAE will be classified according to five different levels of causality. AstraZeneca and the Investigators will use the following definitions to assess the relationship of the serious adverse event to the investigational[1] device or procedures.

1 Not related: Relationship to the device or procedures can be excluded when:

- the event has no temporal relationship with the use of the investigational device or the procedures;

[1] Investigational device: any device object of the clinical investigation, including the comparators

- the serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible;
- the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible - and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event;
- the event involves a body-site or an organ not expected to be affected by the device or procedure;
- the serious event can be attributed to another cause (eg, an underlying or concurrent illness/clinical condition, an effect of another device, drug, treatment, or other risk factors);
- the event does not depend on a false result given by the investigational device used for diagnosis, when applicable;

In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

2 Unlikely: The relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.

3 Possible: The relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible (eg, an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug, or treatment). Cases where relatedness cannot be assessed or no information has been obtained should also be classified as possible.

4 Probable: The relationship with the use of the investigational device seems relevant and/or the event cannot be reasonably explained by another cause, but additional information may be obtained.

5 Causal relationship: the serious event is associated with the investigational device or with procedures beyond reasonable doubt when:

- the event is a known side effect of the product category the device belongs to or of similar devices and procedures;
- the event has a temporal relationship with investigational device use/application or procedures;
- the event involves a body-site or organ that
  - the investigational device or procedures are applied to;
  - the investigational device or procedures have an effect on;

- the serious event follows a known response pattern to the medical device (if the response pattern is previously known);
- the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious event (when clinically feasible);
- other possible causes (eg, an underlying or concurrent illness/clinical condition or/and an effect of another device, drug, or treatment) have been adequately ruled out;
- harm to the participant is due to error in use;
- the event depends on a false result given by the investigational device used for diagnosis, when applicable;

In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

Follow-up of AE/SAE/Medical Device Deficiency

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the AstraZeneca Data Entry Site to elucidate the nature and/or causality of the AE/SAE/medical device deficiency as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide AstraZeneca with a copy of any post-mortem findings including histopathology.
- Suggested bullet in Variable blue text may not be required for studies where death is an endpoint.
- New or updated information will be recorded in the originally completed form.
- The Investigator will submit any updated SAE data to the AstraZeneca Data Entry Site within 24 hours of receipt of the information.

F 5 Reporting of SAEs

SAE Reporting to AstraZeneca Data Entry Site via Paper Data Collection Tool

- Facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the Study Physician.

- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE paper data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE paper data collection tool within the designated reporting time frames.
- Contacts for SAE reporting can be found in the safety handling plan.

F 6 Reporting of SADEs

SADE Reporting to AstraZeneca Data Entry Site

NOTE: There are additional reporting obligations for medical device deficiencies that are potentially related to SAEs that must fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

- Any medical device deficiency that is associated with an SAE must be reported to AstraZeneca within 24 hours after the Investigator determines that the event meets the definition of a medical device deficiency.
- AstraZeneca will review all medical device deficiencies and determine and document in writing whether they could have led to an SAE. These medical device deficiencies will be reported to the regulatory authorities and IRBs/IECs as required by national regulations.
- Contacts for SADE reporting can be found in the study safety handling plan.

Appendix G Protocol Amendment History

The Summary of Changes Table for the current amendment is located directly before the Table of Contents.

CSP Version 5.0 (Amendment 4): 29 August 2023

This modification is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union and in the EU Clinical Trial Regulation Article 2, 2 (13).

Overall Rationale for the Amendment:

The CSP has been amended to comply with the European Union Clinical Trials Regulation

[EU CTR]: (EU) No 536/2014 requirements.

