STATISTICAL ANALYSIS PLAN	
Study Code	D5982C00006
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D5982C00006 Protocol Title: A Randomized, Double-Blind, Parallel Group, Multicenter 24 Week Study to Assess the Efficacy and Safety of Budesonide and Formoterol Fumarate Metered Dose Inhaler Relative to Budesonide Metered Dose Inhaler and Open-Label Symbicort® Turbuhaler® in Participants with Inadequately Controlled Asthma (VATHOS)

LIST OF ABBREVIATIONS

Abbreviation or Specialized Term	Definition
ACQ	Asthma Control Questionnaire
AE	Adverse event
AIR	Anti-Inflammatory Reliever
AIRQ	Asthma Impairment and Risk Questionnaire
ANCOVA	Analysis of covariance
AQLQ(s) +12	Asthma Quality of Life Questionnaire for 12 years and older
AUC_{0-3}	Area Under the Curve 0 to 3 hours
BFF	Budesonide and Formoterol Fumarate
BMI	Body mass index
CCU	Coronary Care Units
CI	Confidence Interval
CCI	CCI
CCI	CCI
CRF	Case Report Form
CSP	Clinical Study Protocol
CSR	Clinical Study Report
ECG	Electrocardiogram
eCRF	electronic Case Report Form
GCP	Good Clinical Practice
EQ-5D	European Quality-of-Life-5 Dimensions Questionnaire
ER	Emergency Room
EU	European Union
eDiary	electronic Diary
FEF_{25-75}	Forced Expiratory Flow at 25-75%
FEV_1	Forced Expiratory Volume in 1 second
FVC	Forced Vital Capacity
HCRU	Healthcare Resource Utilization
HLGT	High-Level Group Term
HLT	High-Level Term
HR	Heart rate
IA	Independent Adjudication
ICE	Intercurrent Event

ICF	Informed Consent Form
ICS	Inhaled Corticosteroid
ICS/BA	Inhaled Corticosteroid together with either Long-Acting β_2-Agonist or Short-Acting Beta-Agonists taken as needed
ICU	Intensive Care Unit
IP	Investigational Product
IPD	Important Protocol Deviation
ISS	Integrated Summary Safety
IRS	Interactive Response System
LABA	Long-Acting β_2-Agonist
LAMA	Long-Acting Muscarinic Antagonist
LLOQ	Lower Limit of Quantification
MAR	Missing at random
MCAR	Missing completely at random
MedDRA	Medical Dictionary for Regulatory Activities
MDI	Metered-Dose Inhaler
MHLW	Ministry of Health Labor and Welfare
MTP	Multiple Testing Procedure
NI	Non-Inferiority
OCS	Oral Corticosteroids
PD	Protocol Deviation
PEF	Peak Expiration Flow
PEFR	Peak Expiratory Flow Rate
PP	Per-Protocol
PRO	Patient Reported Outcome
PSC	Planned Stats Complete
PT	Preferred Term
QEMT	Quality Event Monitoring Team
QTcF	QT interval corrected by Fridericia's formula
RoW	Rest of World
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SMO	Site Management Organisation
SMQ	Standardized MedDRA Queries
SOC	System Organ Class
TA	Therapeutic Area

ULOQ	Upper Limit of Quantification
US	United States
VAS	Visual Analogue Scale

AMENDMENT HISTORY

CATEGORY **Change refers to:**	**Date**	**Description of change**	**In line with Clinical Study Protocol (CSP)?**	**Rationale**
N/A	31AUG2022	Initial approved SAP	CSP V2.0	N/A
Derivation of secondary endpoint(s)	24OCT2023	For the composite estimand, participants that discontinue randomized treatment due to reasons related to the current global/country situation (i.e. epidemic/pandemic, healthcare crisis, natural disaster etc.) will not automatically be considered non-responders. Data following study intervention discontinuation for reasons related to global/country situation will be considered missing and will not be imputed. Intermittently missing data will be classified as non-response.	CSP V3.0	To provide clarity.
Statistical analysis method for primary and secondary endpoints(s)	24OCT2023	The Intent-to-Treat set was replaced with Efficacy analysis set and the modified Intent-to-Treat was removed. A Randomized set was added.	CSP V3.0	The terms "Intent-to-Treat analysis set" and modified Intent-to-Treat analysis set" were replaced with "Efficacy set". Randomized set defined for clarity.
Data Presentation	24OCT2023	Rescue Albuterol Use set deleted from summaries of demographics and baseline characteristics		Population not required for summary analyses.

Statistical analysis method for primary, secondary and exploratory endpoint(s)	24OCT2023	The baseline FEV_1 covariate used in the analyses was amended to baseline trough FEV_1 throughout. Percent Albuterol reversibility was added to all analyses. Severe asthma exacerbation history (0, ≥ 1) added as a covariate to the analysis of change from baseline in the mean number of puffs of rescue medication use and time to first clinically important deterioration (CCI Post-albuterol FEV1 percent predicted is no longer used as a covariate in any analysis.	CSP V3.0	Consistency of covariates across analyses. Covariates deemed clinically relevant to the respective endpoints of interest and have been updated accordingly.
Derivation of primary, secondary and exploratory endpoint(s) Data presentation	24OCT2023	Adjusted analysis-defined visit windows have been defined, where data from repeated visits can be used for visit-based analyses.	CSP V3.0	To map data to closest scheduled visit.
Statistical analysis method for secondary endpoint(s)	24OCT2023	The CCI Type I error control procedure was updated to remove the NI tests for secondary endpoints. The NI test of FEV_1 AUC_{0-3} for the BFF MDI 320/9.6 µg versus Symbicort TBH comparison was added but was kept outside of the procedure for multiplicity control and therefore, not subject to Type I error control. Assay sensitivity of Symbicort TBH vs BD MDI 320 µg was removed as it was deemed not necessary.	CSP V3.0	CCI [redacted]

Statistical analysis method for secondary endpoint(s)	24OCT2023	Hybrid estimand strategy for ICEs was added as a supplemental estimand for primary and secondary endpoints for all regions.	CSP V3.0	The Hybrid estimand approach 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 as unfavorable.
Multiple testing procedure	24OCT2023	The Type I error control procedure for CCI has been updated to: Reflect the use of the Treatment Policy as the primary ICE strategy across registrational endpoints as the primary strategy for CCI The While on Treatment approach and Composite approach are no longer planned to be conducted on registrational endpoints for CCI submission. Include the analysis of severe asthma exacerbation rate in the pooled D5982C00006 and D5982C00005 data as well as in the individual studies as secondary analyses. Additionally, the Treatment Policy estimand strategy for ICEs will be used for the analysis of responder endpoints for US submission instead of the Composite estimand strategy.	CSP V3.0	CCI CCI

Statistical analysis method for secondary endpoint(s)	24OCT2023	The population summary measure for the test of onset of action on Day 1 has been changed to "difference in mean change from baseline" and will no longer be performed as a within-group test but will compare the BFF MDI 320/9.6 µg relative to BD MDI 320 µg in the multiple testing procedure (as well as the BFF MDI 320/9.6 µg relative to the BFF MDI 160/9.6 µg as a supportive/ exploratory analysis). The within-group test was kept as a supportive/ exploratory analysis.	CSP V3.0	To allow assessment of the relative performance of BFF MDI 320/9.6 µg compared with BD MDI 320 µg arm as the onset of effect on Day 1 is expected to be driven by the formoterol component.
Statistical analysis method for secondary endpoint(s)	24OCT2023	An analysis on the rate of moderate/severe asthma exacerbations utilizing the Treatment Policy estimand was added as an exploratory analysis. An analysis of time to first severe asthma exacerbation in the pooled D5982C00006 and D5982C00005 data utilizing the Treatment Policy strategy for ICEs has been added as an exploratory analysis.	CSP V3.0	To support analysis on severe exacerbation rate, included in the multiplicity strategy for CCI
Statistical analysis method for primary, secondary and exploratory endpoint(s)	24OCT2023	Clarified that the model for analysis of repeatedly measured continuous variables is "repeated measures ANCOVA".	CSP V3.0	Model includes both continuous and categorical predictor variables.

Statistical analysis method for secondary endpoint(s)	24OCT2023	It was clarified that the safety objective is for comparing BFF MDI 320/9.6 µg relative to BD MDI and Symbicort TBH. A comparison of BFF MDI 320/9.6 µg relative to and BFF MDI 160/9.6 µg was included to provide supportive safety information.	CSP V3.0	To provide clarity on safety comparisons.
Statistical analysis method for secondary endpoint(s)	24OCT2023	An exploratory objective was added to compare BFF MDI 320/9.6 µg to BFF MDI 160/9.6 µg on lung function, exacerbations, symptoms, and PROs.	CSP V3.0	To evaluate dose response.
Statistical analysis method for exploratory endpoint(s)	24OCT2023	Change from baseline in evening pre-dose peak expiratory flow will not be analyzed by visit.	CSP V3.0	Evening peak expiratory flow is not assessed at clinic visits.
Statistical analysis method for exploratory endpoint(s)	24OCT2023	EQ-5D presentation will be split by questionnaire populations (12-15 years, ≥ 16 years. It was clarified that the EQ-5D index score will be analyzed using repeated measures ANCOVA model similarly to the VAS score.	CSP V3.0	EQ-5D presentation will be split by questionnaire populations due to practical considerations in mapping questions from the 2 questionnaires (adults and adolescents). The analysis on index score was included for clarity.

Statistical analysis methods for primary endpoint(s) Statistical analysis method for secondary endpoint(s)	27NOV2024	3.3.1.2 Intercurrent Events: Update to list of ICEs To remove distinction between attributable and non-attributable ICEs. ICE's of new asthma therapy and prohibited medications consolidated to the ICE of: Initiation of new asthma therapy or administration of prohibited asthma medications thought to impact efficacy For non-inferiority analysis Removal of poor compliance as ICE	CSP V4.0	To align with the removal of hybrid and attributable supportive strategies for ICEs Simplification as key medications identified as biological therapy/ monoclonal antibodies, LABA, LAMA, LTRA, maintenance ICS, or ICS/BA PRN (to capture AIR) Compliance is part of the IPDs

Statistical analysis methods for primary endpoint(s) Statistical analysis method for secondary endpoint(s)	27NOV2024	3.3.4 ICE Estimands Strategies The primary strategies for handling intercurrent events were updated to reflect a composite strategy (treatment failure) if new asthma therapy or administration of prohibitive medication thought to impact efficacy occurs in conjunction with premature IP discontinuation. Otherwise, treatment policy will be used. To simplify reporting to health authorities, the same approach to handling intercurrent events will be used for every Health Authority, instead of having different approaches for different Health Authorities. An approach using "While On Treatment" strategy for intercurrent events will be used as supportive. The supportive Hybrid and Attributable strategies for intercurrent events were removed.	CSP V4.0	CCI [redacted]
Statistical analysis methods for primary endpoint(s) Statistical analysis method for secondary endpoint(s)	27NOV2024	3.3.4 ICE Estimand Strategies: Clarification added of the start and end dates for data to be included within each strategy. 3.3.1.2 Intercurrent events: Clarification added that data collected on the same day as ICE or IPD will be assumed to be post-ICE or IPD	CSP V4.0	To provide clarity for programming the analysis

Statistical analysis method for primary endpoint(s) Statistical analysis method for secondary endpoint(s)	27NOV2024	Section 4.2 Endpoint Analysis Imputations for treatment failure was clarified for all primary and secondary endpoints that uses the primary strategy for handling ICEs. Added additional details to the definitions for end of treatment period/ time at risk/ for different estimands/ endpoints.	CSP V4.0	CCI To provide clarity for the endpoint derivations
Statistical analysis method for primary endpoint(s)	27NOV2024	Section 4.2.1.4 Primary analysis If the model fails to converge, an alternative to the unstructured covariance matrix will be used to model the variance-covariance structure of the repeated measures ANCOVA model. The hierarchical approach proposed to select a simpler covariance structure has been updated from: Unstructured -> Heterogeneous Toeplitz -> Heterogeneous First Order Autoregressive -> Toeplitz -> First Order Autoregressive -> Compound Symmetry to Unstructured -> Heterogeneous Toeplitz -> Toeplitz -> Compound Symmetry	CSP V4.0	To simplify the covariance structure determination and associated programming

Statistical analysis method for primary endpoint(s) Statistical analysis method for secondary endpoint(s)	27NOV2024	Section 4.2.1.7 Subgroup analysis Subgroup analysis of baseline prebronchodilator percent predicted FEV1 (≤60%, >60%) removed. Subgroup analysis of Race: Race categories combined. Number of participants needed in a treatment group within a subgroup category to present model estimates has been reduced from 30 to 10 per arm.	CSP V4.0	The number of subjects with pre-bronchodilator percent predicted FEV1 ≤60% is expected to be very low in this population. Due to low numbers. It was found the models were able to converge with less subjects then the initial 30 per treatment group within a subgroup category. Some categories of subgroups were found to have low numbers and expected to have less than 30 per treatment group. Restriction of 30 patients is too high.
Statistical analysis methods for primary endpoint(s) Statistical analysis method for secondary endpoint(s)	27NOV2024	Appendix 8.2.2 analysis for attributable and hybrid estimands removed.	CSP V4.0	In-line with changes to the estimands.

Statistical analysis methods for primary endpoint(s) Statistical analysis method for secondary endpoint(s)	27NOV2024	Sensitivity analyses: Tipping point (Section 8.2.2). Updated to utilize the Primary strategy for ICE's. Clarity that those values imputed by this strategy will not be tipped. To allow baseline covariates to be included in the model for imputation of non-monotone missing data, the sentence "There will be no conditioning on the covariates for this intermittent imputation." has been deleted. For tipping point analysis, the increment will be started with 100 mL, then 50 mL if it tips, then 10 mL to identify more precisely where it tips.	CSP V4.0	Clarification as to which values will not be tipped. To allow the same factors in the imputation model as in the analysis model This approach was applied for efficiency purpose.
Statistical analysis method for secondary endpoint(s)	27NOV2024	PP Analysis Set amended to exclude those only with an IPD impacting efficacy at baseline and not all IPDs at baseline	CSP V4.0	To select only IPDs expected to impact the efficacy analysis

Statistical analysis method for secondary endpoint(s)	27NOV2024	Section 4.2.3.4 Analysis of rates of severe asthma exacerbations It has been clarified that a negative binomial additive model will be used for the pooled analysis. Furthermore, it has been clarified that all available data from studies D5982C00005 and D5982C00006 will be used in the pooled analysis (except Symbicort TBH arm).	CSP V4.0	CCI [redacted]
Derivation of secondary endpoint(s)	27NOV2024	Section 4.2.5 ACQ Responders Clarification that the mean score for ACQ-7 will be calculated prior to assigning visit windows to the data. Sensitivity analysis using treatment policy approach where missing data due to global/ country situations are set to non-response removed. Analysis amended to use the primary strategy for ICEs with the composite strategy as supportive.	CSP V4.0	Due to Q7 often being entered at a later time by site. CCI [redacted]
Multiple testing procedure	27NOV2024	CCI [redacted] multiplicity strategy Clarity added on the treatments to be contrasted for the onset of action if the primary and key secondary endpoint is statistically significant.	CSP V4.0	To align with amended CSP text.

Data presentation	27NOV2024	Participants randomized at site CCI will be removed from all analysis sets. Safety data from this site and those using CCI will be listed. Text amended to allow for additional sites to be excluded if quality issues are identified prior to database lock with the reason for exclusion to be detailed within the CSR.	CSP V4.0	Suspected serious breach of GCP and data fabrication at site.
Data presentations	27NOV2024	Section 4.1.7 Medications Presentation of medication summary tables harmonised to Efficacy Set	CSP V4.0	To align with the population used for the efficacy analysis.
Data Presentation	27NOV2024	Analysis population for listings of AEs, serious AEs with outcome of death amended to screened set. Listing of overdoses added.	CSP V4.0	To display all AEs within the study.
Data Presentation	27NOV2024	Shift tables of labs will be presented from baseline to min or max value only, to last value has been removed.	CSP V4.0	Simplification
Data Presentation	27NOV2024	Medical history listing removed	CSP V4.0	Streamline to what is required per Health Authority requirement

Other	27NOV2024	3.3.5 Visit Windows Adjusted defined window visit for "Follow-up" was removed Upper time limit for post dose 5 mins spirometry assessments changed from 7 to 10 minutes in Table 6. Table 7 updated to give 4-week intervals for ediary measures in morning and evening. Visit windows updated to only have 1 set of windows for all spirometry assessments.	CSP V4.0	No efficacy data collected during follow-up for data presentation. The window has been extended to reduce the amount of clinically relevant missing data. To provide clarifications for endpoints just using morning or evening measurements. Alignment of spirometry data.

Other	27NOV2024	3.3.1.1 Baselines for Analysis The general reference point for study day 1 definition has been aligned to take the first dose of randomized IP. Hence the baseline definitions have been changed from the last non-missing value before randomization to the last non-missing value before first dose of randomized IP. The baseline definition for morning eDiary measures and evening eDiary measures was added. Baseline for vital signs has been amended from the average of the values prior to dosing to the same general definition.	CSP V4.0	To align baselines to last non-missing value prior to IP on study day 1. To provide clarification on how baseline is derived for eDiary measures in morning or evening To provide clarification on how baseline is derived for vital signs.
Other	27NOV2024	Section 4.1.7 Medications and 8.1 Concomitant medications definition split to define concomitant medications during the screening and treatment periods	CSP V4.0	Concomitant medications during treatment is of interest for CSR.

Other	27NOV2024	Section 4.2.7 Tertiary/ exploratory Evaluation of PEF AUC0-3 added. Exploratory analysis of the percentage of participants with ≥ 12% improvement over baseline in FEV1 at 5 minutes post-dose and at other timepoints on Day 1 added. Night-time awakenings removed from CCI criteria.	CSP V4.0	To be aligned with the objectives and CSP. To align with company standards.
Other	27NOV2024	Section 4.2.10 HRU Subset of endpoints clarified as number of events per-years and how calculated added.	CSP V4.0	To align with Objectives in CSP.
Other	27NOV2024	Sections 4.6.2 AEs and 8.1: AEs occurring during on-treatment period and associated time at risk clarified to be date of first dose of randomized IP ≤ AE onset date ≤ date of last dose of IP + 1 day, date of withdrawal, or date of death Same definition for the on-treatment period added for laboratory and vital sign analyses.	CSP V4.0	Clarified for derivation purposes. Definition added in line with the AE reporting on-treatment period

Other	27NOV2024	Appendix Data handling rules AEs of worsening severity removed from the treatment emergent definition. Definition for treatment period for efficacy removed. Reference to first dose of study drug changed to first dose of randomized IP in imputation methods for handling missing AE start dates. Similarly for definitions of concomitant medications. Partial/ missing concomitant start or end date rules updated.	CSP V4.0	Treatment emergent AEs identified programmatically from onset date within defined study periods. Contained within body of the SAP. Clarified for derivation purposes.
Other	27NOV2024	Appendix Bayesian analysis added.	NA	Due to number of adolescents recruited
Other	27NOV2024	Update to Table 8.2.1 to clarify which endpoints will be reported in the PSC vs Outside the CSR	NA	To provide clarity prior to unblinding data on what will be reported in the CSR
Other	27NOV2024	Section 2 changes to protocol Endpoint clarification on AQLQ for CCI removed	CSP V4.0	Change was included within CSP amendment
Other	27NOV2024	Minor editorial revisions	NA	Minor, therefore not summarized.

1 INTRODUCTION

The purpose of this document is to give details for the statistical analyses of study D5982C00006 (VATHOS) that informs the clinical study report. The reader is referred to the Clinical Study Protocol (CSP) Version 5.0 and the Case Report Form (CRF) for details of study conduct and data collection.

2 CHANGES TO PLANNED PROTOCOL ANALYSIS

3 DATA ANALYSIS CONSIDERATIONS

3.1 Timing of Analyses

All analyses will be performed following clinical data lock.

3.2 Analysis Sets

In the rare event that site needs to be closed during the course of the study for quality reasons (eg. Suspicion of fraud), all participants of this site will be excluded from all analyses and summaries.

Data from participants at sites using CCI will be excluded from all analysis sets in line with MHLW guidance. This is all participants at sites: PPD, PPD. Data from participants at site PPD will also be excluded in line with QEMT investigation. Other sites may be excluded if identified prior to database lock with reasons detailed within the CSR. A list of participants at these sites and their adverse events will be provided in Appendix 12.2 in the Clinical Study Report.

3.2.1 Screened Set

The Screened Set is defined as all participants who signed the Informed Consent Form (ICF).

3.2.2 Randomized Set

The Randomized Set is defined as all participants who are randomized to study intervention.

3.2.3 Efficacy Set

The Efficacy Set is defined as all participants who are randomized to study intervention and receive any amount of randomized study intervention. Participants will be analyzed according to the treatment assigned at randomization, regardless of the actual treatment received.

3.2.4 Per-Protocol (PP) Set

The Per-Protocol (PP) Set is defined as all participants in the Efficacy Set without an IPD impacting efficacy at the date of randomization. Participants will be analyzed according to the treatment assigned at randomization, regardless of the actual treatment received. Since receiving the wrong treatment will be an IPD this is identical to analysis by actual treatment.

3.2.5 Safety Set

The Safety Set is defined as all participants who are randomized to study intervention and receive any amount of randomized study intervention. Participants will be analyzed according to the actual treatment received rather than randomized treatment. The actual treatment is defined as the study intervention that the participant received the most based on number of puffs.

3.2.6 Handling of Participants with Multiple Participation

Participants who participated more than once in the study may be excluded from analysis sets according to the rules presented in Table 1. Data listings for such participants will be provided in Appendix 12.2 in the CSR for observed multiple participation. "Participation" refers to a given instance of an individual being randomized and receiving any amount of investigational product (IP). Overlapping participation refers to multiple participation (at the same or different sites within the LITHOS, VATHOS, KALOS and LOGOS studies), where IP in relation to one participation has not been discontinued prior to a subsequent participation. The participation lasts from first dose of randomized IP until study completion or study discontinuation.

