STATISTICAL ANALYSIS PLAN	
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D5982C00007 Protocol Title: A Randomized, Double-Blind, Double Dummy, Parallel Group, Multicenter 24 to 52 Week Variable Length Study to Assess the Efficacy and Safety of Budesonide, Glycopyrronium, and Formoterol Fumarate Metered Dose Inhaler (MDI) Relative to Budesonide and Formoterol Fumarate MDI and Symbicort® Pressurized MDI in Adult and Adolescent Participants with Inadequately Controlled Asthma (KALOS)

D5982C00008 Protocol Title: A Randomized, Double-Blind, Double Dummy, Parallel Group, Multicenter 24 to 52 Week Variable Length Study to Assess the Efficacy and Safety of Budesonide, Glycopyrronium, and Formoterol Fumarate Metered Dose Inhaler (MDI) Relative to Budesonide and Formoterol Fumarate MDI and Symbicort® Pressurized MDI in Adult and Adolescent Participants with Inadequately Controlled Asthma (LOGOS)

TABLE OF CONTENTS

TITLE PAGE 1
TABLE OF CONTENTS 2
LIST OF ABBREVIATIONS 7
AMENDMENT HISTORY 12
1 INTRODUCTION 29
2 CHANGES TO PROTOCOL PLANNED ANALYSES 29
3 DATA ANALYSIS CONSIDERATIONS 29
3.1 Timing of Analyses 29
3.2 Analysis Populations 29
3.2.1 Screened Analysis Set 30
3.2.2 Randomized Analysis Set 30
3.2.3 Efficacy Analysis Set 31
3.2.4 Per-Protocol Analysis Set 31
3.2.5 Safety Analysis Set 31
3.2.6 Pulmonary Function Test Sub-Study Analysis Set 31
3.2.7 Pharmacokinetic Analysis Set 31
3.2.8 Holter Monitoring Analysis Set 31
3.2.9 Analysis Sets for Pooled Analyses 32
3.2.10 Handling of Participants with Multiple Participation 32
3.3 General Considerations 32
3.3.1 General Study Level Definitions 32
3.3.1.1 Baselines for Analysis 33
3.3.1.2 Intercurrent Events 34
3.3.2 Hypothesis Testing 36
3.3.2.1 Hypothesis Testing for Individual Study 36
3.3.2.2 Hypothesis Testing of Non-Inferiority for Individual Study 38
3.3.2.3 Hypothesis Testing for Pooled Analysis 38
3.3.2.4 Hypothesis Testing of NI for Pooled Analysis 39
3.3.3 Assumptions Checks and Removal of Outliers in Sensitivity Analyses 39
3.3.4 Impact of Variable Length of the Study on the Analyses 39
3.3.5 ICE Estimand Strategies 40
3.3.5.1 Primary strategy for handling ICEs 40
3.3.5.2 While on Treatment 41
3.3.5.3 Supportive Composite strategy applied to responder endpoints 42
3.3.5.4 Principal Stratum 42
3.3.5.5 Objectives and Estimand Strategies for Individual Studies 43
3.3.5.6 Objectives and Estimand Strategies for Pooled Studies 43
3.3.6 Visit Windows 67
3.3.7 Handling of Unscheduled Visits 71
3.3.8 Multiplicity/Multiple Comparisons 71
3.3.8.1 CCI Approach 72

3.3.8.2 CCI Approach 73
3.3.8.3 CCI Approach 76
3.3.8.4 CCI Approach 78
3.3.8.5 CCI NI Tests 79
3.3.9 Handling of Protocol Deviations in Study Analysis 81
4 STATISTICAL ANALYSIS 81
4.1 Study Population 81
4.1.1 Subject Disposition and Completion Status 82
4.1.1.1 Definitions and Derivations 82
4.1.1.2 Presentation 82
4.1.2 Analysis Sets 82
4.1.2.1 Definitions and Derivations 82
4.1.2.2 Presentation 84
4.1.3 Protocol Deviations 84
4.1.3.1 Definitions and Derivations 84
4.1.3.2 Presentation 84
4.1.4 Demographics 84
4.1.4.1 Definitions and Derivations 84
4.1.4.2 Presentation 85
4.1.5 Disease Characteristics 85
4.1.5.1 Definitions and Derivations 85
4.1.5.2 Presentation 88
4.1.6 Medical and Surgical History 88
4.1.6.1 Definitions and Derivations 88
4.1.6.2 Presentation 88
4.1.7 Prior, Concomitant and Post-Treatment Medications 89
4.1.7.1 Definitions and Derivations 89
4.1.7.2 Presentation 89
4.1.8 Baseline Characteristics 90
4.1.8.1 Definitions and Derivations 90
4.1.8.2 Presentation 90
4.1.9 Study Treatment Compliance 91
4.1.9.1 Definitions and Derivations 91
4.1.9.2 Presentation 91
4.2 Endpoint Analyses for Individual Study 92
4.2.1 Primary Endpoint 92
4.2.1.1 Definition 92
4.2.1.2 Derivations 92
4.2.1.3 Handling of Dropouts and Missing Data 92
4.2.1.4 Primary Analysis of Primary Endpoint 93
4.2.1.5 Supportive Analyses of the Primary Endpoint 94
4.2.1.6 Sensitivity Analyses of the Primary Endpoint 94
4.2.1.7 Subgroup and Consistency Analyses of the Primary Endpoint 94
4.2.2 Secondary Endpoint 96
4.2.2.1 Definition 96
4.2.2.2 Derivations 96