Summary of Changes:

Section Number and Name	Description of Change	Brief Rationale	Substantial /Non-substantial
CSP front page	EU CT Number was added on the CSP front page: 2020-001520-34	Conformance with EU CTR.: Regulation (EU) No 536/2014	Non-substantial
Section 1.1 Schedule of Activities	Table 1. Schedule of Activities contained a typo mistake in the footnote (where instead of correct identification reference letter "K" was used incorrect reference letter "P"). Table has been updated with correct reference footnote "K" now.	A technical typo was corrected in Table 1 Schedule of Activities Table Footnote to reflect correct reference letter "K".	Non-substantial
Section 4.5 End of Study Definition	Added a statement: "A participant is considered to have completed the study if they have completed all phases of the study including the last visit Study Intervention Discontinuation and/or Study Withdrawal Visit or 2 weeks (± 2 days) after last dose Follow-Up telephone call".	The "End of the Study" definition as per FDA and EU guidance was added for the clinical trial transparency purposes aligning with the new AstraZeneca CSP template.	Non-substantial

Section Number and Name	Description of Change	Brief Rationale	Substantial /Non-substantial
Table 8 Required ICS Doses (in Combination with LABA) Prior to Visit 1a	In the CSP v4, particle size for budesonide was assessed as "DPI or pMDI, extrafine particle, HFA". Since, D5982C00007 is based on GINA 2020 and the correct particle size for budesonide should be "DPI, including pMDI, standard particle, HFA", corrections were made.	Updates made due to clarification as per memo Update to the Clinical Study Protocol (CSP) v4 Table 8 – Particle size of Budesonide dd. 08 June 2023.	Non-substantial
Appendix A1: Regulatory and Ethical Considerations	Added a statement: "The investigator will be responsible for providing oversight of the conduct of the study at the site and adherence to requirements of 21 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".	Changes were made to comply with AstraZeneca new CSP template guidelines amended. to adhere to the EU CTR: Regulation (EU) No 536/2014 requirements.	Non-substantial
Appendix A Regulatory and Ethical Considerations (A1. Regulatory and Ethical Considerations Regulatory Reporting Requirements for SAEs)	Added statement: "European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations".	Changes were made to comply with AstraZeneca new CSP template guidelines amended to adhere to the EU CTR: Regulation (EU) No 536/2014 requirements.	Non-substantial

Section Number and Name	Description of Change	Brief Rationale	Substantial /Non-substantial
A6. Dissemination of Clinical Study Data	In the statement "Any results, both technical and lay summaries for this trial, will be submitted to EU Clinical Trial Information System within 6 months from global End of Trial Date in all participating countries, due to scientific reasons, as otherwise statistical analysis is not relevant". Timelines were changed to 6 months instead of 1 year.	Changes were made to comply with AstraZeneca new CSP template guidelines amended to adhere to the EU CTR: Regulation (EU) No 536/2014 requirements.	Non-substantial
A7. Data Quality Assurance	Added statement: "Quality tolerance limits (QTLs) will be predefined in the Integrated Quality Risk Management Plan (IQRMP) to identify systematic issues that can impact participant safety and/or reliability of study results. These predefined parameters will be monitored during the study".	Changes were made to comply with AstraZeneca new CSP template guidelines amended to adhere to the EU CTR: Regulation (EU) No 536/2014 requirements.	Non-substantial
Throughout	IVRS was changed to RTSM.	IVRS term was changed to RTSM due to system change.	Non-substantial
Throughout	Minor editorial revisions	Minor, therefore not summarized.	Non-substantial

CSP Version 4.0 (Amendment 3): 21 February 2023

This modification is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union and in the EU Clinical Trial Regulation Article 2, 2 (13).

Overall Rationale for the Amendment:

An amendment was required due to recruitment challenges, to make 1) an update to stop recruitment to the budesonide, glycopyrronium, and formoterol fumarate (BGF) metered dose inhaler (MDI) 320/14.4/9.6 µg treatment arm, 2) an update to the Type I error control procedure and power estimates, and 3) updates to statistical methodology, including changes to estimands, covariates in the analysis models, and populations for analyses.

Summary of Changes

Section Number and Name	Description of Change	Brief Rationale
1.1 Synopsis; 1.2 Schema; 4.1 Overall Design; 6.3 Measures to Minimize Bias: Randomization and Blinding	CCI [redacted]	CCI [redacted]
1.1 Synopsis; 9.1.1 Analysis Methods of Estimands; 9.1.2 Type I Error Control; 9.2 Sample Size Determination	The strategy for controlling the Type I error for BGF MDI was updated as well as power estimates. For comparisons within CCI Type I error control, updated to compare BGF versus combined inhaled corticosteroid/long-acting beta$_2$-agonist. In addition, the BFF MDI non-inferiority (NI) Type I error multiplicity (for CCI Health Authority) was added.	Mitigating the risk of ongoing concerns with enrollment and for CCI NI Type I error control, removing assay sensitivity gate given the study design.