Table 1 Handling of Participants with Multiple Participation in Clinical Studies

Multiple Participation Type	**Analysis Sets**	**Individual LITHOS and VATHOS analysis**	**Pooled LITHOS and VATHOS analysis[a]**
Overlapping participations	Efficacy, PP	Exclude all such participations	Exclude all such participations
Overlapping participations	Safety	Include all such participations	NA

Non-overlapping participations	Efficacy, PP	Include the first such participation within study	Include the first such participation across either of the studies
Non-overlapping participations	Safety	Include all such participations	NA

a: pooled LITHOS and VATHOS analysis will be performed for severe exacerbation endpoints only.

3.3 General Considerations

3.3.1 General Study Level Definitions

3.3.1.1 Baselines for Analysis

In general, the last non-missing assessment on or prior to the first dose of randomized IP will serve as the baseline for analysis variables. This will include repeat and unscheduled values. If there is no value on or prior to the first dose of randomized IP, then the baseline value will not be imputed and will be set to missing.

Exceptions to this rule are as follows:

- For spirometry endpoints [Forced Expiratory Volume in 1 second (FEV_1) and onset of action on Day 1], baseline is defined as the mean of the pre-dose FEV_1 measurements (at -60 and -30 minutes) at Visit 4 (Day 1), where the best value is taken at -60 and -30 from all available scheduled or repeat (rescheduled Visit 4) measures in time window. In participants missing either of these pre-dose assessments, the value will be calculated from the single measurement.

- For daily electronic Diary (eDiary) metrics (rescue medication and asthma symptom scores) and Peak Expiratory Flow rate (PEF) baseline is defined as the average of eDiary metrics measured during the last 7 days before randomization, starting in the evening 7 days prior to first dose of randomized IP (Day -7 PM) and ending the morning of the first randomized IP (Day 1 AM). Any Albuterol use for testing reversibility that may fall within this window will not be used in the baseline calculation of rescue medication use. A subject needs to have a minimum of 5 days of non-missing morning assessments and 5 days of non-missing evening assessments for a variable in order for baselines to be calculated.

    - For morning eDiary metrics, baseline is defined as the average of the morning eDiary metrics measured during the last 7 days before

randomization, starting in the morning 6 days prior to the first dose of randomized IP (Day -6 AM) and ending the morning of the first dose of randomized IP (Day 1). A subject needs to have a minimum of 5 days of non-missing morning assessments in order for baseline to be calculated.

- For evening eDiary metrics, baseline is defined as the average of the evening eDiary metrics measured during the last 7 days before randomization, starting in the evening 7 days prior to the first dose of randomized IP (Day -7 PM) and ending the evening of the day prior to the first dose of randomized IP (Day -1 PM). A subject needs to have a minimum of 5 days of non-missing evening assessments in order for baseline to be calculated.

- For severe asthma exacerbation history in the past 12 months before Visit 1, baseline is the number of severe asthma exacerbations reported on the Respiratory Disease History CRF page.

- Baseline reversibility will use Visit 2 for its baseline value. If the Visit 2 value is missing, then the Visit 3 value will be used.

3.3.1.2 Intercurrent Events

ICEs are defined as events that occur after treatment initiation and either preclude observation of the variable of interest or affect its interpretation.

Superiority analyses:

For the superiority analyses, the ICEs are as follows:

- Premature discontinuation from randomized study intervention.
- Prolonged exposure to systemic corticosteroids or increased ICS dose for greater than 14 consecutive days or a single depot corticosteroid injection. The start date of this ICE is defined as the first day of the additional treatment or increased dose.
- Use of systemic corticosteroids or increased ICS dose for 14 days or less will be considered a temporary ICE only for concurrent lung function assessments (or lung function assessments performed within 7 days following exposure to systemic corticosteroid or increased ICS).
- Initiation of new asthma therapy or administration of prohibited medications thought to impact efficacy: biological therapy/ monoclonal antibodies, LABA, LAMA, LTRA, maintenance ICS, or ICS/BA PRN (to capture AIR) following the first dose of randomized IP either:
  - in conjunction with permanent discontinuation of randomized study intervention (defined as medication start date occurring either 2 weeks prior to or within 4

weeks following premature discontinuation of randomized study intervention); else

- prior to IP discontinuation.

The final list of prohibited medication will be defined following a physician's review prior to clinical data lock of the unique combinations of ATC code classifications and generic terms captured.

The date of an ICE is defined by the first day, when the ICE occurred (e.g. for medications constituting ICE, the date of first dose will be used). Initiation of new asthma therapy or administration of prohibited medication thought to impact efficacy in conjunction with premature discontinuation is defined as medication with a start date occurring either 2 weeks prior to or within 4 week following premature IP discontinuation.

Non-Inferiority analyses:

- Any ICEs listed for the superiority analyses.
- Important protocol deviations thought to impact efficacy: For details of IPDs, refer to section 3.3.8

As time is not collected for all IPD's, data collected on the same day as an IPD will be assumed to be post-IPD.

3.3.2 Hypothesis Testing

3.3.2.1 Hypothesis Testing for Superiority

The primary endpoint is different based on region (i.e. with respect to the Health Authority responsible for reviewing the marketing authorization, not the recruitment/location nationality of the participants). For the CCI Change from Baseline in FEV_1 Area Under the Curve 0 to 3 hours (AUC_{0-3}) at week 24 is the primary endpoint. For CCI (CCI Change from Baseline in morning pre-dose trough FEV_1 over 24 weeks is the primary endpoint. For CCI Change from Baseline in morning pre-dose trough FEV_1 over 12 to 24 weeks is the primary endpoint.

Regardless of the primary endpoint, the null hypothesis for each comparison will be that the outcome of participants taking BFF Metered Dose Inhaler (MDI) 320/9.6 µg BID is equal to that of participants taking BD 320 µg MDI BID versus the alternative hypothesis that the outcome of participants taking BFF MDI 320/9.6 µg BID is not equal to that of participants taking BD 320 µg MDI BID. P-values will thus be reported as two-sided.

The primary null (H_0) and alternative (H_1) hypotheses with λ representing the mean of change from baseline in FEV_1 AUC_{0-3} or the mean of change from baseline in morning pre-dose trough FEV_1 are specified below:

- H_0: $\lambda_{BFF320/9.6} = \lambda_{BD320}$
- H_1: $\lambda_{BFF320/9.6} \neq \lambda_{BD320}$

Secondary efficacy analyses (except the pooled analyses on severe exacerbations rate) will involve the above hypotheses applied to secondary efficacy endpoints.

For the pooled analysis of exacerbation rate the null and alternative hypotheses are:

- H_0: $RR_{BFF\ vs\ BD} = 1$
- H_1: $RR_{BFF\ vs\ BD} \neq 1$

3.3.2.2 Hypothesis Testing of Non-Inferiority for CCI

A NI comparison of BFF MDI 320/9.6 µg versus Symbicort TBH on trough FEV_1 will be conducted in order to support registration of BFF (Asthma) in CCI The NI margin for morning pre-dose trough FEV_1 will be CCI

An additional NI comparison on FEV_1 AUC_{0-3} will be conducted to show numerical similarity of BFF MDI 320/9.6 µg and Symbicort TBH and will be kept outside of the MTP and type I error control. The NI margin for FEV_1 AUC_{0-3} will be CCI

These margins are consistent with those CCI

For change from baseline in morning pre-dose trough FEV_1 over weeks 12 to 24

- H_0: $\lambda_{BFF320/9.6} - \lambda_{Symbicort} \leq$ CCI
- H_1: $\lambda_{BFF320/9.6} - \lambda_{Symbicort} >$ CCI

For change from baseline in FEV_1 AUC_{0-3} over weeks 12 to 24

- H_0: $\lambda_{BFF320/9.6} - \lambda_{Symbicort} \leq$ CCI
- H_1: $\lambda_{BFF320/9.6} - \lambda_{Symbicort} >$ CCI

3.3.3 Assumptions Checks and Removal of Outliers in Sensitivity Analyses

The distribution of residuals and influence statistics will be examined to identify any outliers. In the event that a single, or small number of such outlying values, are found to exist and to be highly influential, the effects may be ameliorated by removal of the outlier as a sensitivity analysis. If warranted, these analyses will be conducted to evaluate the robustness of the results.

3.3.4 ICE Estimands Strategies

For the following estimands, the estimand population is adults and adolescents with inadequately controlled asthma (symptomatic on medium dose ICS or ICS/LABA), with the exception of the estimand used for pooled analyses of severe asthma exacerbations which would broaden to also include subjects on low dose from LITHOS.

Table 2 summarises the estimand approaches to ICEs.

Table 2 Estimands

Objective	Estimand	
Primary	CCI **Approach[a]**	CCI **Approach[a]**
To assess the effect of BFF MDI 320/9.6 µg relative to BD MDI (superiority) on lung function.	• **Treatment**: Randomized treatment of BFF MDI 320/9.6 µg or BD MDI 320 µg • **Population summary measure**: Difference in mean change from baseline	
	• **Endpoint**: Change from baseline in FEV_1 AUC_{0-3} at Week 24	• **Endpoint**: – CCI: 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
	• **Primary method for handling ICEs:** – Premature discontinuation from randomized study intervention: Treatment policy i.e. all observed data used regardless of ICE. – Prolonged exposure of systemic corticosteroids, increased ICS dose for more than 14 days, or depot corticosteroid injection: Treatment policy i.e. all observed data used regardless of ICE. – Initiation of new asthma therapy or administration of prohibited medications thought to impact efficacy following first dose of randomized IP either: o in conjunction with premature discontinuation of randomized study intervention (defined as medication start date occurring either 2 weeks prior to or within 4 weeks following premature discontinuation of randomized study intervention): Composite (treatment failure); else o prior to premature IP discontinuation: Treatment policy i.e. all observed data used regardless of ICE. • **Supportive approach for handling ICEs:** While on Treatment (i.e., data after ICE will not be used) for all ICEs – Premature discontinuation from randomized study intervention: While on Treatment i.e. data after ICE will not be used. – Prolonged exposure of systemic corticosteroids, increased ICS dose for more than 14 days, or depot corticosteroid injection: While on Treatment i.e. 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 i.e. data after ICE will not be used.	

CCI only: To assess the effect of BFF MDI 320/9.6 µg relative to Symbicort TBH (non-inferiority) and BFF MDI 320/9.6 µg relative to BD MDI (assay sensitivity for non-inferiority) on lung function.	**N/A**	• **Endpoint**: Change from baseline in morning pre-dose trough FEV_1 over 12 to 24 weeks • **Handling ICEs (non-inferiority): Principal Stratum** (i.e., data after ICE or any IPD that impacts efficacy will not be used) – Premature discontinuation from study intervention. – Prolonged exposure to systemic corticosteroids, increased ICS dose for more than 14 days, or depot corticosteroid injection. – Initiation of any new asthma therapy or any additional prohibited medications thought to impact efficacy. – Any IPD that impacts efficacy. • **Handling ICEs (superiority for assay sensitivity):** Same as for primary strategy for primary endpoint.
Secondary Endpoints		
To assess the effect of BFF MDI 320/9.6 µg relative to BD MDI 320 µg (superiority) and Symbicort TBH (non-inferiority; CCI only) on lung function.	• **Endpoint:** Change from baseline in morning pre-dose trough FEV_1 at Week 24 • **Population summary measure**: Difference in mean change from baseline • **Handling of ICEs:** Same as for primary endpoint.	• **Endpoint:** – CCI Change from baseline in FEV_1 AUC_{0-3} over 24 weeks – CCI: Change from baseline in FEV_1 AUC_0-3 over 12 to 24 weeks • **Population summary measure**: Difference in mean change from baseline • **Handling of ICEs (superiority):** Same as for primary endpoint. • **Handling of ICEs (non-inferiority):** Same as for primary endpoint non-inferiority analysis (i.e., Principal

		Stratum, using only data prior to ICE or IPD that impacts efficacy).
To assess the effect of BFF MDI 320/9.6 µg relative to BD MDI 320 µg on asthma exacerbations.	• **Endpoint:** Severe asthma exacerbation • **Population summary measure**: Rate Ratio • **Handling of ICEs:** Same as for primary strategy for the primary endpoint.	**N/A**
To assess the effect of BFF MDI 320/9.6 µg or BFF 160/9.6 µg relative to BD MDI 320 µg on asthma exacerbations (pooled data from Studies D5982C00005 and D5982C00006).	• **Endpoint:** Severe asthma exacerbation • **Population summary measure**: Rate Ratio • **Handling of ICEs:** Same as for primary strategy for the primary endpoint. • **Supportive approach for handling of ICEs:** While on Treatment (i.e. data after ICE will not be used) for all ICEs	**N/A**
To assess the effect of BFF MDI 320/9.6 µg relative to BD MDI 320 µg on lung function, symptoms, and PROs.	• **Endpoint**: Change from baseline in the mean number of puffs of rescue medication use (puffs/day) over 24 Weeks	• **Endpoint:** – [redacted]: Change from baseline in the mean number of puffs of rescue medication use (puffs/day) over 24 Weeks – [redacted]: Change from baseline in the mean number of puffs of rescue medication use (puffs/day) over 12 to 24 Weeks
	• **Population summary measure**: Difference in mean change from baseline • **Handling of ICEs:** Same as primary strategy for primary endpoint	
	• **Endpoint:** Percentage of responders in ACQ-7 (≥ 0.5 decrease equals response) at Week 24	• **Endpoint:** – [redacted]: Percentage of responders in ACQ-7 (≥ 0.5 decrease equals response) over 24 Weeks – [redacted]: Percentage of responders in ACQ-7 (≥ 0.5 decrease equals response) over 12 to 24 Weeks

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- **Population Summary Measure:** Odds Ratio
- **Primary method for handling ICEs:**
  - Premature discontinuation from study intervention: Treatment policy i.e., all observed data used regardless of ICE.
  - Prolonged exposure to systemic corticosteroids for more than 14 days, increased ICS dose, or depot corticosteroid injection: Treatment policy i.e., all observed data used regardless of ICE.
  - Initiation of new asthma therapy or administration of prohibited medications thought to impact efficacy following first dose of randomized IP: Composite (treatment failure) if in conjunction with premature discontinuation of randomized study intervention, else Treatment policy i.e., all observed data used regardless of ICE.

Supportive Composite:

- Premature discontinuation from 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 participants from (and including) day of first ICE (Composite strategy).
- Prolonged exposure to systemic corticosteroids for more than 14 days, increased ICS dose, or depot corticosteroid injection: 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).

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- **Endpoint:** Percentage of responders in ACQ-5 (≥ 0.5 decrease equals response) at Week 24
- **Population Summary Measure:** Odds Ratio
- **Handling of ICEs:** As for ACQ-7

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- **Endpoint:**
  - [redacted]: Percentage of responders in ACQ-5 (≥ 0.5 decrease equals response) over 24 Weeks
  - [redacted]: Percentage of responders in ACQ-5 (≥ 0.5 decrease equals response) over 12 to 24 Weeks
- **Population Summary Measure:** Odds Ratio
- **Handling of ICEs:** As for ACQ-7

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	• **Endpoint:** Percentage of responders in AQLQ(s)+12 (≥ 0.5 increase equals response) at Week 24 • **Population Summary Measure:** Odds Ratio • **Handling of ICEs:** As for ACQ-7		• **Endpoint:** – CCI : Percentage of responders in AQLQ(s)+12 (≥ 0.5 increase equals response) over 24 weeks – CCI : Percentage of responders in AQLQ(s)+12 (≥ 0.5 increase equals response) over 12 to 24 weeks • **Population Summary Measure:** Odds Ratio • **Handling of ICEs:** As for ACQ-7	
	• **Endpoint:** Onset of action on Day 1: Absolute change in FEV_1 at 5 minutes post-dose on Day 1 • **Population Summary Measure:** Difference in mean change from baseline • **Handling of ICEs:** Same as primary method for primary endpoint			
Objective	**Population**	**Endpoints**	**Population Summary Measure**	**Strategy for Intercurrent Events**
Safety				
To assess the safety of BFF MDI 320/9.6 µg relative to BD MDI, Symbicort TBH, and BFF MDI 160/9.6 µg.	Participants with inadequately controlled asthma (symptomatic on medium dose ICS or ICS/LABA)	AEs	Percentage and risk difference in exposure-adjusted incidence rate per 100 patient-years (for selected event types)	AEs will be analyzed by study/treatment periods defined in the SAP
		Vital signs	Mean absolute value and mean change from baseline	Only on-treatment observations will be analyzed
		Clinical laboratory values	Mean absolute value and mean change from baseline	Only on-treatment observations will be analyzed

Tertiary/Exploratory				
To further assess the effect of BFF MDI 320/9.6 µg relative to BD MDI 320 µg on lung function, symptoms, PROs, and asthma exacerbations.	Participants with inadequately controlled asthma (symptomatic on medium dose ICS or ICS/LABA)	Percentage of rescue-free days (24-hour period without rescue medication use)	Difference in mean percentage	While on Treatment – Data after any ICE will not be used
		Percentage of symptom-free days (24-hour period without symptoms)	Difference in mean percentage	While on Treatment – Data after any ICE will not be used
		Peak change from baseline in FEV_1 at each visit	Mean difference	While on Treatment – Data after any ICE will not be used
		Time to peak FEV_1 on Day 1	Mean difference	While on Treatment – Data after any ICE will not be used
		Change from baseline in FVC, PEF, and FEF_{25-75} evaluated using AUC_{0-3}	Difference in mean change from baseline	While on Treatment – Data after any ICE will not be used
		Change from baseline in morning pre-dose trough PEF	Difference in mean change from baseline	While on Treatment – Data after any ICE will not be used
		Change from baseline in evening pre-dose PEF	Difference in mean change from baseline	While on Treatment – Data after any ICE will not be used
		Percentage of responders in ACQ-6 (≥ 0.5 decrease equals response)	Odds Ratio	Primary approach for handling ICEs: As for ACQ-7

		Change from baseline in ACQ-5, ACQ-6, ACQ-7 and AQLQ(s)+12	Difference in mean change from baseline	Primary approach for handling ICEs: As for primary endpoint
		Moderate/severe asthma exacerbation	Incidence/annualized rate	While on Treatment – Data after any ICE will not be used
		Severe asthma exacerbation	Incidence/annualized rate	While on Treatment – Data after any ICE will not be used
		Time to severe asthma exacerbation in the combined data from Studies D5982C00005 and D5982C00006 (BFF MDI 320/9 µg or 160/9.6 µg relative to BD MDI)	Hazard ratio	While on Treatment – Data after any ICE will not be used
		Time to first CCI	Hazard ratio	While on Treatment – Data after any ICE will not be used
		Time to first CCI	Hazard ratio	While on Treatment – Data after any ICE will not be used
		Rate of CCI events	Rate Ratio	While on Treatment – Data after any ICE will not be used

		Change from baseline in EQ-5D Questionnaire index score and VAS Questionnaire score	Difference in mean change from baseline	While on Treatment – Data after any ICE will not be used
		The percentage of participant's categorical responses to each of the 5-dimensions in EQ-5D	Percentage	While on Treatment – Data after any ICE will not be used
		AIRQ	Mean value and mean change from baseline	While on Treatment – Data after any ICE will not be used
		AIRQ percentage of participants that are well-controlled, not-well controlled, and very poorly controlled	Percentage	While on Treatment – Data after any ICE will not be used
		Percentage of peak FEV_1 improvement achieved at 5 minutes on Day 1	Percentage	While on Treatment – Data after any ICE will not be used
To evaluate dose response by comparing BFF MDI 320/9.6 µg to BFF MDI 160/9.6 µg on lung function, exacerbations symptoms, and PROs.	Participants with inadequately controlled asthma (symptomatic on medium dose ICS or ICS/LABA)	Same estimands as for the comparison of BFF MDI 320/9.6 µg vs BD MDI 320 µg for primary, secondary, tertiary endpoints.		

Healthcare Resource Utilization Objective				
To assess the overall and asthma-specific Healthcare Resource Utilization of BFF MDI relative to BD MDI.	Participants with inadequately controlled asthma (symptomatic on medium dose ICS or ICS/LABA)	Percentage of participants with ER visits	Percentage	While on Treatment – Data after any ICE will not be used
		Number of visits to ERs per patient-year	Mean Annualized Rate	While on Treatment – Data after any ICE will not be used
		Percentage of participants hospitalized	Percentage	While on Treatment – Data after any ICE will not be used
		Number of participant hospitalizations per patient-year	Mean Annualized Rate	While on Treatment – Data after any ICE will not be used
		Number of days in the hospital per patient-year	Mean Annualized Rate	While on Treatment – Data after any ICE will not be used

[a] Refers to submission strategy with respect to Health Authority responsible for reviewing marketing authorization, not the recruitment location/nationality of the patients.

[ab] For details, refer to Section 3.3.1.2

3.3.4.1 Primary method for handling ICEs

This estimand strategy answers 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 new asthma medication is taken in conjunction with premature discontinuation of randomized study intervention (which will be considered an unfavourable outcome).

For the primary strategy for handling ICEs, data following initiation of new asthma therapy or administration of prohibited medication thought to impact efficacy following first dose of randomised IP in conjunction with premature discontinuation of randomised study intervention will be imputed as treatment failure (with a poor score) at all scheduled visits up to planned last treatment period visit date. Data on the same date of this ICE will be assumed to be after the ICE and will be imputed. The planned treatment period is from the date of first dose of randomized IP to the latest date of the planned last asthma status assessment or planned last visit (treatment period) (for exacerbations +1 day).

For all other ICEs, a treatment policy strategy will be applied, where all available data will be utilized in the analysis irrespective of the ICE.

The analysis of the estimands applying this primary strategy approach to ICEs will be conducted in the Efficacy set.

3.3.4.2 While on Treatment

This estimand strategy answers 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.

The analyses for the estimands applying a While on Treatment approach to ICEs will be conducted using the Efficacy set and only data obtained from the first dose of randomized IP until the day prior to the occurrence of first ICE (for exacerbations this will be the day after the occurrence of the ICE) will be utilized. For participants that complete the planned treatment period in the absence of an ICE, data until the date of last dose (for exacerbations this will be last dose date + 1 day) will be utilized.

3.3.4.3 Composite Strategy for Binary Endpoints

This estimand ICE strategy answers the clinical question of what the treatment effect is comparing the proportions of participants able to both complete the study treatment and achieve an adequate response without the use of an additional treatment.