List of Non-Substantial Modifications

Section Number and Name	Description of Change	Brief Rationale
1.1 Synopsis; 3 Objectives and Endpoints; 9.1.1 Analysis Methods for Estimands; 9.4.2 Efficacy; 9.4.4 Pooled Analyses; 9.4.5 12-Hour Pharmacokinetics Analyses	Hybrid Estimand strategy added, While on Treatment Estimand strategy deleted for Safety analyses, the estimand used for the analysis of Onset of Action on Day 1 changed, Safety analyses clarified, and estimand strategy for Time to Clinically Important Deterioration updated	The Hybrid Estimand is deemed to answer an important clinical question of interest, where outcomes following a non-attributable ICE will use a Treatment Policy strategy and outcomes following an attributable ICE will be considered an unfavorable outcome. For Safety, the only ICE of interest is discontinuation of study intervention. Moreover, data following this ICE is also of interest for some safety analyses. Those analyses are therefore defined outside the estimand framework specified for the Efficacy analysis. The estimand for Onset of Action on Day 1 for the CCI was changed to achieve a consistency with the testing of the primary and other secondary endpoints for the CCI
1.1 Synopsis; 4.1 Overall Design; 8.5.1 Pharmacokinetics	Requirement for all participants from the Pharmacokinetic (PK) sub-study to be included in the 12-hour spirometry and Holter sub-studies removed.	To provide more flexibility with the aim of increasing enrollment across all sub-studies.
1.1 Synopsis; 9.3 Populations for Analyses	Modification to PK population	Providing additional clarity.
1.1 Synopsis; 9.4.2 Efficacy; 9.4.4 Pooled Analyses	Details of covariates updated.	Consistency of covariates across analyses. Covariates are deemed clinically relevant to the respective endpoints of interest and have been updated accordingly.
1.1 Synopsis; 9.3 Populations for Analyses; 9.4.2.3 Tertiary/Exploratory Endpoints	Randomized and Rescue Albuterol User populations were added.	The Rescue Albuterol User population was added for conducting the analysis on rescue medication use as this population is more appropriate to identify treatment effects on this endpoint. Randomized population defined for clarity.

Section Number and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities; 4.1 Overall Design; 5.1 Inclusion Criteria; 8.1.1.2 Spirometry Schedule; 8.1.1.3 Reversibility to Albuterol	Resolved inconsistencies across the sections to reflect Inclusion Criterion relating to historical reversibility in the last 12 months.	Wording throughout the protocol modified to match the inclusion criterion.
3 Objectives and Endpoints, Table 3	Analysis of "at Week 24" removed from the non-inferiority analyses of percentage of responders in Asthma Control Questionnaire (ACQ)-7, ACQ-5, and Asthma Quality of Life Questionnaire for 12 years and older	Non-inferiority comparison is to support CCI submission, thus focus is on "over 24 weeks"
3 Objectives and Endpoints, Table 4	Time to first severe asthma exacerbation added to pooled analyses.	Not included in original protocol in errors.
3 Objectives and Endpoints; 9.4.3.1 Primary Endpoints	Summary statistics for QT interval corrected by Fridericia formula (QTcF) added to the Safety population. QTcF threshold values added to the Holter sub-study and Safety populations.	Additional threshold values added as deemed of clinical interest.
3 Objectives and Endpoints, Table 4; 9.1.2 Type I Error Control; 9.4.4.1 Primary Pooled Analyses	Tests on pooled severe exacerbation rate for participants with percent predicted $FEV_1 \leq 55\%$ and with 1 or more severe exacerbation in the 12 months prior to Visit 1 were added.	To evaluate treatment benefits in participants with more severe disease.
3 Objectives and Endpoints; 9.4.5 12-Hour Pharmacokinetic Analyses	Removed C_{min} from PK parameters	C_{trough} is included therefore C_{min} is redundant
3 Objectives and Endpoints; 9.1.1 Analysis Methods for Estimands	Expanded definitions of ICE to improve clarity.	Providing clarity on estimand strategies. The changes to the Composite Estimand strategy are based on the expectation that missing data following an ICE due to the current global/country situation will occur at random (ie, irrespective of randomized treatment).
4.5 End of Study Definition; 6.1.2 Medical Devices Including Combination Products with a Device Constituent; 8.3.10 Medication Error, Drug Abuse, and Drug Misuse; 8.3.11 Device Constituent Deficiencies; A1 Regulatory	Updated AstraZeneca standard protocol template wording added.	Protocol standard template was recently updated and required wording has been added to this protocol.

Section Number and Name	Description of Change	Brief Rationale
and Ethical Consideration; A6 Dissemination of Clinical Study Data; A7 Data Quality Assurance; B4 Medication Error, Drug Abuse, and Drug Misuse		
5.2 Exclusion Criteria; 6.5.5 Prohibited Medications	Removed reference to intraocular corticosteroids and decreased cessation period for injectable systemic corticosteroids.	Amended to alleviate constraints on study recruitment.
5.5 Screen Failures	Rescreening for participants who fail pre-bronchodilator FEV_1 or ACQ score added.	To potentially allow rescreening for participants who fail initial screening.
6.5.3 Prior Medications, Table 8	For mometasone furoate, specific doses were removed, and a statement added to discuss eligibility with Study Physician.	To align with GINA 2022 and the current knowledge that different dry powder inhaler formulations come in different strengths and require bioequivalence studies to determine what is considered a low, medium, and high dose.
9.4.1.2 Visit Windows	Visit windows for analyses have been introduced.	To map data to closest scheduled visit.
9.4.2.3 Tertiary/Exploratory Endpoints	Change from baseline in evening pre-dose peak expiratory flow will not be analyzed by visit.	Evening peak expiratory flow is not assessed at clinic visits.
9.4.2.3 Tertiary/Exploratory Endpoints	European Quality of Life-5 Dimension Questionnaire presentations will be split by adult and adolescent populations.	Practical considerations in mapping questions from the 2 questionnaires (adults and adolescents)
Throughout	Minor editorial revisions	Minor, therefore not summarized.

CSP Version 3.0 (Amendment 2): 07 January 2022

This modification is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union and the EU Clinical Trial Regulation Article 2, 2 (13).

Overall Rationale for the Amendment:

An amendment was required due to recruitment challenges, and to make) updates to the inclusion and exclusion criteria, 2) adjustment to the multiple testing procedures, 3) a reduction in sample size, and 4) an update to the primary estimand for the CCI approach to address FDA recommendations.