Analyses of the estimands applying this ICE strategy will use the Efficacy set. All observed data from the date of first dose of randomized IP until the day prior to the first occurrence of an ICE will be utilized, and from the day of an ICE non-responder imputation will be

utilized. However, data following IP discontinuation for reasons related to global/country situation will be considered missing and will not be imputed.

For participants that complete the planned treatment in the absence of an ICE, data until the date of last dose will be utilized.

3.3.4.4 Principal Stratum

This estimand ICE strategy answers the question of what the treatment effect is on participants who would 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).

Analyses of the estimands applying this ICE strategy will use the observed treatment difference estimator in the PP set, and this will be used for all NI analysis. All data from and including the day of the first occurrence of an ICE/IPD impacting efficacy will not be included in the analyses.

For participants that complete the planned treatment in the absence of an ICE/IPD impacting efficacy, data until the date of last dose will be utilized.

3.3.5 Visit Windows

For post-randomization visit based analyses, the variables are summarized based on data from scheduled or repeat visits (including premature treatment discontinuation visits) by mapping the visit date to an adjusted analysis-defined visit window irrespective of the visits' label numbering. The adjusted analysis-defined windows are summarized in Table 3, Table 4 and Table 5, where study day is defined in Appendix 8.

Table 3 Visit windows for efficacy measurement other than AIRQ

Adjusted Defined Windows Visit	Scheduled Study Day	Maximum Windows
Baseline	1	Study Day ≤1
Week 4	29	2≤ Study Day ≤56
Week 12	85	57≤ Study Days ≤112
Week 20	141	113≤ Study Day ≤154
Week 24	169	155≤ Study Day ≤182

Table 4 Visit windows for AIRQ

Adjusted Defined Windows Visit	Scheduled Study Day	Maximum Windows
Baseline/Day 1	1	Study Day ≤1
Week 12	85	43≤ Study Day ≤126
Week 24	169	127≤ Study Days ≤182

Table 5 Visit windows for Laboratory Assessments, Height/Weight, Vital Signs and Physical Examination

Adjusted Defined Windows Visit	Scheduled Study Day	Maximum Windows
Baseline	1	Study Day ≤1
Week 24	169	127≤ Study Day ≤182

If multiple assessments are recorded within a single adjusted visit window, the following rules will be applied. These rules will not be applied for the baseline definitions described in Section 3.3.1.1.

- If there are observations from 2 or more visits within the same window, then the non-missing set of observations from the visit closest to the scheduled visit will be used in the analysis. However, for spirometry assessments, if the target day visit has pre- and post- dose assessments per Table of Activities (Table 1 in CSP) and Timing of In-Clinic Spirometry Measurement (Table 2 in CSP), then the closest scheduled or repeat visit that also has pre- and post- dose assessments collected will be chosen.
- If there are observations from 2 or more visits that are equidistant from the scheduled visit, then the non-missing set of observations with the earliest collection date will be used in the analysis. However, for spirometry assessments, if the target day visit has pre- and post- dose assessments per Table of Schedule of Activities (Table 1 in CSP) and Timing of In-Clinic Spirometry Measurement Table (Table 2 in CSP), then the earliest scheduled or repeat visit that also has pre- and post- dose assessments collected will be chosen.
- If 2 observations are collected on the same day then the observation with the earliest collection time will be included in the analysis, unless the observations are dependent on study time window (e.g. FEV_1, onset of action), then the observation with the best value within the respective time window (as defined in Table 6) will be used.

- Scheduled or repeated visits, including premature discontinuation visits will be mapped to an adjusted analysis-defined visit window irrespective of the ICEs

estimand strategy for analysis. However, if the date of an observation (irrespective of its mapped window) falls after the date of an ICE, that observation may be ignored for some estimand strategies as described in Section 3.3.4.

For the analyses of change from baseline in trough FEV_1, onset of action on Day 1 and change from baseline in FEV_1 at each timepoint at Day 1 as well as relevant descriptive statistics by pre- and post-dose time points, the FEV_1 observations will be allocated to derived nominal collection time windows using the time intervals specified for each in Table 6.

If there are multiple spirometry values for the same parameter within the same post-baseline study time window on the same day, the best value will be chosen for analysis.

Table 6 Analysis Study Time Windows for Spirometry Assessments

Calculated Study Time Window	Time Interval for the Study Time Window
Pre-dose 60 min.	≥ 45 minutes prior to dose
Pre-dose 30 min.	≥ 0 to < 45 minutes prior to dose
Post-dose 5 min.[a]	> 3 to 10 min. post-dose
Post-dose 15 min.	11 to 22 min. post-dose
Post-dose 30 min.	23 to 44 min. post-dose
Post-dose 1 hr.	45 to 89 min. post-dose
Post-dose 2 hrs.	90 to 149 min. post-dose
Post-dose 3 hrs.	150 min. to <4.5 hrs. post-dose

[a] Visit 4 only.
Note: If the recorded spirometry time in seconds is between 1 second and 29 seconds, then the spirometry time is first rounded down to the nearest whole minute for the purpose of calculating the time window. This is done because the dose time is recorded only to the nearest minute, whereas the spirometry time is recorded to the nearest second. The minutes are rounded to the nearest whole number before applying time windows.

Four-week intervals will be defined by study day as specified in Table 7. Study day is defined in Appendix 8.1. This will be applied for efficacy endpoints collected on a daily basis (e.g. rescue medication use in puffs/day, morning and evening PEF). The daily data for each participant will be averaged over the respective interval.

Table 7 Definition of 4-Week Intervals

Interval	Time Period
Daily	
1	Day 1 (post dose i.e. PM) to Day 28 PM
2	Day 29 AM to Day 56 PM
3	Day 57 AM to Day 84 PM
4	Day 85 AM to Day 112 PM
5	Day 113 AM to Day 140 PM
6	Day 141 AM to Day 168 PM
Morning	
1	Day 2 AM to Day 28 AM
2	Day 29 AM to Day 56 AM
3	Day 57 AM to Day 84 AM
4	Day 85 AM to Day 112 AM
5	Day 113 AM to Day 140 AM
6	Day 141 AM to Day 168 AM
Evening	
1	Day 1 PM to Day 28 PM
2	Day 29 PM to Day 56 PM
3	Day 57 PM to Day 84 PM
4	Day 85 PM to Day 112 PM
5	Day 113 PM to Day 140 PM
6	Day 141 PM to Day 168 PM

3.3.6 Handling of Unscheduled Visits

Data from unscheduled visits will not be used for by-visit summaries. Any data collected from unscheduled or repeat visits will be used for baseline definitions, for any definitions of maximum value, minimum value or last value, for the end-of-treatment summary, for shift tables and for determining incidence of clinically significant values.

3.3.7 Multiplicity/Multiple Comparisons

All comparisons will be tested for superiority with the exception of the additional NI comparisons for CCI Health Authority (BFF MDI 320/9.6 µg vs Symbicort TBH). Due to variation in the registrational requirements across regions, the multiple testing procedure will be different depending on the region. The change from baseline in FEV_1 AUC_{0-3} will be the primary endpoint for CCI and a 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 CCI and a key secondary endpoint for CCI For these repeated measures assessments, landmark comparisons will be provided for CCI and over time comparisons for CCI and CCI

3.3.7.1 CCI Approach

The type I error control procedure for CCI applies a sequential testing procedure described in Figure 1.

Figure 1 CCI

[a] The tests on change from baseline in puffs of rescue medication and the percentage of responder endpoints for ACQ-7, ACQ-5, AQLQ(s)-12 will be strongly controlled using a Hochberg procedure (Gou et al. 2014).

The procedure is applied to both this study, D5982C00006 (VATHOS), as well as Study D5982C00005 (LITHOS) in order to allow data from both studies to be combined for analyses of severe exacerbation rate, thus utilizing data from higher numbers of participants to support that endpoint. The analyses in Study D5982C00005 will be comparing BFF MDI 160/9.6 µg BID to BD 160 µg MDI BID at Week 12 (except for testing onset of action, where the timepoint of interest is at the 5-minute post-dose timepoint on Day 1, as well as

the analyses on change from baseline in puffs of rescue medication and severe exacerbation rate, where the evaluation is made over the duration of the study). The analyses in this study, D5982C00006, will be comparing BFF MDI 320/9.6 µg BID to BD 320 µg MDI BID at Week 24 (except for testing onset of action, where the timepoint of interest is at the 5-minute post-dose timepoint on Day 1, as well as the analyses on change from baseline in puffs of rescue medication and severe exacerbation rate, where the evaluation is made over the duration of the study).

The procedure starts by testing the primary endpoint, change from baseline in FEV_1 AUC_{0-3} within each of the 2 studies (Study D5982C00005 and Study D5982C00006). If the result is statistically significant (alpha = 0.05, two-sided) within a study, the key secondary endpoint, change from baseline in trough FEV_1 will be tested at two-sided alpha of 0.05 for that study. If the result is statistically significant within that study, the onset of action on Day 1 will be tested at alpha = 0.05 (two-sided) for that study.

If the test for onset of action on Day 1 is statistically significant within a study, 0.025 alpha (two-sided) will be allocated from that study to testing the pooled severe exacerbation rate, and the remaining 0.025 alpha (two-sided) will be allocated to testing the secondary endpoints: change from baseline in puffs of rescue medication, the percentage of responder endpoints for ACQ-7, ACQ-5, AQLQ(s)-12, using individual study data. Those endpoints will be simultaneously tested (alpha=0.025, two-sided) with a Hochberg procedure [Gou et al 2014].

Therefore, if the test for onset of action on Day 1 is statistically significant in both studies, the pooled severe exacerbation rate will be tested at alpha = 0.05 (two-sided). If the test for the pooled severe exacerbation rate is statistically significant, additional 0.025 alpha (two-sided) will be allocated to testing the secondary endpoints for each study: change from baseline in puffs of rescue medication, the percentage of responder endpoints for ACQ-7, ACQ-5, AQLQ(s)-12. Those endpoints will be simultaneously tested (alpha=0.05, two-sided) with a Hochberg procedure [Gou et al 2014].

Otherwise, if the test for onset of action on Day 1 is statistically significant in only one study, the pooled severe exacerbation rate will be tested at alpha = 0.025 (two-sided). If the test for the pooled severe exacerbation rate is statistically significant, additional 0.025 alpha (two-sided) will be allocated to testing the secondary endpoints for the respective study (for which onset of action was statistically significant): change from baseline in puffs of rescue medication, the percentage of responder endpoints for ACQ-7, ACQ-5, AQLQ(s)-12. Those endpoints will be simultaneously tested (alpha=0.05, two-sided) with a Hochberg procedure [Gou et al 2014].

If all endpoints tested within the Hochberg procedure are statistically significant within a study, the severe exacerbation rate will be tested using individual study data for that study.

In addition, comparisons of BFF MDI 320/9.6 µg versus BFF MDI 160/9.6 µg will be conducted to evaluate a numeric trend supporting an increased dose effect. Comparisons including BFF MDI 160/9.6 µg are not inferential and as such, are not part of the procedure to control Type I error.

3.3.7.2 CCI

The type I error control procedure for CCI applies a sequential testing procedure described in Figure 2.

Figure 2 CCI

CCI

[redacted]

[a] The tests on change from baseline in puffs of rescue medication and the percentage of responder endpoints for ACQ-7, ACQ-5, AQLQ(s)-12 will be strongly controlled using a Hochberg procedure (Gou et al. 2014).

The type I error will be strongly controlled across the primary and secondary endpoints of BFF MDI 320/9.6 µg versus BD MDI 320 µg (alpha = 0.05, two-sided), using the primary strategy for handling ICEs. The procedure will test the primary, change from baseline in trough FEV_1, and key secondary, FEV_1 AUC_{0-3}, endpoints over 24 weeks in sequential order. If the result is statistically significant (alpha = 0.05, two-sided) for the primary and

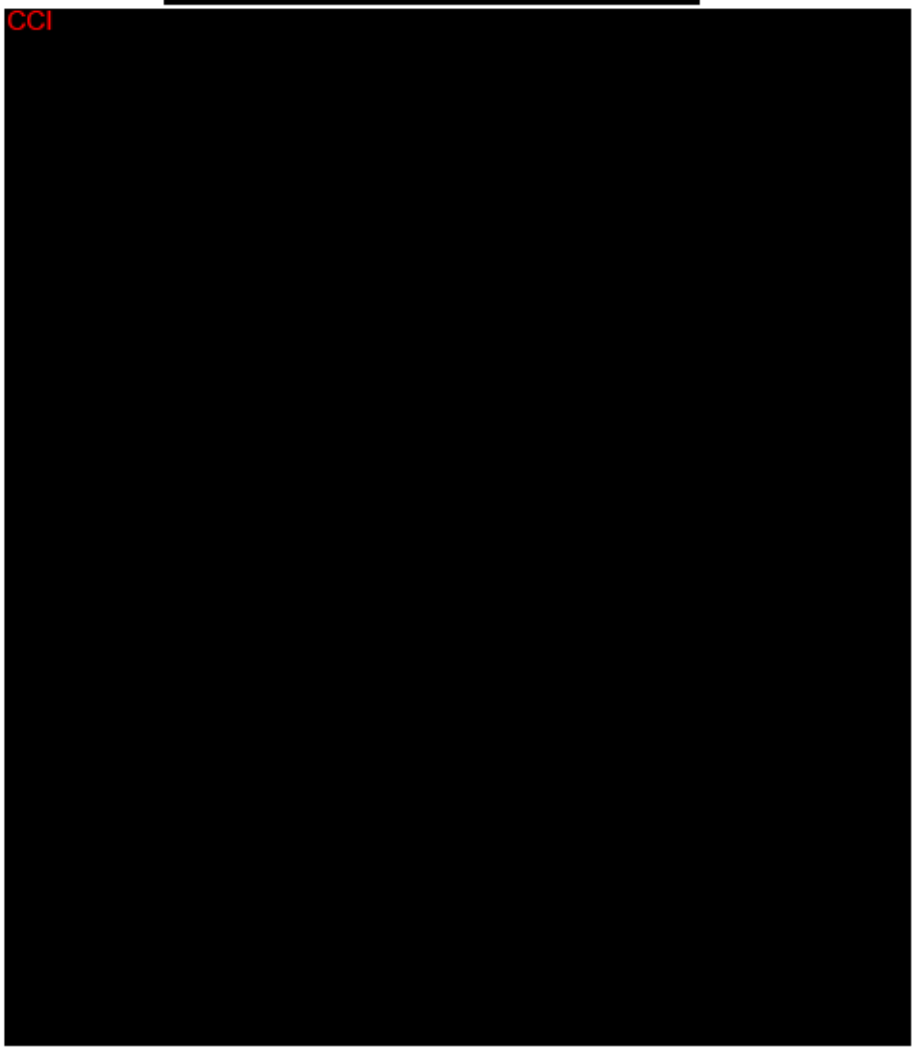
key secondary endpoint, the onset of action on Day 1 will be tested by comparing BFF MDI 320/9.6 µg vs BD MDI 320 µg (alpha=0.05 two-sided). If that test is statistically significant, the remaining secondary endpoints (change from baseline in puffs of rescue medication, the percentage of responder endpoints for ACQ-7, ACQ-5 and AQLQ(s)-12) will be simultaneously tested (alpha=0.05, two-sided) with a Hochberg procedure (Gou et al 2014).

In addition, comparisons of BFF MDI 320/9.6 µg versus BFF MDI 160/9.6 µg will be conducted to evaluate a numeric trend supporting an increased dose effect. Comparisons including BFF MDI 160/9.6 µg are not inferential and as such, are not part of the procedure to control type I error.

3.3.7.3 CCI Approach

The type I error control procedure for CCI applies a sequential testing procedure described in Figure 3.

Figure 3 CCI



[a] The tests on change from baseline in puffs of rescue medication and the percentage of responder endpoints for ACQ-7, ACQ-5, AQLQ(s)-12 will be strongly controlled using a Hochberg procedure (Gou et al. 2014).

[b] NI of FEV_1 AUC_{0-3} will not be subject to type I error control as the objective is to show numerical similarity.

Strong control of the Type I error rate will be maintained at the two-sided 0.05 level for the primary endpoint, change from baseline in trough FEV_1 over 12 to 24 weeks, across treatment comparisons using a sequential approach as detailed below. The Type I error control will be strongly controlled to test the primary and secondary endpoints within each treatment comparison.

The superiority comparison of BFF MDI 320/9.6 µg versus BD MDI 320 µg for the primary endpoint, change from baseline in trough FEV_1, will be conducted first in order to demonstrate assay sensitivity. If this comparison is statistically significant (alpha = 0.05,

two-sided), the non-inferiority comparison of BFF MDI 320/9.6 µg versus Symbicort TBH for change from baseline in trough FEV_1 will be conducted, using the Principal Stratum estimand strategy for ICEs. If this comparison statistically excludes (alpha = 0.025, one-sided) the non-inferiority margin of CCI mL, then the procedure will proceed to testing of the secondary endpoints for superiority.

Within the comparisons of BFF MDI 320/9.6 µg versus BD MDI 320 µg, the key secondary endpoint, change from baseline in FEV_1 AUC_{0-3} over 12 to 24 weeks will be tested next. If the result is statistically significant (alpha = 0.05, two-sided) for the key secondary endpoint, FEV_1 AUC_{0-3}, the remaining secondary endpoints will be simultaneously tested (alpha=0.05, two-sided) for the BFF MDI 320/9.6 µg versus BD MDI 320 µg comparison using a Hochberg-type procedure [Gou et al 2014].

The NI comparison of BFF MDI 320/9.6 µg versus Symbicort TBH for change from baseline in FEV_1 AUC_{0-3} will be conducted outside of the MTP with no type I error control applied, since the objective is to evaluate numerical similarity only.

3.3.8 Handling of Protocol Deviations in Study Analysis

IPDs, including those related to global/country situation (i.e., epidemic/pandemic, healthcare crisis, natural disaster etc.) will be tabulated in the Clinical Study Report (CSR) for randomized participants (not screening failures). In addition, a listing of all IPDs will be provided. IPDs are defined as PDs which may significantly affect the completeness, accuracy and/or reliability of the study data, or which may significantly affect a participant's rights, safety or well-being. Important PDs in this trial will be grouped under one of the following categories:

- Inclusion criteria deviation
- Exclusion criteria deviation
- Discontinuation Criteria for study product met but participant not withdrawn from study intervention
- Discontinuation Criteria for overall study withdrawal met but patient not withdrawn from study
- IP deviation
- Excluded medications taken
- Deviations related to study procedure
- Other Important Protocol Deviations

4 STATISTICAL ANALYSIS

This section provides information on definitions, derivation and analysis/data presentation per domain.

All safety and efficacy parameters will be summarized by treatment unless specified otherwise.

Continuous variables will be summarized with descriptive statistics: the number of non-missing values, mean, standard deviation (SD), median, minimum, and maximum. Additionally, the 25th and 75th percentiles will be presented when appropriate based on historical knowledge of the normality or non-normality of the distribution of underlying data.

Categorical variables will be summarized with frequency counts and percentages (where appropriate).

Outputs may also be produced by region and/or country for regional submissions.

4.1 Study Population

The term study population covers subject disposition and treatment vs study completion status, analysis sets, IPDs, demographics, baseline characteristics, disease characteristics, medical and surgical history, prior, concomitant and post-treatment medications, and study intervention compliance.

4.1.1 Subject Disposition and Completion Status

4.1.1.1 Definitions and Derivations

Subject disposition will be summarized using all participants in the screened set. The number and percentage of participants within each treatment group will be presented by the following categories: screened, screen failures (and reason), randomized (GCP breach identified), randomized (excluding GCP breach), randomized but not treated (and reason), started treatment, completed treatment, discontinued treatment early (and reason, for participants who consented to stay on study and participants who did not consent to stay on study), completed study (participants who completed IP and study, and participants who discontinued IP but completed study assessments), and withdrawn from study. Disposition summaries will also be produced for the age subgroups at study entry: adults (≥18) and adolescents (≥ 12 to <18).

Randomization is stratified by baseline asthma treatment (ICS versus ICS/LABA) and age (≥ 12 to < 18 years of age versus ≥ 18 years of age). The factor baseline asthma treatment will use the IRS data.

Participant recruitment by region, country and site will also be summarized by treatment group. The following regions are defined: US & Canada, Asia, and Europe (EU). If there are too few participants within a group, then the groups may be further collapsed.

4.1.1.2 Presentation

A disposition table for all participants will be provided. Disposition table by age subgroups (adults and adolescents) will also be provided. The numbers of participants randomized will also be summarized by region, country, site, and treatment. A table will be presented of the mis-stratification between IRS and eCRF data.

4.1.2 Analysis Sets

4.1.2.1 Definitions and Derivations

Analysis sets will be summarized by treatment group for participants randomized. The number of participants included or excluded (and reason) from an analysis set within each treatment group will be presented for the following analysis sets: Efficacy, PP and Safety.

The following reasons for exclusion from the respective sets are defined.

- For the Efficacy and Safety sets:
  - Participant did not receive randomized study intervention.
- For the PP set, the first condition met according to the following priority order will be defined as the reason for exclusion:
  - Participant did not receive randomized study intervention.
  - Participant had an IPD impacting efficacy at randomization.

4.1.2.2 Presentation

A summary of all analysis sets will be provided. Participants excluded from any analysis set will be listed. A separate listing will be presented for participants excluded from analysis due to a serious breach in GCP.

4.1.3 Protocol Deviations

4.1.3.1 Definitions and Derivations

IPD categories are specified in Section 3.3.8 and will be identified and documented by the study team prior to unblinding of the trial at the primary clinical data lock. As far as possible, the occurrence of important PDs will be monitored (blinded) during the trial, with the emphasis on their future prevention.

The study PDs Plan outlines the management of IPDs and includes the proposed specific categories of IPDs in this trial. Any PDs not defined as important will not be reported or discussed in the CSR.

4.1.3.2 Presentation

The number and percentage of participants for each IPD will be presented by randomized treatment for all participants randomized. Participants with IPDs will also be listed.