Summary of Changes

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
1.1 Synopsis, Figure 1, 4.1 Overall Design, 4.5 End of Study Definition, 9.1.2 Type I Error Control, 9.2 Sample Size Determination, 9.5 Interim Analyses	Sample size reduced to 2200 participants. BSSR was updated to include an assessment of lung function in addition to severe exacerbations; planned study end may change depending on the outcome of the BSSR. Maximum increase in sample size was also updated. The assumption of SD for morning pre-dose trough FEV_1 was updated to 280 mL. Interim analysis was removed. Holter sub-study sample size was updated.	Given the recruitment challenges in the setting of the COVID-19 pandemic, the sample size to achieve the primary endpoint on lung function for the study was reassessed, the potential for an interim analysis was removed and the BSSR strategy and Type I error control were updated. The update to the assumption of SD was based on a reassessment of the 6-month GP MDI Phase II/III dose-ranging study.	Substantial
1.1 Synopsis, 3 Objectives and Endpoints, 9.1.1 Analysis Methods for Estimands, 9.1.2.3 CCI Approach, 9.4.2.1 Primary Endpoints. 9.4.2.2 Secondary Endpoints	Added a multiple testing approach for the CCI Health Authority submission.	While a multiple testing procedure was included for study D5982C00008 (LOGOS), one was not included for this study (KALOS). Since the multiple testing procedure includes data from both studies given the CCI Health Authority is interested in the results from both studies, it was added to the protocol for this study. Endpoints and estimands were also added accordingly.	Substantial
1.3 Schedule of Activities, 8, Study Assessments and Procedures	Suggested order of assessments added.	Order of assessment added for clarity.	Non-substantial
3 Objectives and Endpoints	Safety objectives were updated to include an assessment of the	This safety objective was included in study D5982C00008 (LOGOS). This objective was added to	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
	safety of BFF MDI relative to Symbicort pMDI.	this study (KALOS) to support the CCI of CCI in CCI	
3 Objectives and Endpoints, 9.1.1 Analysis Methods for Estimands, 9.1.2.3 CCI Approach, 9.4.4 Pooled Analysis	Added the NI tests for the CCI Health Authority submission for the NI comparison of BFF MDI vs Symbicort pMDI.	This NI tests was included for study D5982C00008 (LOGOS). The strategy was updated to also include for this study (KALOS) to support the CCI of CCI in CCI	Substantial
3 Objectives and Endpoints, 9.1.1 Analysis Methods for Estimands, 9.3 Populations for Analyses	Initiation of LAMA was added as an intercurrent event (ICE).	LAMA is part of the triple combination being evaluated as an escalation to ICS/LABA, so the initiation of LAMA will interfere with the treatment effect and was added as part of the ICE.	Non-substantial
3 Objectives and Endpoints, 9.1.1 Analysis Methods for Estimands, 9.4.2.1 Primary Endpoints, 9.4.2.2 Secondary Endpoints	Based on advice received from the CCI Health Authority, for the CCI submission, the primary estimand was changed from the While on Treatment estimand to the Treatment Policy estimand. The While on Treatment estimand will be considered as supportive.	From a CCI regulatory perspective, the analyses of efficacy endpoints based on the Treatment Policy estimand will be considered as primary, and analyses based on the While on Treatment estimand as supportive.	Substantial
3 Objectives and Endpoints, 9.4.2.2 Secondary Endpoints	Added percentage of responders in ACQ-7, ACQ-5 and AQLQ(s)+12 as secondary endpoints for the pooled analysis.	To increase sample size and power, these endpoints were added as a secondary endpoint for the pooled analysis.	Non-substantial
5.1 Inclusion Criteria, 8.1.1.3 Reversibility to Albuterol, 8.2.1.1 Respiratory Medical History	Inclusion criterion #4 removed. Inclusion criterion #7 updated. Conditional Inclusion #19 removed.	Inclusion criteria were removed or updated to aid recruitment.	Substantial
5.2 Exclusion Criteria, 6.5.5 Prohibited Medications	Exclusion criterion #12: LAMA as maintenance treatment 12 months prior Visit 1, switched to 12 weeks of use of LAMA, either alone or inhaled	Exclusion criteria were updated or removed to improve clarity and/or aid recruitment and/or to optimise safety monitoring.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
	combination therapy 12 weeks prior to Visit 1. Exclusion criterion #23: The QTcF was changed from ≥500 msec to >480 msec.		
6.1 Study Intervention(s) Administered, 6.1.2 Medical Devices, 8.3.11 Medical Device Deficiencies, Appendix F	Updated to reflect drug-device combination.	The section was added to clarify device deficiency in reporting obligations.	Non-substantial
6.5.4.1 Vaccinations	Text added to specify a window of at least 7 days between a SARS-CoV-2 vaccination dose and subsequent spirometry assessments.	Instructional text added to note the window between SARS-CoV-2 vaccinations and spirometry assessments.	Non-substantial
9.3 Populations for Analyses	Removed ITT and mITT analysis sets. Added Efficacy population. Changed "analysis set" into "analysis population".	To avoid any confusion with analysis sets and analysis populations, the reference to sets was removed from this section as it refers to analysis populations. The terms "ITT analysis set" and "mITT analysis set" replaced with "Efficacy Population" to be better align with the estimand framework.	Substantial
9.4.2.3 Tertiary/Exploratory Endpoints 9.4.4.4 12-Hour PFT Pooled Sub-Study Analyses	For time to peak FEV_1 on Day 1 and peak FEV_1 at Week 12, the covariate logarithm of baseline blood eosinophil count was removed from the model.	Blood eosinophil count is not considered as an important factor for the Peak FEV_1 endpoint.	Non-substantial
9.4.4.1 Primary Pooled Analysis	For the rate of severe asthma exacerbations, country in the analysis model was replaced by region. Also, the categories (0, 1, ≥2) are added for the covariate baseline severe asthma exacerbation history.	Rates are expected to be similar across different countries within the same region. For clarification purposes, categories are added for the covariate baseline severe asthma exacerbation history.	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
9.4.4.4 12-Hour PFT Pooled Sub-Study Analyses	The analysis of FEV_1 AUC_{0-12} and change from baseline in FEV_1 at Day 1 was added. The analysis model for Week 12 was switched from a linear mixed analysis of covariance model into a repeated measures analysis of covariance with visit as the repeated effect for the following endpoints: 1. FEV_1 AUC_{0-12} 2. FEV_1 AUC_{0-6}, FEV_1 AUC_{6-12}, and peak FEV_1 3. FVC, PEF and FEF_{25-75} evaluated using AUC_{0-12}	FEV_1 AUC_{0-12} and change from baseline in FEV_1 will be available at Day 1 and Week 12, so the analysis was added for Day 1. The analysis model was switched to a repeated measures analysis of covariance to include data from Day 1 and data from Week 12.	Non-substantial
Throughout	Minor editorial revisions	Minor, therefore not summarized.	Non-substantial

CSP Version 2.0 (Amendment 1): 27 October 2020

This modification is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union and the EU Clinical Trial Regulation Article 2, 2 (13).

Overall Rationale for the Amendment:

Clarity was required for the Type I Error Control for each region, an equivalence table was added for oral corticosteroids in the treatment of asthma exacerbations, and contraceptive language was updated to address Europe's (EU) recommendation for contraception and pregnancy testing in clinical trials.

Summary of Changes

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
1.3. Schedule of Activities	Pregnancy tests to be performed on all women of childbearing potential.	Wording updated to require pregnancy testing for women of childbearing potential to address EU's recommendation for contraception and pregnancy testing in clinical trials.	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
4.1. Overall Design; 9.5. Interim Analysis	Details of interim analysis added.	In the event of delay in study completion, an interim analysis may be conducted.	Non-substantial
5.1. Inclusion Criteria	Inclusion criterion 11 addition of definition of women of childbearing potential and appropriate contraception use.	Wording updated to include definition of women of childbearing potential and appropriate contraception use to address EU's recommendation for contraception and pregnancy testing in clinical trials.	Substantial
5.2. Exclusion Criteria	Exclusion criterion 22 changed from calculated creatinine clearance to estimated glomerular filtration rate (eGFR).	Terminology updated to reflect what is actually analyzed.	Non-substantial
5.5. Screen Failures	Pregnancy tests to be performed on all women of childbearing potential.	Wording updated to require pregnancy testing for women of childbearing potential to address EU's recommendation for contraception and pregnancy testing in clinical trials.	Substantial
6.5.2. Prednisolone or Equivalent for Treatment of Severe Exacerbation	An oral corticosteroid equivalence table was added.	To add clarity if an oral corticosteroid other than prednisolone is used to treat a severe asthma exacerbation, this equivalence table was added.	Substantial
8.2.7. Clinical Safety Laboratory Assessments	Definition of highly sensitive urine pregnancy test and pregnancy tests to be performed on all women of childbearing potential have been added and calculated creatinine clearance has been changed to eGFR.	The definition of highly sensitive urine pregnancy test was added to provide information for the tests that will be performed. Wording updated to require pregnancy testing for women of childbearing potential to address EU's recommendation for contraception and pregnancy testing in clinical trials.	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
		Terminology for eGFR updated to reflect what is actually analyzed.	
8.3.5. Adverse Events Associated with Use of ICS, LAMAs, and LABAs	The terminology "hoarseness candidiasis" has been removed.	This terminology did not correctly reflect what is recorded in the Investigator's Brochure and Product Labels so was incorrectly included.	Substantial
9.1.2. Type I Error Control; 9.2. Sample Size Determination	Details of Type I error control by region has been added.	Additional detail adds clarity as to how the Type I error will be controlled for each region based on the primary and secondary endpoints for that region.	Substantial
Throughout	Minor editorial and document formatting revisions	Minor, therefore have not been summarized.	Non-substantial

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