4.1.4 Demographics

4.1.4.1 Definitions and Derivations

Demographic variables summarized will include the following:

- Age
- Age group (≥12 to <18, ≥18 to <65 and ≥65)
- Gender
- Race
- Ethnic group
- Country

4.1.4.2 Presentation

Demographics will be summarized for the Efficacy analysis set. Note demographics will be summarized for the Safety Set in the ISS.

4.1.5 Disease Characteristics

4.1.5.1 Definitions and Derivations

Disease background characteristic variables will be summarized and include the following:

- Baseline reversibility (mL) calculated as Post-Albuterol FEV_1 - Pre-Albuterol FEV_1 (participants randomized and dosed, using Visit 2 (V2) if non-missing and Visit 3 (V3) otherwise)
- Baseline reversibility (%) calculated as (Post-Albuterol FEV_1 - Pre-Albuterol FEV_1)/ Pre-Albuterol FEV_1 x100 (participants randomized and dosed, using V2 if non-missing and V3 otherwise)
- Baseline reversibility (>=20, <20) (participants randomized and dosed, using V2 if non-missing and V3 otherwise)
- Historical reversibility (ml) for participants randomized based on historical reversibility – includes only participants, who were randomized based on historical reversibility, i.e. they did not meet the inclusion criteria (IC) at V2 or V3

- Historical reversibility (%) for participants randomized based on historical reversibility – includes only participants, who were randomized based on historical reversibility, i.e. they did not meet the inclusion criteria (IC) at V2 or V3
- Reversibility at screening (ml) for participants randomized based on reversibility measurements at V2/V3 – includes only participants, who were randomized based on reversibility at V2 or V3 (participants may have also met historical reversibility)
- Reversibility at screening (%) for participants randomized based on reversibility measurements at V2/V3 – includes only participants, who were randomized based on reversibility at V2 or V3 (participants may have also met historical reversibility)
- Baseline severe asthma exacerbation history (0, ≥1) within the prior year.
- Baseline severe asthma exacerbation history within the prior year (numerical value)
- Baseline blood eosinophil count (cells per mm^3)
- Baseline blood eosinophil count (cells per mm^3) (<150, >=150 to < 300, >=300)
- Baseline pre-bronchodilator percent predicted FEV_1 (%)
- Baseline pre-bronchodilator FEV_1 (L)
- Prior asthma medication (ICS, ICS/LABA)
- Smoking status (former smoker, never smoker)
- Number of Pack Years Smoked
- PEF stability limit at Visit 4 (L/min)

Characterization of Reversibility:
Reversibility to albuterol will be evaluated for participant qualification and characterization purposes. The reversibility criteria must be met at Visit 2 or Visit 3 in participants without evidence of historical reversibility in the 12 months prior to Visit 1. If there is evidence of historical reversibility in the 12 months prior to visit 1 or reversibility criteria are met at Visit 2, reversibility testing will not be repeated at Visit 3. If reversibility criteria are not met in the 12 months prior to Visit 1 or at Visit 2, participants may continue to Visit 3 and repeat reversibility testing, and results from Visit 3 will be reported.

Reversibility will be a comparison of the average best FEV_1 effort obtained at 60 and 30 minutes (or the observed result if only one of the timepoints is completed) prior to administration of albuterol compared to the best FEV_1 effort obtained at 30 minutes (or up to 60 minutes, if repeated and a higher best effort was recorded) post 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%.

Baseline reversibility will use the measurements taken at Visit 2 irrespective if the reversibility criteria were met or not. If the Visit 2 value is missing, then the Visit 3 value will be used.

PEF Stability Limit:
At Visit 4, a PEF baseline will be calculated to define a stability limit. The stability limit is defined as the average of the available morning PEF eDiary recordings during the last 7 days before Visit 4 (i.e., the baseline PEF), multiplied by 0.8.

4.1.5.2 Presentation

Baseline disease characteristics will be summarized for the Efficacy set and will also be summarized by subgroups adult (≥ 18 years) and adolescents (≥12 to <18 years) using the Efficacy set.

4.1.6 Medical and Surgical History

4.1.6.1 Definitions and Derivations

Medical and surgical history will be collected at Visit 1. Events that occurred before the enrolment or were ongoing at enrolment should be captured and presented as medical and surgical history.

Asthma characteristics at study entry will be recorded on a separate respiratory disease history electronic Case Report Form (eCRF) page. Variables summarized from this asthma history eCRF page will include the following:

- Time to randomization since asthma diagnosis (years)
- Time to randomization since asthma symptoms started (years)
- Time to Visit 1 since most recent severe exacerbation (years)
- Most recent severe exacerbation was within 12 months prior to Visit 1 (Yes, No)
- Number of severe exacerbations in 12 Months prior to Visit 1
- Allergies (None, Respiratory allergies, non-Respiratory allergies, Respiratory and non-respiratory allergies)
- Nasal polyps (Yes, No)

4.1.6.2 Presentation

For medical and surgical history, the number and percentage of participants will be tabulated by treatment group, for each Medical Dictionary for Regulatory Activities (MedDRA) primary system organ class (SOC), and for each MedDRA preferred term (PT) within a SOC for the Efficacy set.

Medical history related to asthma will be summarized for the Efficacy set.

4.1.7 Prior, Concomitant and Post-Treatment Medications

4.1.7.1 Definitions and Derivations

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 will be recorded in the Prior and Concomitant Medications eCRF page.

Coding: Verbatim medication/treatment terms will be coded and assigned a PT and an ATC (anatomic therapeutic class) term using the latest version of the World Health Organization Drug Dictionary (WHO-DD) available at the time of clinical data lock.

Multiple ATC assignments: If there are multiple ATC codes assigned to the same concomitant medication, the "primary" one based on medical evaluation will be used.

Prior medication is any medication taken prior to Visit 1, even if this medication continued to be taken on the day of the start of study intervention in the study or afterward.

Concomitant medication during screening period is any medication reported as being taken any time between Visit 1 and the date that is one day before first dose of randomized IP.

Concomitant medication during treatment period is any medication reported as being taken any time between the first dose of randomized IP and the date that is one day before the date of discontinuation from or completion of study intervention.

Post-Treatment medication is any medication that was used at any time on or after the day of treatment completion or treatment discontinuation.

Any medication which cannot be identified as Prior, Concomitant, or Post-Treatment will be considered as being in each of the categories that are possible from the available information.

A separate table will be presented for participants who took disallowed concomitant medications. Disallowed medications include medications defined as prohibited according to Section 6.5.4 of the CSP. They will be defined following a physician review (prior to primary clinical data lock) of the unique combinations of ATC code classifications and generic terms captured.

4.1.7.2 Presentation

Prior (within 12 months prior to Visit 1) asthma related treatment will be tabulated for the Efficacy set by categories: ICS; ICS+LABA; ICS+LABA+Other Controller (LAMA);

ICS+LABA+Other Controller (LTRA); ICS+LABA+Other Controller (OCS); ICS+LABA+Other Controller (LAMA+LTRA); ICS+LABA+Other Controller (LAMA+OCS); ICS+LABA+Other Controller (LTRA+OCS); ICS+LABA+Other Controller (LAMA+LTRA+OCS). Subjects are classified in the category corresponding to all medications taken throughout the past 12 months prior to visit 1 even if they have not been taken simultaneously (only the combination ICS/LABA is required to be taken simultaneously).

The number and percentage of participants receiving each medication (by ATC classification system codes and generic name) will be presented by treatment for the Efficacy Set. Separate tables will be presented for all medications received during each of the following periods: Prior, Concomitant (screening period), Concomitant (treatment period).

The number and percentage of participants receiving disallowed concomitant medication (by ATC classification system codes and generic term) will also be presented by treatment for the Efficacy Set.

4.1.8 Baseline Characteristics

4.1.8.1 Definitions and Derivations

Baseline characteristic variables summarized will include the following:

- Weight (kg)
- Height (cm)
- Body Mass Index (BMI) (kg/m²), calculated as Weight (kg) / [Height (m)]^2

Weight/Height/BMI:

Weight, height and BMI will be summarized by age group (≥12 to <18, ≥18).

4.1.8.2 Presentation

Baseline characteristics will be summarized for the Efficacy set.

4.1.9 Study intervention Compliance

4.1.9.1 Definitions and Derivations

Percent compliance with study intervention is defined as (total number of puffs of study intervention taken on a study day/total expected puffs taken on a study day) averaged across all days of a participant's dosing between start day of study intervention and last day on study intervention x 100. The actual total number of puffs will be calculated using the data collected from eDiary.

The expected number of puffs for a test day which is the last date of treatment will be 2, and the expected number of puffs for the last date of treatment which is not a test day will be 4 when an evening dose is taken but will be 2 otherwise; the expected number of puffs on dates prior to the last date of treatment will be 4.

4.1.9.2 Presentation

Descriptive statistics for percent compliance with study intervention will be summarized for the efficacy set and study intervention compliance will be categorized into different groups depending on the degree of compliance: $0 - < 20\%$, $\geq 20 - < 40\%$, $\geq 40 - < 60\%$, $\geq 60 - < 80\%$, $\geq 80 - \leq 100\%$, $> 100 - \leq 120\%$, and $> 120\%$ for the Efficacy Set.

Exposure to IP will be listed.

4.2 Endpoint Analyses

All details related to the endpoint analyses such as primary, secondary, exploratory endpoints including sensitivity and supportive analyses are summarized in Table 2.

4.2.1 Primary Endpoint

Analyses for the primary endpoint are presented in this section.

4.2.1.1 Definition

The primary endpoint is different across different regions. For CCI Change from Baseline in FEV_1 AUC_{0-3} at week 24 is the primary endpoint. For CCI , Change from Baseline in morning pre-dose trough FEV_1 over 24 weeks is the primary endpoint. For CCI Change from Baseline in Morning Pre-dose Trough FEV_1 over 12 to 24 weeks is the primary endpoint.

Treatment comparisons and estimand strategy for handling ICEs are specified in Section 3.3.2.

4.2.1.2 Derivations

The FEV_1 AUC_{0-3} will be calculated for the changes from baseline using the trapezoidal rule and will be normalized into a time weighted average by dividing by the time (in hours) from dosing to the last spirometry measurement occurring within 4.5 hours post-dose i.e., the upper limit of the "post-dose 3 hours" analysis defined time window (the last measure is expected to typically be at 3 hours post-dose). The value at time 0 will be the change from baseline in morning pre-dose trough at the respective visit. 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 (nominal) time will be used.

Change from baseline in morning pre-dose trough FEV_1 at each visit is defined as the mean of the 60- and 30-minute pre-dose values minus baseline. In participants missing either of these pre-dose assessments, the value will be calculated from the single measurement. In participants missing both pre-dose values, morning pre-dose trough FEV_1 at that visit will not be calculated.

For the primary strategy for handling ICEs, data following IP discontinuation in conjunction with new medication will be imputed with the minimum FEV_1 value of 12% decrease from the participant's baseline and the participant's worst observed value post-baseline during the study (scheduled or repeat measure).

4.2.1.3 Handling of Dropouts and Missing Data

Intermittent missing data will not be imputed and will be handled through the analysis model.

Missing data not handled by the imputation following the initiation of new asthma therapy or administration of prohibited medications thought to impact efficacy in conjunction with premature discontinuation of study intervention will be assumed to be missing at random and will not be imputed

4.2.1.4 Primary Analysis of Primary Endpoint

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 maintenance medication (ICS versus ICS/LABA), and treatment-by-visit interaction as categorical covariates and baseline trough FEV_1 and percent Albuterol reversibility (as defined in Section 4.1.5.1) as continuous covariates.

Unstructured covariance will be assumed to model the relationship between pairs of response variables taken at different visits on the same participant. To allow for the possibility that this model fails to converge with unstructured covariance, the following hierarchical approach is proposed to select a simpler covariance structure if the preceding covariance structure fails to converge: Unstructured -> Heterogeneous Toeplitz -> Toeplitz -> Compound Symmetry.

Before concluding non-convergence at any step of the hierarchy, an attempt will first be made to resolve convergence problems by using different starting values of the underlying algorithm and/or adjusting singularity options. The Kenward-Roger approximation to estimating the degrees of freedom will used for tests of fixed effects derived from this model.

A contrast will be used to obtain an estimate of the treatment difference at week 24 for CCI Two-sided p-values and point estimates with 95% Confidence Intervals (CIs) will be produced for the treatment difference. The two-sided p-values and point estimates with 95% Confidence Intervals (CIs) for other visits, over 12-24 weeks and over 24 weeks will also be reported.

Change from Baseline in Morning Pre-dose Trough FEV1 (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 an estimate of the treatment difference over 24 weeks for CCI and over 12 to 24 weeks for CCI Two-sided p-values and point estimates with

95% CIs will be produced for each treatment difference. The two-sided p-values and point estimates with 95% Confidence Intervals (CIs) for other visits will also be reported.

In addition, for CCI the NI analysis of the primary endpoint will utilize the Principal Stratum strategy to ICEs using the PP set for the comparison BFF MDI 320/9.6 µg vs Symbicort.

For this comparison, the null hypothesis for each pair-wise comparison will be that the lower 95% Confidence Interval (CI) of the mean treatment difference ($\lambda_{BFF320/9.6} - \lambda_{Symbicort}$) is less than or equal to the NI margin. The alternative hypothesis is that the lower 95% CI of the mean treatment difference is greater than the NI margin. The confidence interval will be two-sided with 95% confidence and p-values will reflect the test for NI and be one sided at 2.5%. As such significance in this test will correspond to the confidence interval being above the NI margin.

The assay sensitivity for NI is the superiority analysis comparing BFF MDI 320/9.6 µg vs BD MDI 320 µg.

4.2.1.5 Supportive Analyses of the Primary Endpoint

As supportive analyses, the primary endpoint will be analyzed using a While on Treatment strategy to ICEs.

4.2.1.6 Sensitivity Analyses of the Primary Endpoint

For the primary endpoint, sensitivity analyses will be conducted to evaluate the robustness of the analysis findings to missing data and assumptions. For the primary strategy for handling ICE, the analyses of FEV_1 AUC_{0-3} at Week 24 for CCI and morning pre-dose trough FEV_1 over 24 weeks for CCI and over 12-24 week for CCI uses a maximum likelihood based approach with a MAR assumption (Little and Rubin, 2002). In order to evaluate the robustness of the findings to this assumption, sensitivity analyses will be performed assuming all data beyond study withdrawal/ lost to follow up are missing not at random (MNAR) and a two-dimensional decrementing method will be applied. Missing values that have been replaced with imputed values as per the primary strategy for handling ICEs will not be tipped. These analyses will be performed only in case of a statistically significant result for the primary endpoint.

Tipping-point analyses will be conducted to examine the impact of varying the treatment mean for data following study withdrawal. Multiple imputation technique will be used to impute the missing data for these participants by varying the mean. For details, refer to Appendix 8.2.2.

4.2.1.7 Subgroup and Consistency Analysis of the Primary Endpoint

To explore the consistency of the overall treatment effect, subgroup analyses based on the primary analysis (primary strategy for handling ICE's) will be performed for the following factors:

- Region (Japan, Rest of World except Japan)
- Region (North America, Rest of World except Canada and US)
- Age with the following categories:
  - ≥12 and <18
  - ≥18 and <65
  - ≥65
- Baseline asthma treatment (ICS, ICS/LABA)
- Reversibility (≥20%, <20%)
- Sex (female, male)
- Race with the following categories:
  - Asian
  - Black or African American
  - White
  - Other (includes the following three categories recorded in eCRF: American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, and Other. Also includes participants where multiple race is specified.)
- Baseline severe asthma exacerbation history (0, ≥1)

To investigate the interaction effect between subgroup and treatment comparison BFF MDI 320/9.6 µg and BD MDI 320 µg for change from baseline in FEV_1 AUC_{0-3} ([CCI] primary endpoint) a similar model to the primary endpoint (Section 4.2.1.4) will be fitted overall (combined subgroup categories) and will also include subgroup, treatment by subgroup interaction, subgroup by visit interaction, treatment by subgroup by visit interaction. The 3-way interaction, treatment by subgroup by visit, means the 2-way interaction between treatment and subgroup varies across visits.

A contrast will be computed at Week 24 to test the interaction effect between treatment and subgroup. A two-sided P-value will be presented for the interaction effect of interest. Contrasts will be used to obtain estimates of the treatment effect at Week 24, over 24 weeks and over 12 to 24 weeks, within each subgroup category. Point estimates with two-sided P-value and 95% confidence interval (CI) will be produced for each treatment difference.

An unstructured (UN) correlation matrix will be used to model the variance-covariance structure. If this model fails to converge a similar process for the primary analysis will be used (Section 4.2.1.4). In the event of too small a sample size in the ≥ 12 to < 18 years

group this category may be removed from the model first if the model fails to converge. For small numbers in other subgroup categories, they may be removed or combined.

To investigate the interaction effect between subgroup and treatment for change from baseline in morning pre-dose trough FEV_1 (CCI primary endpoint) a similar model to the one used for FEV_1 AUC_{0-3} will be used. A contrast will be computed over 24 weeks for CCI and over 12-24 weeks for CCI to test the interaction effect between subgroup and treatment. A two-sided P-value will be presented for the interaction effect. Contrasts will be used to obtain estimates of the treatment effect at Week 24, over 24 weeks and over 12 to 24 weeks, within each subgroup category. Point estimates with two-sided P-value and 95% confidence interval (CI) will be produced for each treatment difference.

If a treatment group within a subgroup category has less than 10 participants, then model estimates will not be presented for that subgroup category. Descriptive statistics will be provided for the primary endpoint for adults and adolescents.

To further explore the treatment effect in the adolescent population, Bayesian borrowing from the adult population will be used and is described in Section 8.2.4.

A forest plot will be used to summarize the treatment effect estimates for the comparison of BFF MDI 320/9.6 µg and BD MDI 320 µg for the above subgroups and the overall result from the primary analysis.

4.2.2 Secondary Endpoint

4.2.2.1 Definition

Change from baseline in morning pre-dose trough FEV_1 at week 24 is the key secondary endpoint for the CCI For CCI, the secondary endpoint is change from baseline in FEV_1 AUC_{0-3} over 24 weeks. For CCI the key secondary endpoint is change from baseline in FEV_1 AUC_{0-3} over 12 to 24 weeks.

Treatment comparisons are different for different regions and are specified in Section 3.3.2.

4.2.2.2 Derivations

The derivations of secondary endpoint are described in Section 4.2.1.2.

4.2.2.3 Handling of Dropouts and Missing Data

Handling of dropouts and missing data is identical to the primary endpoint as specified in Section 4.2.1.3.

4.2.2.4 Primary Analysis of Secondary Endpoint

The primary analysis of the secondary endpoint will utilize the primary strategy for handling ICEs using the Efficacy Set. For details, refer to Section 4.2.1.4.

In addition, for CCI the NI analysis of the secondary endpoint will utilize the Principal Stratum strategy to ICEs using the PP set. For details, refer to Section 4.2.1.4.

4.2.2.5 Supplementary Analyses of the Secondary Endpoint

The same supportive estimand strategy to ICEs (i.e., While on Treatment) as specified in Section 4.2.1.5 will be utilized.

4.2.2.6 Sensitivity Analyses of the Secondary Endpoint

Sensitivity analyses will be performed for morning pre-dose trough FEV_1 at week 24. For details, refer to Section 4.2.1.6.

4.2.2.7 Subgroup and Consistency Analyses of the Secondary Endpoint

The subgroup analyses are similar as the subgroup analyses for the primary endpoint specified in Section 4.2.1.7.

To further explore the treatment effect in the adolescent population, Bayesian borrowing from the adult population will be used and is described in Section 8.2.4.

4.2.3 Other Secondary Endpoint: Rate of Severe Asthma Exacerbations (CCI

4.2.3.1 Definition

For definition details, refer to section 8.2.7 of the CSP.

4.2.3.2 Derivation

Onset and Duration of Asthma Exacerbation

For severe asthma exacerbations, the duration is defined by the duration of the prescribed treatment. 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.

- 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.

The start and end dates of asthma exacerbation will be recorded in eCRF. The duration is the end date minus the start date plus 1 day. 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 gap between ICS or systemic corticosteroid treatments, then separate exacerbations should be recorded in the eCRF.

For any severe asthma exacerbation, if the end date of the exacerbation is unknown, then the end date of the exacerbation will be assumed to be six days after the start date of the exacerbation, for a default duration of 7 days. If the end date of an asthma exacerbation is precisely known but the start date is unknown or only partially known, then the start date will be imputed assuming a 7-day duration, within the constraints of what is possible based on the partial date. If both the start and end dates are partially missing where the month and year are known, the earliest 7-day window that is consistent with the partial dates will be imputed. If only the year is known, the exacerbation will not be counted.

For the primary strategy for handling ICEs, data following new asthma medication in conjunction with premature IP discontinuation will be imputed. Subjects will be assumed to have an additional exacerbation prior to planned treatment completion. A subjects' time at risk will continue until their planned last visit. This imputation of event and additional time at risk will only occur if there is sufficient time for a participant to have this additional exacerbation, (e.g there would not be if they were having an exacerbation when the ICE occurred and the planned last visit date is within 7 days of this exacerbation). The additional exacerbation will be assumed to be severe and occur midway between the start of this ICE and the planned last visit date (or earliest time it could of occurred). The duration of the additional exacerbation will be 5 days, the following 7 days will also be removed from the time at risk (only if there is time for this prior to planned last visit date during treatment period).

4.2.3.3 Handling of Dropouts and Missing Data

Any remaining missing data will be assumed to be missing at random and will not be imputed.

4.2.3.4 Primary Analysis of Secondary Endpoint

The rates of severe asthma exacerbations will be analyzed using negative binomial regression in the D5982C00005 and D5982C00006 studies separately. The negative binomial model for each study will include treatment, baseline trough FEV_1, percent albuterol reversibility, baseline severe asthma exacerbation history ($0, \geq 1$), prior maintenance medication (ICS versus ICS/LABA), and region as covariates.

Furthermore, the rates of severe asthma exacerbations will be analyzed for the pooled individual participant data from both studies (D5982C00006: BFF 320/9.6 µg, BFF 160/9.6 µg, BD 320 µg. D5982C00005: BFF 160/9.6 µg, BD 160 µg treatment arms). The pooled analysis will use all available data (over the planned 12-week treatment period in D5982C00005 and over the 24 week treatment period for study D5982C00006) to maximize the amount of data included. For the pooled analysis a negative binomial additive model will be used with the same covariates, except it will also include study, and budesonide (1 if the budesonide dose is 320 µg, and 0 if the budesonide dose is 160 µg) and formoterol (1 if the formoterol dose is 9.6 µg, and 0 if no formoterol dose) instead of treatment as covariates. The comparison of interest is the formoterol effect. For the pooled analysis one dispersion parameter will be estimated. The covariate, region, will have the following categories in the analysis model: US & Canada, EU, and Asia.

The logarithm of the time at risk of experiencing a severe exacerbation will be used as an offset variable in the model.

For the individual studies and the pooled analysis, p-values and CIs will not be presented if the incidence of exacerbations is less than 10 per arm. The number of exacerbations, the percentage of participants who experience exacerbations, exacerbation rate per year, adjusted rate per year and rate ratios comparing treatments will be summarized.

For the asthma severe exacerbation analyses, if convergence is not attained in the initial analysis then covariates will be removed from the model one-by-one until convergence is attained, with the order of removal being: region, percent albuterol reversibility, prior maintenance medication, baseline trough FEV_1, and baseline severe asthma exacerbation history.

In general, time at risk is defined as follow-up time (defined differently for different estimands) minus the time when a participant is not at risk for a new event.

A participant is at risk for an exacerbation at any time during the follow-up time when the participant does not have an exacerbation, and also on the first date of an exacerbation. But the participant is not at risk of a new exacerbation during the remaining days of an exacerbation, and also not during the 7 days after an exacerbation (of equal or greater severity). Note that if an exacerbation ends later than the last follow-up date, then only the

portion of the exacerbation that is during the follow-up period will be taken into account. Hence the time at risk is derived as total follow-up time minus days of exacerbations (including 7 days after the exacerbations) during the follow-up time plus the number of exacerbations during the follow-up time (this last term accounts for the first day of the exacerbation).

For the primary strategy for handling ICEs, the follow-up time is defined as the time from first dose of randomized IP up to the last recorded date (of any asthma status assessment, last study visit in the planned treatment phase) for the participant. If a participant has a new asthma medication in conjunction with premature IP discontinuation, then the follow up time will be to the planned last visit date (treatment period).

For the While on Treatment estimand strategies, the follow-up time is until the day following the occurrence of first ICE, or until the day after last dosing date if no ICE occurred. The day after last dosing date should be included to account for any exacerbation that led to the discontinuation but started on the day after last dose.

Analyses will be conducted on the Efficacy analysis set utilizing the primary strategy for handling ICEs. The While on Treatment strategy for all ICEs will be utilized as a supportive strategy for the pooled analysis. Time at risk of an exacerbation is defined as follow-up time (defined differently for different estimand strategies) minus the time when a participant is not at risk for a new event.

4.2.4 Other Secondary Endpoint: Change from Baseline in the Mean Number of Puffs of Rescue Medication Use (puffs/day)

4.2.4.1 Definition

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".

4.2.4.2 Derivation

The mean daily number of puffs of rescue medication use will be calculated for each of the 4-week intervals during the 24-week Treatment Period. For every time period 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 where only the morning or evening is recorded for that day) with non-missing values.

For the primary strategy for handling ICEs, data following new asthma medication in conjunction with premature IP discontinuation will be imputed with the maximum of: participant's highest observed mean daily number of puffs of each 4-week interval, participant's baseline + 2 puffs.

4.2.4.3 Primary Analysis of Other Secondary Endpoint: Change from Baseline in Mean Number of Puffs of Rescue Medication

Analysis will be performed with the primary strategy for handling ICEs and While on Treatment estimand approach to ICEs will be supportive for the Efficacy set.

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 6), prior maintenance medication (ICS versus ICS/LABA), severe asthma exacerbations history (0, ≥1) and the treatment-by-4-week interval interaction as categorical covariates and baseline daily rescue albuterol use, baseline trough FEV_1, and percent albuterol reversibility as continuous covariates.

A similar hierarchical approach to the covariance structure will be used as for the primary. For details, refer to Section 4.2.1.4.

Contrasts will be used to obtain estimates of the treatment differences over 24 weeks and over 12 to 24 weeks. Two-sided p-values and point estimates with two-sided 95% CIs will be produced for each treatment difference.

4.2.5 Other Secondary Endpoints: Percentage of Responders

4.2.5.1 Definition

The Asthma Control Questionnaire (ACQ) is completed in the clinic and requires participants to recall how their asthma has been during the previous week (7 days) prior to the study visit by responding to 1 bronchodilator use question and 5 symptom questions. The ACQ-5 measures 5 symptoms (woken at night by symptoms, wake in the morning with symptoms, limitation of daily activities, shortness of breath, and wheeze); the ACQ-6 is the same 5 symptom items plus daily rescue medication use as recalled by the participant; and the ACQ-7 is the ACQ-6 plus airway caliber as measured by pre-bronchodilator FEV_1 percent predicted. Questions are weighted equally and scored from 0 (totally controlled) to 6 (severely uncontrolled).

The AQLQ(s) +12 is a 32-item questionnaire that measures health-related quality of life experienced by participants with asthma who are 12 years or older in age (Juniper 2005, Juniper 1999, 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. The questionnaire will be

completed at each visit, starting at randomization. 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 32 items of the AQLQ(s)+12 are assigned to a domain as follows:

- Symptoms: 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 29, 30
- Activity Limitation: 1, 2, 3, 4, 5, 11, 19, 25, 28, 31, 32
- Emotional Function: 7, 13, 15, 21, 27
- Environmental Stimuli: 9, 17, 23, 26

4.2.5.2 Derivations

The ACQ-5 score is the mean of the responses to the relevant 5 items. ACQ-6 is the mean of the responses to the 5 items in ACQ-5 plus a further 6th question on one bronchodilator use. The ACQ-7 score is the mean of the response to the relevant 6 items in ACQ-6 plus FEV_1 as reported by the clinician. The mean response to ACQ-7 will be calculated prior to assigning visit windows to the data. If question 7 is missing, then the answer will be derived from the spirometry data on the same date. The mean response will only be calculated if all 7 questions are answered. The ACQ-7 mean response will be assigned the earliest date and time of all 7 questions. Scores of $\leq$0.75 indicate well-controlled asthma, scores between 0.75 and <1.5 indicate partly controlled asthma, and a score $\geq$1.5 indicates not well-controlled asthma (Juniper, 2006). Individual changes of at least a 0.5 decrease are considered clinically meaningful; higher scores indicate worse control status.

For AQLQ(s) +12, 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; higher scores indicate better health status.

For over 24 weeks and over 12 to 24 Weeks analyses, if a participant is considered a responder (i.e., improvement of $\geq$0.5 points over baseline) 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.

4.2.5.3 Primary Analysis of Other Secondary Endpoint: Percentage of Responders

Responder analyses will be performed for ACQ-7, ACQ-5, AQLQ(s) +12 at week 24, over 24 weeks, and over 12 to 24 weeks using the primary strategy for ICEs with the Composite approach for binary endpoints as supportive. The analysis uses the Efficacy Set.

Responders are defined as participants with an improvement of $\geq$0.5 points over baseline (decrease in ACQ scores, increase in AQLQ(s) +12 score).

Under the primary strategy for handling ICEs all available data will be utilized to determine response irrespective of any ICEs except new asthma medication in conjunction with premature IP discontinuation where a subject will be considered non-responders.

For supportive analyses, participants who experience an ICE for any reason (except for discontinuation of IP for reasons related to global/country situation) will be classified as non-responders for time points subsequent to the ICE under the Supportive Composite approach to ICEs. Data following IP discontinuation for reasons related to global/country situation will be considered missing and will not be imputed. Those datapoints are considered to be MCAR and will be excluded from the analysis. Intermittently missing data will be classified as non-response.

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

4.2.6 Other Secondary Endpoint: Onset of Action on Day 1

4.2.6.1 Definition

The onset of action on Day 1 is defined as absolute change from baseline in FEV_1 at 5 minutes post-dose on Day 1.

4.2.6.2 Derivations

For the onset of action on Day 1, baseline is defined in Section 3.3.1.1.

For the primary strategy for handling ICEs, data following new asthma medication in conjunction with premature IP discontinuation will be imputed with the worst FEV_1 value of: 12% decrease from participant's baseline value, participant's worst observed value post baseline during the study, at each timepoint.

4.2.6.3 Primary Analysis of Secondary Endpoint

The onset of action will be evaluated on Day 1 by comparing BFF MDI 320/9.6 µg vs BD MDI 320 µg in the mean change from baseline in FEV_1 at the 5 minutes post-dose timepoint for the primary strategy for handling ICE's with Efficacy Set. Comparisons will also be made at additional timepoints but will not be controlled for multiplicity.

A repeated measures analysis of covariance (ANCOVA) will be fitted to the Day 1 post-baseline data. This model will include treatment, timepoint, prior maintenance medication (ICS versus ICS/LABA), and treatment-by-timepoint interaction as categorical covariates and baseline trough FEV_1 and percent reversibility as continuous covariates.

A similar hierarchical approach to the covariance structure will be used as for the primary. For details, refer to Section 4.2.1.4.

Contrasts will be used to obtain estimates of the treatment differences on Day 1 at the 5-minutes post dose timepoint. Two-sided p-values and point estimates with two-sided 95% CIs will be produced for each treatment difference. Furthermore, descriptive statistics will be presented by treatment group.

A supportive 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 for each treatment group. The within-group analysis will be reported outside of the CSR, refer to Appendix 8.2.5.

4.2.6.4 Subgroup Analyses of Other Secondary Endpoint: Onset of Action on Day 1

For all regions, the same subgroup analyses described in Section 4.2.1.7 will be performed for the onset of action evaluation, except no subgroup analysis on regions will be performed. The subgroup analyses will be reported outside of the CSR, refer to Appendix 8.2.5.

4.2.7 Tertiary/Exploratory Endpoints: Lung Function

4.2.7.1 Definition

Exploratory lung function endpoints include the following:

- Peak change from baseline in FEV_1
- Time to peak FEV_1 on Day 1
- Change from baseline in forced vital capacity (FVC), PEF, and forced expiratory flow at 25-75% (FEF_{25-75}) evaluated using AUC_{0-3}
- Change from baseline in morning and evening pre-dose PEFR
- Percentage of peak FEV_1 improvement achieved at 5 minutes on Day 1

4.2.7.2 Analysis of Exploratory Lung Function Endpoints

Analyses of exploratory lung function endpoints will be performed using a While on Treatment estimand approach to ICEs with the Efficacy set.

The lung function endpoints will be reported outside of the CSR, refer to Appendix 8.2.5.

Peak Change from Baseline in FEV_1

Peak change from baseline in FEV_1 will be analyzed over 24 weeks, over 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 endpoint analyses (Section 4.2.1.4).

Time to Peak FEV_1 on Day 1

Time to peak FEV_1 on Day 1 will be analyzed with an analysis of Covariance (ANCOVA) model to compare the treatment groups, adjusted for prior maintenance medication (ICS versus ICS/LABA), baseline trough FEV_1 and percent albuterol reversibility. The time to peak will be based on the actual rather than nominal assessment time.

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

Change from baseline in FVC, PEF and FEF_{25-75} evaluated using AUC_{0-3} will be analyzed over 24 weeks, over 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 endpoint analysis (Section 4.2.1.4).

Change from Baseline in Morning Pre-Dose PEF

Change from baseline in morning pre-dose PEF based on eDiary daily data will be analyzed using a repeated measures analysis of covariance model. The model will include treatment, 4-week interval (interval 1 to 6), prior maintenance medication (ICS versus ICS/LABA), and the treatment-by-4-week interval interaction as categorical covariates and baseline morning pre-dose trough PEF, baseline trough FEV_1 and percent albuterol reversibility as continuous covariates.

A similar hierarchical approach to the covariance structure will be used as for the primary. For details, refer to Section 4.2.1.4.

Contrasts will be used to obtain estimates of the treatment differences over 24 weeks, over 12 to 24 weeks and over each 4-week interval. Two-sided p-values and point estimates with two-sided 95% CIs will be produced for each treatment difference.

Change from Baseline in Evening Pre-Dose PEF

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

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

For each participant, this endpoint is defined as change from baseline in FEV_1 at 5 minutes on the day of first dose of randomized IP divided by peak change from baseline in FEV_1 on the day of first dose of randomized IP within the participant.

Descriptive statistics will be presented by treatment group for the percentage of peak FEV_1 improvement achieved at 5 minutes on the Day 1.

The percentage of participants with ≥ 12% improvement over baseline in FEV_1 at 5 minutes post dose and at other timepoints on Day 1 will be compared between treatment groups using logistic regression adjusted for prior maintenance medication (ICS versus ICS/LABA), baseline trough FEV_1, and percent reversibility.

4.2.8 Tertiary/Exploratory Endpoints: PRO

4.2.8.1 Definition

Exploratory PROs endpoints included the following:

- Percentage of responders in ACQ-6 (≥0.5 decrease equals response)
- Change from baseline in ACQ-5, ACQ-6, ACQ-7 and AQLQ(s)+12
- Time to CCI
- Time to first Composite exacerbation (CCI
- Rate of CCI events
- Change from baseline in EQ-5D questionnaire index score and VAS questionnaire score
- The percentage of participant's categorical responses to each of the 5-dimensions in EQ-5D
- Asthma Impairment and Risk Questionnaire (AIRQ)

End of study visit (for EQ-5D analysis and time to event analyses) is defined as the planned last visit other than follow-up visit.

4.2.8.2 Derivations

ACQ

For the derivation details of ACQ, refer to Section 4.2.5.2.

Time to CCI

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

- CCI
- [redacted]

Time to CCI is calculated as time in days from the date of first dose of randomized IP to the earliest date when participants meet any of above criteria.

CCI

CCI

CCI

CCI

CCI

EQ-5D

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 aged between 12 and 15 years old at randomization and EQ-5D-5L for the participants aged 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-Y and EQ-5D-5L index score can be calculated based upon participants' responses to the 5 dimensions and using an appropriate value set (EQ-5D User Guides 2020). A value set provides values (weights) for each health state description according to the preferences of the general population of a country. The weights for the UK will be used for presenting results in the CSR. Other country-specific weights will be applied as post-hoc analyses, where weights for the respective region will be applied in case that no weight is listed for a specific country.

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 6 site visits throughout the treatment period.

AIRQ

The Asthma Impairment and Risk Questionnaire (AIRQ™) is a PRO tool intended to identify participants 12 years and older whose health may be at risk because of uncontrolled asthma (Murphy, 2020). It has 10 questions that ask about respiratory symptoms, activity limitation, sleep, rescue medication use, social activities, exercise, difficulty controlling asthma, and exacerbations. All items have a yes/no response option and the tool is scored by summing the total number of 'yes' responses. This sum score is used to assess level of asthma control where: 0-1 is well controlled, 2-4 is not well controlled, and 5-10 is very poorly controlled. Thus, a higher score indicates worse control status.

The AIRQ items have two different recall periods: The first seven impairment items are evaluated over the past 2 weeks and the last three risk items over the past 3 months or the past year. This study will use the past 3 months recall.

4.2.8.3 Analysis of Exploratory PRO Endpoints

Analyses of exploratory PROs endpoints will be performed for the primary strategy for handling ICEs for percentage of responders in ACQ-6 and change from baseline in ACQ-5, ACQ-6, ACQ-7 and AQLQ(s)+12 and While on Treatment approach to ICEs for the other PRO endpoints with Efficacy set.

The analysis of exploratory PRO endpoints will be reported outside of the CSR, refer to Appendix 8.2.5.

Percentage of responders in ACQ-6

Percentage of responders in ACQ-6 will be analyzed similarly to the percentage of responders in ACQ-7 specified in Section 4.2.5.3.

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. The model will include treatment, visit, prior maintenance medication (ICS versus ICS/LABA), and the 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.

A similar hierarchical approach to the covariance structure will be used as for the primary. For details, refer to Section 4.2.1.4.

Contrasts will be used to obtain estimates of the treatment differences by visit for measures assessed at clinic visits, over 24 weeks, and over 12 to 24 weeks. Two-sided p-values and point estimates with two-sided 95% CIs will be produced for each treatment difference.

For the primary strategy for handling ICEs, data following new asthma medication in conjunction with premature IP discontinuation will be imputed with the worst score of: worst observed score (i.e. highest for ACQ and lowest for AQLQ(s)+12) post baseline for the participant, participant's baseline score +0.5 (-0.5 for AQLQ(s)+12).

Time to CCI

Time to CCI will be analyzed with a Cox regression model to compare the treatment groups, adjusted for severe asthma exacerbation history (0, ≥1), prior maintenance medication (ICS versus ICS/LABA), region, baseline trough FEV_1 and percent albuterol reversibility.

Participants who experience an ICE without any CCI will be censored at the time of the ICE +1 day. Participants not having any CCI or any ICE will be censored at the date of last dose + 1.

Two-sided p-values and point estimates with two-sided 95% CIs will be produced for each treatment difference for the While on Treatment estimand approach to ICEs.

Time to first CCI

Time to first CCI (i.e., a diary event or severe asthma exacerbation) will be analyzed in a manner similar to the analysis of time to CCI There will be two analyses for time to first CCI

First analysis will include only data up to and including Visit 8 (Week 12). For the While on Treatment ICE strategy, participants who did not have an event by then would be censored at the minimum of (their Week 12 Visit + 1 day, date of last dose + 1).

The second analysis will include all observed data. For the While on Treatment ICE strategy, participants who experience an ICE without any CCI event will be censored at the date of the ICE + 1 day. Participants not having any CCI event or any ICE will be censored at the date of last dose + 1 day.

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

Rate of CCI events

The number of CCI events and the percentage of participants who experience CCI events, event rates, and rate ratios comparing treatments will be summarized for the While on Treatment estimand approach to ICEs.

The rate of CCI will be analyzed using negative binomial regression. Treatments will be compared adjusting for severe asthma exacerbation history (0, ≥1), prior maintenance medication (ICS versus ICS/LABA), region, baseline trough FEV_1, and percent albuterol reversibility. The logarithm of time at risk of experiencing an CCI event will be used as an offset variable in the model.

If convergence is not attained the covariates will be removed from the model one-by-one until convergence is attained, with the order of removal being: region, percent albuterol reversibility, prior maintenance medication, trough FEV_1 and severe asthma history.

The time at risk is defined as follow up time minus the time when the participant is not a risk of a new CCI event. For the While on Treatment estimand, the follow up time is between the date of first dose of randomized IP until the day following the occurrence of the first ICE or if no ICE occurred until the day after last dose, minus the number of days while the participant was experiencing any CCI event and minus the seven days subsequent to any CCI event. An exception is that the start day of the CCI is not subtracted from the time at risk.

CCI events will be considered separate if more than 7 days are between the recorded stop date of the earlier event and start date of the later event.

EQ-5D

For EQ-5D, 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 change from baseline in index score and VAS will be presented by treatment group.

The index score and the VAS scores at weeks 4, 12, 20, 24 and end of study visit (as defined in Section 4.2.7.1) will be analyzed using repeated measures analysis of covariance model with age and baseline score as continuous covariates and prior medication (ICS vs ICS/LABA), region, gender, treatment, visit and treatment-by-visit as categorical covariates.

A similar hierarchical approach to the covariance structure will be used as for the primary. For details, refer to Section 4.2.1.4.

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

AIRQ

The AIRQ percentage of control Well (0 to 1), Not Well (2 to 4) and Very Poorly (5 to 10) will be presented at each visit by treatment group. The absolute total score and change from baseline for AIRQ will be summarized by visit and treatment group.

4.2.9 Tertiary/Exploratory Endpoints: Symptoms and Exacerbations

4.2.9.1 Definition

Exploratory symptoms and other endpoints include the following:

- Percentage of rescue-free days (24-hour period without rescue medication use)
- Percentage of symptom-free days (24-hour period without symptoms)
- Time to severe asthma exacerbation
- Rate of severe asthma exacerbations
- Rate of moderate/severe exacerbations

4.2.9.2 Derivations

Percentage of rescue-free days/ symptom-free days

For rescue free/symptom free days this relates to a 24-hour period without rescue medication use/symptom-free, which consists of diary entries from daytime+nighttime where daytime is on the actual day recorded and nighttime is the night before. For each time period for which the percentage of rescue-free days/symptom free days 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 with non-missing values.

Asthma Exacerbations

Severe Exacerbations are defined in Section 4.2.3.1.

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.

Time to first severe asthma exacerbation is the time from the first dose of randomized IP to the time of onset of the first severe asthma exacerbation.

4.2.9.3 Analysis of Exploratory Symptoms and Exacerbations

Analyses of exploratory symptoms and exacerbations endpoints will be performed for the While on Treatment estimand approach to ICEs with Efficacy set.

Percentage of Rescue-Free and Symptom-Free Days

A repeated measures analysis of covariance model will be used to analyse the percentage of rescue-free days and symptom-free days, respectively, with treatment, the number of the relevant 4-week interval (interval 1 to 6), prior maintenance medication (ICS versus ICS/LABA), severe asthma exacerbations history (0, ≥1) 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 Albuterol reversibility will be continuous covariates.

A similar hierarchical approach to the covariance structure will be used as for the primary. For details, refer to Section 4.2.1.4.

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 two-sided 95% CIs will be produced for each treatment difference.

The percentage of rescue-free and symptom free days will be reported outside of the CSR, refer to Appendix 8.2.5.

Note: For the While on Treatment ICE strategy, for participants experiencing an ICE, data prior to the first occurrence of an ICE will be utilized, otherwise data until the date of last dose will be used.

Exacerbations

Time to first severe asthma exacerbation will be analyzed with a Cox regression model in the D5982C00005 and D5982C00006 studies separately and with the pooled individual patient data from both studies (D5982C00006: BFF 320/9.6 µg, BFF 160/9.6 µg, BD 320 µg. D5982C00005: BFF 160/9.6 µg, BD 160 µg treatment arms. The Symbicort treatment arm in study D5982C00006 will not be included in the pooled analysis). The While on Treatment strategy for ICEs will be utilized.

The Cox regression model will be adjusted for severe asthma exacerbation history (0, ≥◦1), prior maintenance medication (ICS versus ICS/LABA), region, baseline trough FEV_1, and percent albuterol reversibility. For the While on Treatment strategy, participants will be censored the day after the date of their last dose if no ICE occurred, otherwise they will be censored the day following the occurrence of first ICE. For the pooled analysis a cox regression additive model will be used which will also include study, and budesonide (1 if the budesonide dose is 320 µg, and 0 if the budesonide dose is 160 µg) and formoterol (1 if

the formoterol dose is 9.6 µg, and 0 if no formoterol dose) instead of treatment as covariates. The comparison of interest is the formoterol effect.

A Kaplan-Meier curve will be provided for each treatment arm for each study. For the pooled data from both studies a Kaplan-Meier curve for the Formoterol arms stratified by study will be provided.

The rate of severe exacerbations utilizing the primary strategy for handling ICEs is described in Section 4.2.3.4 . In addition, the rate of severe exacerbations will be analysed utilizing the WoT strategy using data from Vathos alone. Furthermore for Vathos alone, the rate of moderate/severe exacerbations will be analysed utilizing the WoT strategy. For more details of the rate of severe exacerbations and moderate/severe exacerbations analyses refer to Section 4.2.3.4.

The time at risk for the primary strategy for handling ICEs is defined in Section 4.2.3.4. For the While on Treatment estimand, the follow-up time is until the occurrence of first ICE + 1 day after or date of last dose + 1 day if no ICE occurred. The day after the last dosing date should be included to account for any exacerbation that led to the discontinuation but started on the day after last dose.

The rate of severe exacerbations utilizing the while on treatment approach to ICE and moderate/severe exacerbations will be reported outside of this CSR, refer to Appendix 8.2.5.

4.2.10 Healthcare Resource Utilization

4.2.10.1 Definitions and Derivations

Data on HCRU will be collected at baseline and all visits post-baseline and summarized by treatment group.

4.2.10.2 Presentations

Descriptive statistics will be provided by treatment and relationship to asthma and overall (asthma-related, not asthma-related, and combined).

The percentage of participants will be presented by treatment for the following variables: Ambulance transport, hospitalizations to intensive care, coronary care, general care, emergence room visits, visits and telephone calls to specialist, primary health care physicians, or other healthcare visits.

Descriptive statistics will be provided by treatment for the following variables: number of ambulance transports, number of days hospitalised, number of emergency room visits, number of visits and telephone calls to specialists, to primary health care physicians, and other health care providers.

Analyses will be performed for the While on Treatment Estimand approach to ICEs with the Efficacy set utilizing data up to date of last dose + 1 day for participants without an ICE or the date of the first ICE + 1 day.

The number of days hospitalized (for intensive care, corona care and general care) will be adjusted per year. The number of days adjusted per year will be calculated as follows: (the number of days participant experienced the parameter of interest within time of exposure) * 365.25 / (time of exposure), where time of exposure is the number of days from the first dose of randomized IP to either the participant's date of last dose +1 day for participants without an ICE or the date of the first ICE +1 day.

The healthcare resource utilization endpoints will be presented in a supplemental payer CSR, refer to Appendix 8.2.5.

4.3 Pharmacodynamics

Not Applicable.

4.4 Pharmacokinetics Endpoints

Not Applicable.

4.5 Immunogenicity

Not Applicable.

4.6 Safety Analyses

The term safety covers exposure, AEs, clinical laboratory, vital signs, and physical examination.

Tables are provided for the Safety set, and listings are provided for the Screened set or the Safety set depending on the availability of data. Hypothesis testing will not be performed for any safety analyses.

4.6.1 Exposure

4.6.1.1 Definitions and Derivations

Participant's exposure to a study intervention will be determined by the duration of time (days) for which the doses were administered, defined as "((End date of treatment – Date of first dose of randomized IP) + 1)".

4.6.1.2 Presentation

The number of days of exposure to study intervention will be summarized for each treatment. Summary statistics will also be provided for the cumulative duration of

exposure. The total person-years of exposure for a treatment group, defined as the total exposure in the study across all participants in the treatment, will also be provided by treatment for the Safety set.

Overdose will be presented in a listing for the Screened set.

4.6.2 Adverse Events

4.6.2.1 Definitions and Derivations

AEs 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 Serious Adverse Events (SAE) will be recorded from the time of signing of ICF.

AEs will be categorised for analysis according to their onset date into the following study periods:

- AEs occurring during screening/run-in period: date of Visit 1 ≤ AE onset date < date of first dose of randomized IP
- AEs occurring during on-treatment period: date of first dose of randomized IP ≤ AE onset date ≤ (date of last dose of IP + 1 days, date of withdrawal of consent, or date of death)
- AEs occurring during post-treatment period (for participants still being followed up then): date of last dose of IP + 1 days < AE onset date ≤ study completion or study withdrawal date
- AEs occurring during on-study period: date of first dose of randomized IP ≤ AE onset date ≤ study completion or study withdrawal date.

Partial dates will be imputed in order to determine if an AE is on-treatment using the imputation rules in Appendix 8.1; however, imputed dates will not be provided in the data listings.

Additionally, if an AE has an onset date during on-treatment and has an outcome of death, that death will be considered on treatment even if the date of death is after the last date of treatment+1.

Analysis endpoints for AEs include both the numbers of AEs as observed by the investigational team or reported by the participant, and the numbers of participants experiencing AEs. The event rate is defined as the number of participants with AEs divided by the total number of days at risk for AEs across all participants in given group, multiplied by 365.25 multiplied by 100. The time at risk is defined as the time from date of first dose of randomized IP to the date of first event if an AE occurs, or to the minimum of (date of last dose of IP + 1 day, date of withdrawal of consent, date of death) if no AE occurs.

AEs will be coded using the latest version of the (MedDRA) available at the time of the clinical data lock. Coded terms will be updated as later versions of MedDRA become available so that at the time of clinical data lock, all terms will be coded as of the latest version of the dictionary.

The medical concept/grouping and standardized MedDRA v27.1 queries (SMQs) proposed to be used in the assessment of AEs associated with ICS and LABAs are listed below. If a different version of MedDRA is used these will be updated prior to lock. SMQs will be utilized when possible and a selection of high-level group terms (HLGTs), high-level terms (HLTs), and PTs in other situations (as per supplementary document Standard MedDRA Queries for VATHOS). When using the PTs of SMQ, use only the PT terms of narrow SMQs.

Cardiovascular effects

- Arrhythmia
  - Arrhythmia related investigations, signs and symptoms (20000051) Narrow SMQ
  - Cardiac arrhythmia terms (incl bradyarrhythmias and tachyarrhythmias) (20000050) Narrow SMQ
- Torsade de pointes/QT prolongation (20000001) Narrow SMQ
- Palpitations (10033557) (PT)
- Cardiac failure (20000004) Narrow SMQ
- Ischaemic heart disease (20000043) Narrow SMQ
- Hypertension (20000147) Narrow SMQ

Respiratory Effects

- Bronchospasm Paradoxical (10006486) PT
- Infective pneumonia (20000231) Narrow SMQ
- Bronchitis
  - Bronchitis (10006451) PT
  - Bronchitis viral (10053160) PT
  - Bronchitis bacterial (10061736) PT
  - Lower respiratory tract infection (10024968) PT
  - Lower respiratory tract infection viral (10065188) PT
  - Lower respiratory tract infection bacterial (10063890) PT

Cerebrovascular Effects

- Haemorrhagic central nervous system vascular conditions (20000064) Narrow SMQ
- Ischaemic central nervous system vascular conditions (20000063) Narrow SMQ

Ocular Effects

- Visual Disorders NEC (10047541) (HLT)
- Glaucoma (20000146) Narrow SMQ
- Lens disorders (20000155) Narrow SMQ

Metabolic Effects

- Hyperglycaemia/new onset diabetes mellitus (20000041) Narrow SMQ
- Hypokalaemia (20000233) Narrow SMQ

Local ICS Effects

- Oral candidiasis
  - Oesophageal candidiasis (10030154) PT
  - Oral candidiasis (10030963) PT
  - Oropharyngeal candidiasis (10050346) PT

Systemic ICS Effects

- Fractures (10017322) HLGT
- Osteoporosis/osteopenia (20000178) Narrow SMQ
- Adrenal Suppression (10001382) PT
- Adrenal cortical hypofunctions (10001343) HLT

Oropharyngeal Effects (collection of PTs)

- Dry mouth (10013781) PT
- Dysphonia (10013952) PT
- Aphonia (10002953) PT
- Throat irritation (10043521) PT
- Dysgeusia (10013911) PT
- Ageusia (10001480) PT

Systemic LABA Effects

Tremor (excl congenital) (10044566) HLT

Psychiatric effects

- Depression
  - Depression (10012378) PT
  - Depressed mood (10012374) PT
  - Depressive symptom (10054089) PT
  - Dysphoria (10013954) PT
  - Euphoric mood (10015535) PT
  - Psychotic disorder (10061920) PT
  - Depression suicidal (10012397) PT
  - Agitated depression (10001496) PT
- Agitation (10001497) PT
- Anxiety (10002855) PT

Insomnia

- Insomnia
  - Insomnia (10022437) PT
  - Initial insomnia (10022035) PT

- Sleep disorder (10040984) PT
- Terminal insomnia (10068932) PT
- Middle insomnia (10027590) PT

4.6.2.2 Presentation

The number of events and number of participants with AEs in any of these categories below will be summarized for the Safety set during on-treatment period.

- Any AE
- Any SAE
- Any SAE with outcome death
- Any AE leading to discontinuation of IP
- Any possibly related AE
- Any possibly related SAE

Possibly related is defined as reasonable possibility that the AE was caused by investigational product as assessed by investigator.

The following is a list of summary tabulations that will be prepared for the Safety set during the on-treatment period by treatment group:

- Number of participants with AEs by SOC and PT
- Number of participants with AEs in ≥2% participants in either of the BFF MDI treatment groups and exposure adjusted rate by PT, sorted by decreasing frequency in the BFF MDI 320/9.6 µg treatment group
- Adverse events occurring at an incidence of >=2%, and more common in participants treated with either BFF then any comparator
- Adverse events per subject years
- Non-serious adverse events occurring in more than 5% of participants in any treatment group
- Number of participants with SAEs in >=2% participants in any treatment arm by PT, sorted by Total (pooled treatment arms) frequency
- Number of participants with AEs, by maximum intensity on SOC and PT
- Number of participants with possibly related AEs by SOC and PT
- Number of participants with SAEs with outcome death and exposure adjusted event rate, by SOC and PT

- Serious AEs with outcome death - key participant information
- Serious adverse events by SOC and PT
- Number of participants with SAEs and exposure adjusted rate, by SOC and PT
- Serious adverse events by decreasing frequency on PT in total treatment group reported by >=2% of participants in any treatment group
- Serious AEs - key participant information
- Number of participants with AEs leading to discontinuation of IP and exposure adjusted rate, by SOC and PT
- Adverse events leading to discontinuation of IP by SOC and PT
- Number of participants with AEs associated with use of ICS and LABAs and exposure adjusted event rate, by medical concept and PT

In addition, the following summaries will be prepared for the Safety set during the on-study period by treatment group:

- Number of participants with AEs by SOC and PT
- Number of participants with SAEs, by SOC and PT
- Number of SAEs, by SOC and PT

No hypothesis tests will be performed. However, comparisons between treatment groups (risk difference) and 95% CI will be estimated for AEs occurring in more than 2% of participants in either BFF MDI treatment group, SAEs with outcome of death, all SAEs, AEs leading to discontinuation, and AEs associated with the use of ICS and LABA by SOC and PT during the on-treatment period based on the Miettinen and Nurminen method comparing the difference in exposure adjusted proportion of participants with events (Liu et al 2006). Comparisons between the following treatment groups will be performed: BFF 320/9.6 µg vs BD MDI 320 µg, BFF 320/9.6 µg vs Symbicort and BFF 320/9.6 µg vs BFF 160/9.6 µg.

All AEs (including during screening/run-in period) will be included in the listing for the Screened Set.

Separate listings of AEs will be provided for randomized participants not included in the safety set due to sites found to have a serious GCP breach.

4.6.3 Clinical Laboratory

4.6.3.1 Definitions and Derivations

Clinical chemistry, haematology and urinalysis will be performed by a central laboratory according to the schedule and the variable specifications described in the CSP.

Lab parameters collected include the following as specified in Table 9.

Table 9 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
Highly sensitive urine pregnancy test for women of childbearing potential	Potassium
	Calcium, total
	Sodium
	Glucose

In all analyses of continuous laboratory variables, any value recorded only as below Lower Limit of Quantification (LLOQ) will be set to LLOQ and included in the analysis. Any value recorded only as above Upper Limit of Quantification (ULOQ) will be set to ULOQ and included in the analysis.

Central laboratory normal reference ranges will be used for the identification of the individual clinically important abnormalities. Absolute values will be compared to the relevant normal reference range, and classified as low (below range), normal (within range or on the limits) or high (above range). All values falling outside the normal reference ranges will be flagged. These classifications will also be used for shift tables. For the purposes of shift tables, baseline will be defined as specified in Section 3.3.1.1. Minimum and maximum values calculated across all visits in the relevant study period will use all available values, including those from unscheduled and repeat visits.

4.6.3.2 Presentations

Summary statistics (n, mean, SD, minimum, 1st quartile, median, 3rd quartile, maximum) of the absolute value and change from baseline for haematology and clinical chemistry laboratory variables will be tabulated by treatment and visit. These summaries will be

prepared for baseline, each scheduled post-baseline visit and end of treatment visit. End of treatment visit is defined as the last non-missing on-treatment assessment available. Data from unscheduled visits will not be used for the by-visit summaries, but both scheduled-visit data and unscheduled-visit data are candidates for the end-of-treatment summary. Data from both scheduled and unscheduled visits will be listed. No hypothesis tests will be performed.

During treatment period, participants with absolute values or change of baseline values outside laboratory reference ranges will be flagged and summarized. The on-treatment period is defined from the first dose of randomized IP to the minimum of (date of last dose of IP +1 day, date of withdrawal of consent or date of death).A shift tables will display low, normal and high values at baseline vs maximum and minimum on-treatment observation values for each variable.

4.6.4 Vital Signs

4.6.4.1 Definitions and Derivations

Vital signs will be measured according to the schedule and the variable specifications described in the CSP. Changes from Baseline will be evaluated, where baseline is defined as specified in Section 3.3.1.1.

Absolute values and changes from baseline (where applicable) will be compared to the relevant reference range specified in Table 10, and classified as low (below range), normal (within range or on the limits) or high (above range). All values falling outside the reference ranges will be flagged.

The on-treatment period is defined from the first dose of randomized IP to the minimum of (date of last dose of IP + 1 day, date of withdrawal of consent, or date of death).

Table 10 Vital signs reference ranges

Parameter	Standard Units	Lower Limit	Upper Limit	Change from Baseline Criteria
Diastolic BP (sitting)	mmHg	60	100	±15
Systolic BP (sitting)	mmHg	90	160	±30
Pulse rate (sitting)	beats/min	50	100	±20
Weight	Kg	40	150	

4.6.4.2 Presentations

Summary statistics (n, mean, SD, minimum, 1st quartile, median, 3rd quartile, maximum) of the absolute value and change from baseline for vital signs will be tabulated by treatment and visit. These summaries will be prepared for baseline, each scheduled post-baseline visit and end of treatment visit. End of treatment visit is defined as the last non-missing on-treatment assessment available. Data from unscheduled visits will not be used for the by-visit summaries, but both scheduled-visit data and unscheduled-visit data are candidates for the end-of-treatment summary. Data from both scheduled and unscheduled visits will be listed. No hypothesis tests will be performed.

During treatment period, participants with absolute values or change from baseline values outside vital signs reference ranges will be flagged and summarized.

4.6.5 Physical Examination

4.6.5.1 Definitions and Derivations

Any physical examination abnormality reported after the start of treatment for a participant is to be reported as an AE.

4.6.5.2 Presentations

Physical examination abnormality will be included in listings of AEs and summarized in AE summaries. Abnormalities seen at the Screening physical examinations will be recorded as Medical History.

5 INTERIM ANALYSIS

Not Applicable.

6 OTHER INFORMATION

6.1 Statistical Software

Data processing, statistical screening, descriptive reporting and analysis of the efficacy and safety data will be performed using SAS (Version 9.4 or higher). Graphs may also be produced using R (R Development Core Team, 2003).

6.2 Sample Size Determination

Sample size calculations assumed either a While on Treatment or Treatment Policy strategy for ICEs.

A total of CCI participants will be recruited with CCI participants in the BFF MDI 160/9.6 µg arm and CCI participants in the BFF MDI 320/9.6 µg, BD MDI 320 µg and Symbicort TBH arms. The BFF MDI 160/9.6 µg arm will be included to demonstrate a dose response.

Under the While on Treatment estimand strategy for ICEs, a sample size of CCI participants per treatment arm will provide more than 90% power to detect a CCI mL difference in the analysis of change from baseline in trough FEV_1 over 24 Weeks between BFF MDI 320/9.6 µg versus BD MDI 320 µg and over 99% power to detect a CCI mL difference in the analysis of change from baseline in FEV_1 AUC0-3. Each comparison is based on a two-sided alpha=CCI test and SD of CCI mL for trough FEV_1 and CCI mL for FEV_1 AUC0-3 at each visit with effective SD of CCI mL and CCI mL, respectively. The effective SD for each endpoint over 24 Weeks assumes 2 post-dose visits assessing FEV_1 AUC0-3 and 3 post-dose visits assessing trough FEV_1 over the interval and that the correlation among visits is CCI This sample size assumes that approximately CCI% of randomized participants will have discontinued study intervention prior to Week 12, and CCI% at Week 24. Using the Treatment Policy estimand strategy for ICEs, a smaller treatment difference of CCI mL for trough FEV_1 is assumed, providing a power at 24 weeks in trough FEV_1 of 84%. Assuming a smaller treatment effect of CCI mL for FEV_1 AUC0-3, the power would be at least 99%. The treatment effect and variability for the power calculation was based on 4 Symbicort studies CCI

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8 APPENDIX

8.1 Data Handling Rules

Programming of the tables, listings and figures will be performed using SAS Version 9.4 or a more recent version. The following table presents the algorithms to be used in SAS to calculate the derived variables, including rules for handling other missing data or partial dates, or irregular/unexpected data issues.

Category	Description	Data Handling Rule
1. Pulmonary Function Testing data	ERT Spirometry data transferred	Only data of rank =1 (best effort) will be mapped to SDTM from the raw data; mapped data will be grade 1 = acceptable, grade 2 = borderline, or grade = 3 (unacceptable). Only data of grade = 1 or grade = 2 will be included in baseline or on-treatment spirometry calculations.
2. Informed consent/assent	Date of ICF	In case of rescreening, the date of re-signing the ICF for rescreening prior to randomization will be used as the date of ICF
3. Asthma History	Missing month of "First appearance of asthma symptoms date", "Date Asthma first diagnosed date", "Most recent Severe exacerbation date".	If the year is before the informed consent/assent year, then the missing month will be imputed as June. If the year is the same as the informed consent/assent year, then the missing month will be imputed as June (if the informed consent/assent date is after June), or the latest month in which the 1st will be before the informed consent/assent date (if the informed consent/assent date is on or prior to June).
	Missing day of "First appearance of asthma symptoms date", "Asthma first	The missing Day of Diagnosis will be imputed for all participants as the 1st of the month.

Category	Description	Data Handling Rule
	diagnosed date", "Most recent Severe exacerbation date"	
	Years since asthma diagnosis and Years since asthma symptoms started	(Date of first dose of randomized IP in the Study – Date of Event)/365.25.
	Years since most recent severe exacerbation	(Date of Visit 1 – Date of Most Recent Severe Exacerbation)/365.25.
4. Medical History	Medical History Begin Date of Condition	Missing month of Condition will be imputed as June, unless June 1st of the year of Condition is after informed consent/assent date or after the Condition End date, in which case the month of the informed consent/assent or the End Date respectively will be used. Begin date of Condition will be imputed for all participants as the 1st of the month.
	Medical History End Date of Condition	Other than for 'Ongoing' conditions, missing month of End Date of Condition will be imputed as June, unless June 1st of the year of Condition is after informed consent/assent date or before Start date, in which case the month of the informed consent/assent or the Start date respectively will be used. End date of Condition will be imputed for all participants as the 1st of the month.
5. Surgical History	Surgical History Date of Surgery	Missing month of Surgery will be imputed as June, unless June 1st of the year of Surgical History Event is after informed consent/assent date, in which case the month of the informed consent/assent date will be used. Date of

Category	Description	Data Handling Rule
		Surgery will be imputed for all participants as the 1st of the month.
6. First and Last Treatment Dates	Date/time of first and last dose of a study intervention	The date and time (24 hr. clock) of the first dose of randomized IP will be taken from the Dosing Exposure eCRF. The date of the last dose of study intervention will from the Dosing Exposure eCRF for the treatment.
7. Last Visit Date	Date of Last Visit	Date of last visit according to the Visit eCRF.
8. Study Day Definitions	**Study Day** for assessment/event which occurs on or after the randomization date	Study Day = Date of assessment/event – date of first dose of randomized IP (First Dose Day) + 1.
	Study Day for assessments/events on days prior to the randomization date	Study Day = date of assessment/event – date of first randomized dose of IP (First Dose Day).
	Study Day Post-Treatment of Assessment or event which occurs after study intervention	Study Day = 'P' concatenated with the number of days post-treatment that the assessment or event occurred which is defined as Date of assessment/event – date of last dose of study intervention.
	First Dose Day	**First Dose Day** in the study is defined as the study day of the first dose of randomized IP in the study (Study Day 1).
	Last Dose Day	Last Dose Day in the study is defined as the study day of the last dose of study intervention after randomization in the study (defined as the later of the last date of dosing from the eDiary

Category	Description	Data Handling Rule
		and the last date of dosing from the Dosing Exposure CRF pages).
	Last Study Day	**For participants who did not receive study intervention in the study (e.g., Screen-failure participants)**, Last Study Day is defined as (the later of the last visit date and the date of last contact for participants lost-to-follow-up from the Disposition CRF) – Date of Screening Visit + 1. For participants who received study intervention in the study, Last Study Day is defined as (the later of the last visit date and the date of last contact for participants lost-to-follow-up from the Discontinuation of Investigational Product End of Treatment or End of Study Disposition CRF) – date of first dose of randomized IP + 1.
	Days Since Last Dose for event (e.g., Death)	**Days Since Last Dose** is defined as date of event – date of last dose of study intervention.
9. Duration of event	The duration of any event	The duration of any event is defined as (stop date – start date + 1).
10. Special Lab Value Handling	Lab values with a prefix such as: '>', '<', '+' and 'Less than' etc.…	• '>': use the available original value +0.001 in the analyses. • '<': use the available original value –0.001 in the analyses. • '+': use the available original value without the prefix in the analyses. • '>=': use the available original value in the analyses. • '<=': use the available original value in the analyses.

Category	Description	Data Handling Rule
11. AE	Missing severity	For the AE summary by severity, an AE with missing severity will be deemed as Severe. Imputed values will not be listed in data listings.
	Missing relationship to IP	For AE summary by relationship, an AE with a missing relationship to IP will be deemed as related. Imputed values will not be listed in data listings.
	Treatment-emergent AE	An AE is considered treatment-emergent (or synonymously, on-treatment) if an event occurs on or after the date of first dose of randomized IP and on or before the earliest of the date of last dose of IP + 1, date of withdrawal of consent, or date of death. An AE that begins on the same date as the first dose of randomized study medication is treatment-emergent if the AE begins after the time of first dose or if the time of AE onset is unknown. A non-serious AE or SAE will not be considered to be treatment-emergent if its date of onset is after the last day of randomized treatment + 1 day. Such AEs or SAEs will be deemed to have occurred during the post-treatment-discontinuation follow-up. A death is considered to be treatment-emergent if any of the AEs that led to the death are treatment emergent; otherwise a death is not considered to be treatment-emergent if its date is after the last day of randomized treatment + 1 day, in which case the death would be deemed to have occurred during the post-treatment-discontinuation follow-up.

Category	Description	Data Handling Rule
	AE Start Date	If the AE start date is partial/missing, then: • Missing day - Impute the 1st of the month unless month is same as month of first dose of randomized IP then impute first dose date. • Missing day and month – impute 1st January unless year is the same as first dose date then impute first dose date. • Completely missing – impute first dose date unless the end date suggests it could have started prior to this in which case impute the 1st January of the same year as the end date. When imputing a start date ensure that the new imputed date is sensible i.e. is prior to the end date of the AE. If start date is found to be after end date, then set start date to equal end date. Also, duration of AE should not be derived using imputed dates.
12. Concomitant Medication/ Prohibited Medication	Phase	Concomitant medication phase • Prior: If start date or end date is before enrolment date. If it cannot be identified, then it is considered prior. • Concomitant medication during screening period: If start date (or end date if start is missing) is on or after enrolment date and prior to first dose of randomized IP. • Concomitant medication during treatment period: If start date (or end date if start date is missing) is on or after first dose of randomized IP and the date that is one day before treatment end date.

Category	Description	Data Handling Rule
		• Post-Treatment period: start date is on or after treatment end date.
	Concomitant medication start and end dates	If concomitant medication's start date is partial/missing, and the investigator has filled in that the study medication is taken prior to study, then: • Missing day – Impute the 1st of the month. • Missing day and month – impute 1st January. • Completely missing – impute 1st January with year of enrolment. If concomitant medication's start date is partial/missing, and the investigator has not filled in that the study medication is taken prior to study, then: • Missing day – Impute the 1st of the month or participants visit 1 date whichever is later. • Missing day and month – impute 1st January. or participants visit 1 date whichever is later. • Completely missing – impute participants visit 1 date. If concomitant medication's end date is partial/missing, then: • Missing day – impute last day of the month or participant's end of study date whichever is earlier. • Missing day and month – impute 31st December or participant's end of study date whichever is earlier. • Completely missing – impute participant's end of study date.

Category	Description	Data Handling Rule
		When imputing a start date ensure that the new imputed date is sensible i.e. is prior to the end date. If start date is found to be after end date, then set start date to equal end date.
13. Treatment Duration	Treatment Duration	Treatment duration is defined as Date of last dose of randomized IP - Date of first dose of randomized IP +1.
14. Hard coding	Hard coding for data analysis	Hard Coding is not allowed during data analysis unless if agreed in writing by AstraZeneca.
15. AUC calculation for spirometry endpoints	AUC_{0-3}	AUC_{0-3} will be calculated using the trapezoidal rule and actual time of assessment when available and nominal time of assessment otherwise.
16. HCRU	Number of days in CCU and ICU	Unknown responses will be included in the no. If the response was yes that there was a stay in the ICU/CCU, but the number of days is missing, then the average value for ICU/CCU stays in the treatment group should be used.

8.2 Details of Statistical Methods

8.2.1 Assumption Checks and Removal of Outliers in Sensitivity Analyses

In general, the distribution of spirometry measures is well approximated by a normal distribution. Under some circumstances, however, for example during an asthma exacerbation unrelated to treatment, extreme and atypical values can arise. Such values have high influence on estimation of variance parameters and on standard errors of fixed effect estimates. The distribution of residuals and influence statistics for FEV_1 AUC_{0-3} and morning pre-dose trough FEV_1 will be examined to identify such cases. In the event that a

single value, or small number of such outlying values, is found to exist and to be highly influential, the effects will be ameliorated by removal of the outlier or by the use of nonparametric methods. These analyses will be conducted if warranted to demonstrate the robustness of the results.

The assumption of normality in the data for FEV_1 AUC_{0-3} and morning pre-dose trough FEV_1 will be checked by visually inspecting the distribution of the residuals. Also, model fit and the assumption of homogeneity of variance will be verified by inspection of scatter plots of predicted vs. residuals, residuals vs. baseline trough FEV_1, residuals vs. treatment, residuals vs Albuterol reversibility, residuals vs. baseline asthma medication (ICS vs. ICS/LABA) and by box plots of residuals for model variables with a potential effect on variance (treatment, visit, baseline asthma treatment).

Over-dispersion of ACQ-7, ACQ-5, ACQ-6, and AQLQ+12 responder data will be checked for logistic regression models by visually inspecting the distribution of the residuals and applying the Deviance and Pearson Goodness-of-Fit Statistics. Any potential outliers will also be identified by inspection of the residuals. If a single or a small number of outlying values exist and are highly influential, then either the outlier will be removed or nonparametric methods will be used for analyses. These analyses will be conducted if warranted to demonstrate the robustness of the results.

Model fit of rate of severe asthma exacerbations and rate of CCI will be checked for negative binomial models by visually inspecting the distribution of the residuals and applying the Deviance and Pearson Goodness-of-Fit Statistics. Any potential outliers will also be identified by inspection of the residuals. If a single or a small number of outlying values exist and are highly influential, then either the outlier will be removed or nonparametric methods will be used for analyses. These analyses will be conducted if warranted to demonstrate the robustness of the results.

The proportional hazards assumption of the Cox model will be checked for time to CCI time to severe asthma exacerbations and time to first CCI The proportional hazards assumption for Cox regression will be checked by visual inspection through a plot of log{-log(survival function)} versus log(time) (LOGLOGS Plot) and by adding an interaction of treatment and the logarithm of time in the model. If the LOGLOGS plot shows parallel curves, then the proportional hazards assumption holds. A treatment by log-time interaction term (the interaction between treatment and the logarithm of time) will be included in the Cox model to check the extent of its influence and output will be saved in a text file.

8.2.2 Sensitivity Analysis Using a Tipping Point Analysis Under a MNAR Assumption for FEV_1 AUC_{0-3} and Morning Pre-dose Trough FEV_1

The following description of the tipping point analysis is for the endpoint of change from baseline in FEV_1 AUC_{0-3} and morning pre-dose trough FEV_1.

The estimation and inference performed for the Primary strategy for handling ICEs is valid under the MAR assumption. The tipping point analysis will address the question of robustness of the treatment effect estimates and statistical significance with respect to the MAR assumption for data missing beyond study withdrawal, lost to follow-up, by considering alternative distributions for the missing data, i.e., under a MNAR condition. Missing values that have been replaced by imputed values as per the Primary strategy for handling ICEs will not be tipped.

The tipping point analyses will be performed for BFF 320/9.6 µg vs. BD respective control group. Particularly, the effect of BFF 320/9.6 µg will be gradually worsened and the effect of the control group will be gradually improved, to the point where the comparison becomes not statistically significant, or the amount of worsening or improvement reaches a level that is not believed to be realistic. This will be achieved by considering a class of normal distributions defined by adjusting the BFF 320/9.6 µg and control group means by pre-specified constants δ_1 and δ_2, respectively. δ_1 and δ_2 will be ranging from 0 (no change) to 500 mL. At the same time, the distribution for the other treatment arms will not be modified, and will be assumed to be MAR.

Under this scenario, estimation of treatment effect for each given pair (δ_1, δ_2) will be performed via MI. The imputation approach is outlined below.

8.2.2.1 Imputation for the Tipping Point Analysis for FEV_1 AUC_{0-3} and Morning Pre-dose Trough FEV_1: the Primary Strategy for Handling ICEs

It is expected that the great majority of missing data will be caused by participants withdrawing from the study prematurely where not due to IP discontinuation in conjunction with new medication. The resulting missing data will have a monotone pattern, meaning that, once a participant has missing data for some visit, data will be missing for all subsequent visits. The methodology described below will be used to address this type of missing data pattern. It is also expected that a small amount of non-monotone missing data (when particpants skip intermediate visits, but return for evaluations at subsequent visits) will be present. The intermittent missing data will be imputed prior to the imputation of the monotone missing data. Intermittent missing data will be imputed using the Monte Carlo Markov Chain (MCMC) approach and then the imputed values will be adjusted by δ_1 or δ_2 as defined in the following section. Using the MCMC approach, missing visits will be imputed from the posterior distributions, derived from the joint distribution of morning trough FEV_1 at all visits within each treatment. For datasets with monotone missingness,

regression-based imputation for monotone missingness (Rubin, 1987) will be applied and has the flexibility that it may be performed in a sequential manner using univariate models with a number of predictor variables. For example, the earliest visit will be imputed first, then the next one, and so on using outcomes from previous visits as predictors. This sequential approach is considered to perform well in practice with monotone missingness even when normality assumptions do not hold (Little, 2002; Molenberghs and Kenward, 2007; White, Royston, and Wood, 2011).

A sequential regression-based MI procedure was suggested for the implementation of the delta-adjustment strategy in the National Research Council (NRC) report on missing data (National Research Council of National Academy of Sciences, 2010) so that time points are imputed one at a time and that δ adjustment can be propagated through time by using the adjusted values as predictors. This procedure follows the general principles of pattern mixture models with identifying restrictions (assumptions) discussed above and is summarized as follows:

i. Missing values at time point 1 (Week 4 for FEV_1 trough and Day 1 for FEV_1 AUC_{0-3}) will be imputed using a regression based MI method for monotone missingness (10 iterations per time point per δ_1 and δ_2). All covariates in the final RM model (except for visit and treatment by visit interaction) will be included in the modelling (prior maintenance medication (ICS versus ICS/LABA, baseline trough FEV_1, percent Albuterol reversibility and randomized treatment). At this stage, the imputed values will not yet be adjusted for any participant.
ii. After imputations are obtained in Step (i), for BFF 320/9.6 µg participants missing data at time point 1, the imputed value at time points 1 will be decreased by a value of δ_1, while for the control group participants the imputed value will be increased by δ_2. No adjustments will be made for missing values for other arms.
iii. All remaining time points will be imputed sequentially by repeating Steps (i–ii) for each time point including lag values from earlier time points in the imputation model (lag values will include imputed values from the previous step) in addition to the covariates specified above in Step (i). Data from participants who have already had their responses adjusted in the previous step(s) will not be further adjusted again since the regression on the previous value carries this change forward. This principle also extends to the preliminary step of imputing intermittently missing visits.

Negative values of FEV_1 will not be imputed. If a negative value is produced at any stage of the imputation, it will be replaced by zero.

8.2.2.2 Estimation for the Tipping Point Analysis for FEV_1 AUC_{0-3} and Morning Pre-dose Trough FEV_1

For the Primary strategy for handling ICEs, estimation of treatment effects will be done using the primary analysis model, applied to each pair (δ_1, δ_2) and imputation m.

The results from individual imputations are then combined using Rubin's rules (PROC MIANALYZE), and p-values for the BFF 320/9.6 µg vs. control arm contrasts reported as functions of (δ_1, δ_2).

8.2.2.3 The Choices of δ in the Tipping Point Analysis

The tipping point analysis is to be conducted for BFF MDI 320/9.6 µg vs. BD MDI. If in the main analysis the p-value for the comparison is not significant per type I error control procedure ($p \geq p_0$), there is no need to perform the tipping point analysis for that comparison . It will thus be assumed that $p < p_0$ in the main analysis, and the tipping point is defined as the value of the pair (δ_1^*, δ_2^*) such that $p(\delta_1^*, \delta_2^*) = p_0$.

To estimate (δ_1^*, δ_2^*), $p(\delta_1, \delta_2)$ will be evaluated for δ_1 and δ_1 ranging from 0 to 500 mL, in increments of 100 mL. A two-dimensional decrementing method will be applied. The mean change from baseline will be decremented by up to 500 mL in the treatment arm and incremented by up to 500 mL in the comparator arm. We will start with change of 100 mL, then 50 mL if it tips, then 10 mL to identify more precisely where it tips. The result at $\delta_1 = \delta_2 = 0$ should agree with the main analysis, because it corresponds to the MAR imputations, up to the Monte-Carlo error. If $p(-500,500) < p_0$, the result is robust to deviations from the MAR assumption, and no further analyses need to be performed. Otherwise, the p-value function will be estimated over a grid, where the deltas will be varied from 0 ml to -500 ml for BFF MDI 160/9.6 µg, and from 0 to 500 ml for BD, covering the square region $[-500,0] \times [0,500]$ of the (δ_1, δ_2) space. If a tipping point is observed with analysis using 100 mL increments, smaller increments of 50 then 10 may be explored in the relevant range to determine the tipping point more precisely.

Smoothing of the estimated $p(\delta_1, \delta_2)$ may be performed to reduce the noise from the Monte Carlo error, and (δ_1^*, δ_2^*) may be estimated as the crossing point of p_0 by the smoother.

8.2.3 Setup and Notation for Negative Binomial Modelling/Analysis of Severe Asthma Exacerbations

Setup and Notation

Observed variables for participant i:

- Randomised treatment group indicator variables Z_{1i}: having $Z_{1i} = 1$ denotes the treatment group; having $Z_{1i} = 0$ denotes the control group.
- For the pooled analysis: randomised treatment group indicator variables Z_{1i} and Z_{2i}: having Z_{1i}=1 if the budesonide dose is 320 µg, and 0 if the budesonide dose is 160 µg and Z_{2i}=1 if the formoterol dose is 9.6 µg, and 0 if no formoterol dose
- X_i - baseline covariate(s)
- τ_i - planned duration of follow-up
- Y_{il} - number of events during the relevant follow-up period
    - up to the occurrence of an ICE+1 day or or participant's last dose + 1 day if no ICE under the While-on-Treatment strategy
    - up to latest date of asthma status assessment in planned treatment period or last visit in planned treatment or the planned last treatment period visit if had IP discontinuation in conjunction with new medication (includes observed data up to the day of ICE (start date of new medication) +1 day and one additional imputed exacerbation if there is time to have one)for primary strategy for handling ICEs strategy)
- T_{il} - time to end of relevant follow-up

Standard Efficacy Analysis

Fit a negative binomial model where Y_i is the dependent variable, X_i and Z_i are covariates, and $\log(T_{il})$ is an offset. This can be fitted using PROC GENMOD in the usual way. To set up the notation, we assume the rate for participant i is given by:

$$\gamma_i \exp\left(\beta_0^{(m)} + \beta_1^{(m)} X_i + \beta_2^{(m)} Z_{1i} + \beta_3^{(m)} Z_{2i} + \beta_4^{(m)} Z_{3i}\right) \quad (1)$$

where γ_i denotes participant i's random effect. We assume that $\gamma_i \sim Ga(k, 1/k)$, where k denotes the shape parameter and the scale is $1/k$. Note that what SAS PROC GENMOD refers to as the dispersion parameter is $1/k$.

8.2.4 Bayesian Borrowing Analysis of Adolescent Population

Bayesian borrowing from the adult population is proposed to contribute information for estimation of the treatment effect in adolescents. This analysis is proposed for, Morning Trough FEV_1, and FEV_1 AUC 0-3 hours, using Primary Strategy for handling ICEs .

8.2.4.1 Morning Trough FEV_1 and FEV_1 AUC 0-3 Hours

The population summary measure of interest for both endpoints is the difference in mean change from baseline between treatment arms, which can be approximated by a Normal distribution. A Robust Mixture Prior approach is used, first specifying the initial weight w for the adult population. This prior is a mixture of two linear elements. The first is the "informative" element, or the estimated adult distribution. The second is the "uninformative" element, a distribution typically with mean of no effect (e.g. mean of 0 for the difference) and large variance but still proper, as the method requires proper distributions. The initial weight w is assigned to the informative element and (1- w) is placed on the uninformative element. This weight w is updated during the posterior calculation depending on the degree to which the observed treatment effect agrees with the adult treatment effect, and the updated weight is part of the final posterior distribution.

The analysis process follows these steps:

1. Standard frequentist regression model is fit to the adult (≥18 years) and adolescent (≥12 years to <18 years) data. The treatment effect on adults is used to obtain the Normal approximation for the adult difference in mean change from baseline between treatment arms (mean and variance).

2. The Normal approximation obtained in the previous step is then used as the informative prior $\pi_1(\theta|Y_{adult})$. The vague prior $\pi_2(\theta)$ is assumed to be Normal with mean of 0 (no difference) and estimated variance equivalent to that which would be provided by a single participant. This is the Empirical Bayes unit-information prior. This variance is calculated using the squared standard error of the difference in mean change from baseline obtained from adolescents, multiplied by N_p, where N_p is the total adolescent sample size. Usage of Normal distributions allows conjugacy, easily calculating the posterior.

3. The robust mixture prior is $\pi(\theta) = w\pi_1(\theta|Y_{adult}) + (1 - w)\pi_2(\theta)$.

4. The posterior for the treatment effect in adolescents is calculated by assuming an approximate Normal likelihood $L(\theta|Y_{adol})$ for the difference in mean change from baseline obtained from the treatment effect estimated on adolescents from the model fit in step 1. This likelihood is combined with

the robust mixture prior using the following conjugate model results to obtain the posterior mixture distribution for the difference in mean change from baseline in adolescents. Assume the informative prior $\pi_1(\theta|Yadult)$ has mean m_1 and variance v_1, denoted as $N(m_1, v_1)$ and the vague prior $\pi_2(\theta)$ is $N(m_2, v_2)$. Denote the Normal approximation of the likelihood for adolescents as $N(m_p, v_p)$. The final posterior for θ is then also a mixture of two Normal distributions

$$P(\theta|Y_{adol}, Y_{adult})=w*N(m_1^*, v_1^*) + (1 - w^*)N(m_2^*, v_2^*)$$

where

- $m_1^* = v_1^*\left(\frac{m_1}{v_1} + \frac{m_p}{v_p}\right)$ and $1/v_1^* = 1/v_1 + 1/v_p$
- $m_2^* = v_2^*\left(\frac{m_2}{v_2} + \frac{m_p}{v_p}\right)$ and $1/v_2^* = 1/v_2 + 1/v_p$
- $w^* = \frac{w\,c_1}{wc_1+(1-w)c_2}$ where

$c_1 = \frac{\exp\{-0.5(m_p-m_1)^2/(v_p+v_1)\}}{\sqrt{v_p+v_1}}$ and $c_2 = \frac{\exp\{-0.5(m_p-m_2)^2/(v_p+v_2)\}}{\sqrt{v_p+v_2}}$

The standard frequentist regression model referenced in steps 1 and 4 is (and the standard error for adolescents used in Step 2 is from) the same repeated measures analysis covariance model specified for the primary analysis of Morning Trough FEV_1 and FEV_1 AUC 0-3 Hours. The data from adults and adolescents will be used. The model will also include subgroup (adult vs adolescent), treatment by subgroup interaction, subgroup by visit interaction, treatment by subgroup by visit interaction Estimated means and variances from this regression model are used to construct the Normal approximations for $\pi_1(\theta|Y_{adult})$ and $L(\theta|Y_{adol})$. The treatment effect is considered significant if the 95% credible interval does not contain zero, and the effect is concluded to be in the direction of the interval.

The initial value of w is currently assumed to be $w = 0.5$. This choice allows the posterior weight w^* (and hence the dynamic update) to depend only on the data. and 4 is (and the standard error for adolescents used in Step 2 is from)

Unstructured covariance will be assumed to model the relationship between pairs of response variables taken at different visits on the same participant. To allow for the possibility that this model fails to converge with unstructured covariance, the same hierarchical approach will be used as per the primary analysis (Section 4.2.1.4).

8.2.5 Efficacy Tables

Title	PSC or Reported Outside of CSR
Overview of Key Efficacy	
Overview of key efficacy results for [redacted] Primary strategy for handling ICEs	PSC
Overview of key efficacy results for [redacted]: Primary strategy for handling ICEs	PSC
Overview of key efficacy results for [redacted] Primary strategy for handling ICEs	PSC
FEV1 AUC0-3	
Change from baseline in FEV1 AUC0-3 (L) (descriptive statistics) over time: Primary strategy for handling ICEs (Efficacy set)	PSC
Change from baseline in FEV1 AUC0-3 (L) (descriptive statistics) over time: while on treatment estimand (Efficacy set)	PSC
Change from baseline in FEV1 AUC0-3 (L) treatment comparisons by timepoint: Primary strategy for handling ICEs (Efficacy set)	PSC
Change from baseline in FEV1 AUC0-3 (L) treatment comparisons by timepoint: while on treatment estimand (Efficacy set)	PSC
Change from baseline in FEV1 AUC0-3 (L) treatment comparisons over 12-24 weeks for NI analysis: principal stratum estimand (Per-protocol set)	PSC
Change from baseline in FEV1 AUC0-3 (L) treatment comparisons at Week 24: tipping point analysis, Primary strategy for handling ICEs (Efficacy set)	Supplemental CSR - supportive estimands / Impact of missing data
Change from baseline in FEV1 AUC0-3 (L) treatment comparisons at week 24 for subgroup analysis: Primary strategy for handling ICEs (Efficacy set)	PSC
Change from baseline in FEV1 AUC0-3 (L) treatment comparisons over 24 weeks for subgroup analysis: Primary strategy for handling ICEs (Efficacy set)	PSC
Change from baseline in FEV1 AUC0-3 (L) treatment comparisons over 12-24 weeks for subgroup analysis: Primary strategy for handling ICEs (Efficacy set)	PSC

pre-dose trough FEV1	
Change from baseline in morning pre-dose trough FEV1 (L) (descriptive statistics) over time: Primary strategy for handling ICEs (Efficacy set)	PSC
Change from baseline in morning pre-dose trough FEV1 (L) (descriptive statistics) over time: while on treatment estimand (Efficacy set)	PSC
Change from baseline in morning pre-dose trough FEV1 (L) treatment comparisons by timepoint: Primary strategy for handling ICEs (Efficacy set)	PSC
Change from baseline in morning pre-dose trough FEV1 (L) treatment comparisons by timepoint: while on treatment estimand (Efficacy set)	PSC
Change from baseline in morning pre-dose trough FEV1 (L) treatment comparisons over 12-24 weeks for NI analysis: principal stratum estimand (Per-protocol set)	PSC
Change from baseline in morning pre-dose trough FEV1 (L) treatment comparisons at Week 24: tipping point analysis, Primary strategy for handling ICEs (Efficacy set)	Supplemental CSR - supportive estimands / Impact of missing data
Change from baseline in morning pre-dose trough FEV1 (L) treatment comparisons over 24 weeks: tipping point analysis, Primary strategy for handling ICEs (Efficacy set)	Supplemental CSR - supportive estimands / Impact of missing data
Change from baseline in morning pre-dose trough FEV1 (L) treatment comparisons over 12 -24 weeks: tipping point analysis, Primary strategy for handling ICEs (Efficacy set)	Supplemental CSR - supportive estimands / Impact of missing data
Change from baseline in morning pre-dose trough FEV1 (L) treatment comparisons at week 24 for subgroup analysis: Primary strategy for handling ICEs (Efficacy set)	PSC
Change from baseline in morning pre-dose trough FEV1 (L) treatment comparisons over 24 weeks for subgroup analysis: Primary strategy for handling ICEs (Efficacy set)	PSC
Change from baseline in morning pre-dose trough FEV1 (L) treatment comparisons over 12-24 weeks for subgroup analysis: Primary strategy for handling ICEs (Efficacy set)	PSC
Exacerbations	-
Rate of severe asthma exacerbation (pooled LITHOS and VATHOS data) treatment comparison: Primary strategy for handling ICEs (Efficacy set)	PSC

Rate of severe asthma exacerbation treatment comparison: Primary strategy for handling ICEs (Efficacy set)	PSC
Time to first severe asthma exacerbation (pooled LITHOS and VATHOS data): While on Treatment (Efficacy set)	PSC
Time to first severe asthma exacerbation treatment comparison: while on treatment (Efficacy set)	PSC
Rate of severe asthma exacerbation (pooled LITHOS and VATHOS data) treatment comparison: While on Treatment (Efficacy set)	PSC
Rate of severe asthma exacerbation treatment comparison: while on treatment estimand (Efficacy set)	Supplemental (publications only)
Rate of moderate or severe asthma exacerbation treatment comparison: while on treatment estimand (Efficacy set)	Supplemental (publications only)
Onset of action	-
Change from baseline in Onset of action (FEV1 (L)) (descriptive statistics) over time: Primary strategy for handling ICEs (Efficacy set)	PSC
Change from baseline in Onset of action (FEV1 (L) on day 1) treatment comparison: Primary strategy for handling ICEs (Efficacy set)	PSC
Change from baseline in Onset of action (FEV1 (L) on day 1) treatment comparison for subgroup analysis: Primary strategy for handling ICEs (Efficacy set)	Supplemental (publications only)
Change from baseline in Onset of action (FEV1 (L) on day 1) within group T-test: Primary strategy for handling ICEs (Efficacy set)	Supplemental (publications only)
Rescue medication	
Change from baseline in mean daily number of puffs of rescue medication use (puffs/day) (descriptive statistics) over time: Primary strategy for handling ICEs (Efficacy set)	PSC
Change from baseline in mean daily number of puffs of rescue medication use (puffs/day) treatment comparisons by timepoint: Primary strategy for handling ICEs (Efficacy set)	PSC
Percentage of rescue-free days treatment comparisons by timepoint: while on treatment estimand (Efficacy set)	Supplemental (publications only)

Percentage of symptom-free days treatment comparisons by timepoint: while on treatment estimand (Efficacy set)	Supplemental (publications only)
ACQ	
Percentage of responders in ACQ-7 by timepoint: primary strategy for handling ICEs (Efficacy set)	PSC
Percentage of responders in ACQ-7 by timepoint: Supportive strategy for binary endpoints (Efficacy set)	PSC
Percentage of responders in ACQ-5 by timepoint: primary strategy for handling ICEs (Efficacy set)	PSC
Percentage of responders in ACQ-5 by timepoint: Supportive strategy for binary endpoints (Efficacy set)	PSC
Percentage of responders in AQLQ+12 by timepoint: primary strategy for handling ICEs (Efficacy set)	PSC
Percentage of responders in AQLQ+12 by timepoint: Supportive strategy for binary endpoints (Efficacy set)	PSC
Change from baseline in ACQ-7 (descriptive statistics) over time: primary strategy for handling ICEs (Efficacy set)	PSC
Change from baseline in ACQ-7 treatment comparisons by timepoint: primary strategy for handling ICEs (Efficacy set)	PSC
Change from baseline in ACQ-5 (descriptive statistics) over time: primary strategy for handling ICEs (Efficacy set)	PSC
Change from baseline in ACQ-5 treatment comparisons by timepoint: primary strategy for handling ICEs (Efficacy set)	PSC
Change from baseline in AQLQ(s)+12 (descriptive statistics) over time: primary strategy for handling ICEs (Efficacy set)	PSC
Change from baseline in AQLQ(s)+12 treatment comparisons by timepoint: primary strategy for handling ICEs (Efficacy set)	PSC
Percentage of responders in ACQ-6 by timepoint: primary strategy for handling ICEs (Efficacy set)	Supplemental (publications only)
Change from baseline in ACQ-6 (descriptive statistics) over time: primary strategy for handling ICEs (Efficacy set)	Supplemental (publications only)
Change from baseline in ACQ-6 treatment comparisons by timepoint: primary strategy for handling ICEs (Efficacy set)	Supplemental (publications only)
Peak FEV1, FVC, PEFR AUC0-3, FEF25-75, and trough PEFR	
Peak change from baseline in FEV1 (L) treatment comparisons by timepoint: while on treatment estimand (Efficacy set)	Supplemental (publications only)

Time to peak FEV1 on day 1 treatment comparison: while on treatment estimand (Efficacy set)	Supplemental (publications only)
Percentage (%) of peak FEV1 (L) improvement achieved at 5 minutes (descriptive statistics) over time: while on treatment estimand (Efficacy set)	Supplemental (publications only)
Change from baseline in FVC AUC0-3 (L) treatment comparisons by timepoint: while on treatment estimand (Efficacy set)	Supplemental (publications only)
Change from baseline in PEFR AUC0-3 (L) treatment comparisons by timepoint: while on treatment estimand (Efficacy set)	Supplemental (publications only)
Change from baseline in FEF25-75 AUC0-3 (L) treatment comparisons by timepoint: while on treatment estimand (Efficacy set)	Supplemental (publications only)
Change from baseline in morning pre-dose PEFR (L) treatment comparisons by timepoint: while on treatment estimand (Efficacy set)	Supplemental (publications only)
Change from baseline in evening pre-dose PEFR (L) treatment comparisons by timepoint: while on treatment estimand (Efficacy set)	Supplemental (publications only)
Percentage of subjects with >= 12% improvement in FEV1 over baseline on Day 1 at each timepoint: while on treatment (Efficacy Set)	Supplemental (publications only)
CCI	
Time to first clinically important deterioration (CCI while on treatment estimand (Efficacy set)	Supplemental (publications only)
CCI	
Time to first composite exacerbation (CCI while on treatment estimand (Efficacy set)	Supplemental (publications only)
Time to first composite exacerbation (CCI over 12 Weeks: while on treatment estimand (Efficacy set)	Supplemental (publications only)
Rate of composite exacerbation (CCI for treatment comparison: while on treatment estimand (Efficacy set)	Supplemental (publications only)
EQ-5D	
EQ-5D dimensions categorical responses: while on treatment estimand (Efficacy set) EQ-5D-Y	Supplemental (publications only)

EQ-5D dimensions categorical responses: while on treatment estimand (Efficacy set) Adolescents EQ-5D-5L	Supplemental (publications only)
Change from baseline in EQ-5D index score (descriptive statistics) over time: while on treatment estimand (Efficacy set)	Supplemental (publications only)
Change from baseline in EQ-5D visual analog scale (descriptive statistics) over time: while on treatment estimand (Efficacy set)	Supplemental (publications only)
EQ-5D index score treatment comparisons by timepoint: while on treatment estimand (Efficacy set)	Supplemental (publications only)
EQ-5D visual analog scale treatment comparisons by timepoint: while on treatment estimand (Efficacy set)	Supplemental (publications only)
AIRQ	
AIRQ control categories: while on treatment estimand (Efficacy set)	Supplemental - payer outputs
Change from baseline in AIRQ (descriptive statistics) over time: While on treatment estimand	Supplemental (publications only)
HCRU	
Summary of Healthcare Resource Utilization over the treatment period for non-asthma related: while on treatment estimand (Efficacy set)	Supplemental - payer outputs)
Summary of Healthcare Resource Utilization over the treatment period for combined asthma and non-asthma related: while on treatment estimand (Efficacy set)	Supplemental - payer outputs
Summary of Healthcare Resource Utilization over the treatment period for asthma related: while on treatment estimand (Efficacy set)	Supplemental - payer outputs
Bayesian borrowing	
Change from baseline in FEV1 AUC0-3 (L) treatment comparisons at 12 weeks with Bayesian Borrowing for Adolescents (Efficacy Set)	Supplemental CSR
Change from baseline in morning pre-dose trough FEV1 (L) comparisons at 12 weeks with Bayesian Borrowing for Adolescents (Efficacy Set)	Supplemental CSR

8.2.6 CTCAE v5.0 Laboratory Test Criteria

CTCAE laboratory test criteria for shift tables and central laboratory reference ranges for use in flagging abnormal values.

Investigations				
	Grade			
Laboratory Analyte	1	2	3	4
Alanine aminotransferase increased	>ULN – 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 – 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 – 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Alkaline phosphatase increased	>ULN – 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal	>2.5 – 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal	>5.0 – 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Aspartate aminotransferase increased	>ULN – 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 – 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 – 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal

Investigations				
	Grade			
Laboratory Analyte	1	2	3	4
Blood bilirubin increased	>ULN – 1.5 x ULN if baseline was normal; > 1.0 - 1.5 x baseline if baseline was abnormal	>1.5 – 3.0 x ULN if baseline was normal; >1.5 - 3.0 x baseline if baseline was abnormal	>3.0 – 10.0 x ULN if baseline was normal; >3.0 - 10.0 x baseline if baseline was abnormal	>10.0 x ULN if baseline was normal; >10.0 x baseline if baseline was abnormal
Cholesterol high	>ULN – 300 mg/dL; >ULN -7.75 mmol/L	>300 – 400 mg/dL; >7.75 -10.34 mmol/L	>400 – 500 mg/dL; >10.34 -12.92 mmol/L	>500 mg/dL; >12.92 mmol/L
Creatinine increased	>ULN -1.5 x ULN	>1.5 – 3.0 x baseline; >1.5 -3.0 x ULN	>3.0 baseline; >3.0 – 6.0 xULN	>6.0 x ULN
GGT increased	>ULN – 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal	>2.5 – 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal	>5.0 – 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Hemoglobin increased (a)	Increase in >0 – 2 gm/dL above ULN (a)	Increase in >2 – 4 gm/dL above ULN (a)	Increase in >4 gm/dL above ULN (a)	n/a

Investigations				
	Grade			
Laboratory Analyte	1	2	3	4
Anemia (hemoglobin decreased)	LLN- 10g/dL; <LLN – 6.2 mmol/L; <LLN – 100 g/L	<10.0 – 8.0 g/dL; <6.2 – 4.9 mmol/L; <100 – 80g/L	<8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated	Life-threatening consequences; urgent intervention indicated
Leukocytosis (White blood cell increased) (b)			>100,000/mm^3	Clinical manifestations of leucostasis (sic); urgent intervention indicated Note that the spelling is often "leukostasis" in the literature.
White blood cell decreased	<LLN – 3000/mm^3; <LLN – 3.0 x 10^9/L	<3000 – 2000/mm^3; <3.0 – 2.0 x 10^9 /L	<2000 – 1000/mm^3; <2.0 – 1.0 x 10^9 /L	<1000/mm^3; <1.0 x 10^9 /L
Platelet count decreased	<LLN - 75,000/mm3; <LLN - 75.0 x 10^9/L	<75,000 - 50,000/mm3; <75.0 - 50.0 x 10^9/L	<50,000 - 25,000/mm3; <50.0 - 25.0 x 10^9/L	<25,000/mm3; <25.0 x 10^9/L

Metabolism and Nutrition Disorders				
	Grade			
Adverse Event	1	2	3	4
Acidosis	pH <normal, but >=7.3	-	pH <7.3	Life-threatening consequences
Alkalosis	pH >normal, but <=7.5	-	pH >7.5	Life-threatening consequences
Hypercalcemia	Corrected serum calcium of >ULN - 11.5 mg/dL; >ULN - 2.9 mmol/L; Ionized calcium >ULN - 1.5 mmol/L	Corrected serum calcium of >11.5 - 12.5 mg/dL; >2.9 - 3.1 mmol/L; Ionized calcium >1.5 - 1.6 mmol/L; symptomatic	Corrected serum calcium of >12.5 - 13.5 mg/dL; >3.1 - 3.4 mmol/L; Ionized calcium >1.6 - 1.8 mmol/L; hospitalization indicated	Corrected serum calcium of >13.5 mg/dL; >3.4 mmol/L; Ionized calcium >1.8 mmol/L; life-threatening consequences
Hyperkalemia	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L; intervention initiated	>6.0 - 7.0 mmol/L; hospitalization indicated	>7.0 mmol/L; life-threatening consequences
Hypermagnesemia	>ULN - 3.0 mg/dL; >ULN - 1.23 mmol/L	n/a	>3.0 - 8.0 mg/dL; >1.23 - 3.30 mmol/L	>8.0 mg/dL; >3.30 mmol/L; life-threatening consequences

Metabolism and Nutrition Disorders				
	Grade			
Adverse Event	1	2	3	4
Hypernatremia (Sodium Increased)	>ULN - 150 mmol/L	>150 - 155 mmol/L; intervention initiated	>155 - 160 mmol/L; hospitalization indicated	>160 mmol/L; life-threatening consequences
Hypertriglyceridemia	150 mg/dL - 300 mg/dL; 1.71 mmol/L - 3.42 mmol/L	>300 mg/dL - 500 mg/dL; >3.42 mmol/L - 5.7 mmol/L	>500 mg/dL - 1000 mg/dL; >5.7 mmol/L - 11.4 mmol/L	>1000 mg/dL; >11.4 mmol/L; life-threatening consequences
Hypoalbuminemia (Albumin Decreased)	<LLN - 3 g/dL; <LLN - 30 g/L	<3 - 2 g/dL; <30 - 20 g/L	<2 g/dL; <20 g/L	Life-threatening consequences; urgent intervention indicated
Hypocalcemia (Calcium Decreased)	Corrected serum calcium of <LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L; Ionized calcium<LLN - 1.0 mmol/L	Corrected serum calcium of <8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L; Ionized calcium <1.0- 0.9 mmol/L; symptomatic	Corrected serum calcium of <7.0 - 6.0 mg/dL; <1.75 - 1.5 mmol/L; Ionized calcium <0.9- 0.8 mmol/L; hospitalization indicated	Corrected serum calcium of <6.0 mg/dL; <1.5 mmol/L;Ionized calcium <0.8 mmol/L;life-threatening consequences

Metabolism and Nutrition Disorders				
	Grade			
Adverse Event	1	2	3	4
Hypoglycemia (Glucose Decreased)	<LLN - 55 mg/dL; <LLN - 3.0 mmol/L	<55 - 40 mg/dL; <3.0 - 2.2 mmol/L	<40 - 30 mg/dL; <2.2 - 1.7 mmol/L	<30 mg/dL; <1.7 mmol/L; life-threatening consequences; seizures
Hypokalemia (Potassium Decreased)	<LLN - 3.0 mmol/L	Symptomatic with <LLN - 3.0 mmol/L; intervention indicated	<3.0 - 2.5 mmol/L; hospitalization indicated	<2.5 mmol/L; life-threatening consequences
Hypomagnesemia (Magnesium Decreased)	<LLN - 1.2 mg/dL; <LLN - 0.5 mmol/L	<1.2 - 0.9 mg/dL; <0.5 - 0.4 mmol/L	<0.9 - 0.7 mg/dL; <0.4 - 0.3 mmol/L	<0.7 mg/dL; <0.3 mmol/L; life-threatening consequences
Hyponatremia (Sodium Decreased)	<LLN - 130 mmol/L	125-129 mmol/L and asymptomatic	125-129 mmol/L symptomatic; 120-124 mmol/L regardless of symptoms	<120 mmol/L; life-threatening consequences

Renal and Urinary Disorders				
	Grade			
Adverse Event	1	2	3	4
Chronic kidney disease	eGFR (estimated Glomerular Filtration Rate) or CrCl (creatinine clearance) <LLN -60 ml/min/1.73 m^2 or proteinuria 2+ present; urine protein/creatinine >0.5	eGFR or CrCl 59 - 30 ml/min/1.73 m^2	eGFR or CrCl 29 - 15 ml/min/1.73 m^2	eGFR or CrCl <15 ml/min/1.73 m^2; dialysis or renal transplant indicated
(a) Definition: A finding based on laboratory test results that indicate increased levels of hemoglobin above normal – i.e. above ULN. (b) Grade 1 and Grade 2 not categorized in CTCAE 5; Grade 1 and 2 based on reference laboratory alert criteria of 49.999999 GI/L (Covance)				

8.2.7 AstraZeneca Laboratory Criteria

Parameter	Lower limit	Upper limit	Change from baseline	Explanation	Business Rule
Hemoglobin	<80 g/L, (<8.0 g/dL)		Increase >40 g/L to a value above the ULN	Lower limit- CTCAE4 Grade 3 Upper limit – not defined by CTCAE4	Clinical Development does not perform medical monitoring for screening labs or eligibility criteria
White Blood Cell Count	<2 x 10^3/µL	>35 x 10^3/µL		Lower limit- CTCAE4 Grade 3 Upper limit – not defined in CTCAE4.	
Platelet Count	<50 x 10^3/µL	>999 x 10^3/µL		Lower limit- CTCAE4 Grade 3 Upper limit – not defined in CTCAE4.	
eGFR-EPI	decrease in ≥ 1 CTCAE grade change in eGFR and ≥ 20% change from baseline in all studies			Provides dynamic change in renal function (grade + %); ≥ 20% change from baseline is well outside the expected annual percentage change in eGFR	

Parameter	Lower limit	Upper limit	Change from baseline	Explanation	Business Rule
Aspartate Aminotransferase		>3 x ULN		Potential Hy's Law (when concurrent with Total Bilirubin >2ULN)	
Alanine Aminotransferase		>3 x ULN		Potential Hy's Law (when concurrent with Total Bilirubin >2ULN)	
Total Bilirubin		>2 x ULN		Potential Hy's Law	
Sodium	< 120 mmol/L			CTCAE4 – Grade 4	
Serum Potassium	<3.0 mmol/L	>6.0 mmol/L		CTCAE4 – Grade 3 for both Upper and lower limit	
Blood Glucose (random values)	<40 mg/dL; 2.2 mmol/L	>250 mg/dL; 13.9 mmol/L if no history of diabetes >500 mg/dL; 27.8 mmol/L regardless of baseline		Low- CTCAE4 (grade 3) High - CTCAE4 grade 3 (> 250) but DM common comorbidity in COPD, therefore if abnormal at Baseline- higher threshold used.	

8.3 Additional Reporting to Assess the Impact of Study Disruption Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis

In order to assess the impact of the study disruptions due to cases of civil crisis, natural disaster or public health crises, including the COVID-19 pandemic on the planned analyses, further additional summaries and analyses will be conducted. These are described below, with the section of the main Statistical Analysis Plan (SAP) in which they relate to.

8.3.1 Protocol Deviations

All COVID-19 related IPDs related to global/country situation will be grouped and summarized together with all other related IPDs. A listing of all PDs related to global/country situation (important and non-important PDs) will be provided.

8.3.2 Disposition Due to Global/Country Situation

Disposition table due to global/country situation will be provided. The following will be summarized: participants who completed treatment; participants who discontinued treatment due to global/country situation; participants who completed study; and participants who withdrew from study due to global/country situation.

8.3.3 Summary of Global/Country Situation Study Disruptions

Summary of global/country situation study disruptions will be provided: Participants with at least one global/country situation disruption: participants with visit impacted; participants with study intervention impacted; participants who withdrew from study due to global/country situation.

8.3.4 Summary of AEs

The number and percentage of participants reporting COVID-19 AEs (as defined based on the COVID-19 MedDRA terms) will be summarized by SOC and PT for the on-treatment and on-study periods.

AEs in participants reporting COVID-19 AEs will also be listed.

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