4.2.2.3 Handling of Dropouts and Missing Data 96
4.2.2.4 Primary Analysis of Secondary Endpoint 96
4.2.2.5 Supportive Analyses of the Secondary Endpoint 97
4.2.2.6 Sensitivity Analyses of the Secondary Endpoint 97
4.2.2.7 Subgroup and Consistency Analyses of the Secondary Endpoint 97
4.2.3 Other Secondary Endpoints: PROs 97
4.2.3.1 Definition 97
4.2.3.2 Derivations 98
4.2.3.3 Primary Analysis of Other Secondary Endpoint: PROs 99
4.2.4 Other Secondary Endpoint: Onset of Action on Day 1 99
4.2.4.1 Definition 99
4.2.4.2 Derivations 99
4.2.4.3 Primary Analysis of Other Secondary Endpoint: Onset of Action on Day 1 100
4.2.4.4 Subgroup Analyses of Other Secondary Endpoint: Onset of Action on Day 1 100
4.2.5 Other Secondary Endpoint: Rate of Severe Exacerbations CCI 100
4.2.5.1 Definition 100
4.2.5.2 Derivations 100
4.2.5.3 Primary Analysis of Other Secondary Endpoint: Rate of Severe Asthma Exacerbations CCI 100
4.2.6 Non-Inferiority Test Endpoints (CCI Only) 100
4.2.6.1 Definition 101
4.2.6.2 Derivations 101
4.2.6.3 Analysis of NI Primary Endpoint 101
4.2.6.4 Analysis of NI Other Endpoints 101
4.2.7 Tertiary/Exploratory Endpoints: Lung Function 101
4.2.7.1 Definition 101
4.2.7.2 Analysis of Exploratory Lung Function Endpoints 101
4.2.8 Tertiary/Exploratory Endpoints: PROs and Time to Event 103
4.2.8.1 Definition 103
4.2.8.2 Derivations 103
4.2.8.3 Analysis of Exploratory PRO Endpoints 106
4.2.9 Tertiary/Exploratory Endpoints: Symptoms and Other 109
4.2.9.1 Definition 109
4.2.9.2 Analysis of Exploratory Symptoms and Other Endpoints 109
4.2.10 Healthcare Resource Utilization 111
4.2.10.1 Definition 111
4.2.10.2 Analysis of HCRU Endpoints 112
4.3 Endpoint Analyses for Pooled Studies 114
4.3.1 Primary Endpoint for Pooled Analyses: Rate of Severe Asthma Exacerbations 114
4.3.1.1 Definition 114
4.3.1.2 Derivations 115
4.3.1.3 Handling of Dropouts and Missing Data 116
4.3.1.4 Primary Analysis of Primary Endpoint for Pooled Analyses 116

4.3.1.5 Sensitivity Analyses of the Primary Endpoint for Pooled Analyses 118
4.3.1.6 Subgroup Analyses of the Primary Endpoint for Pooled Analyses 118
4.3.2 Secondary Endpoints for Pooled Analyses: Asthma Exacerbations 118
4.3.2.1 Definition 118
4.3.2.2 Primary Analysis of Secondary Endpoints for Pooled Analyses 118
4.3.3 Secondary Endpoints for Pooled Analyses: PROs 120
4.3.3.1 Definition 120
4.3.3.2 Primary Analysis of Secondary Endpoints for Pooled Analyses 120
4.3.4 Non-Inferiority Test Endpoints for Pooled Studies [redacted] Only) 120
4.3.4.1 Definition 120
4.3.4.2 Derivations 120
4.3.4.3 Analysis of NI Primary Endpoints 120
4.3.4.4 NI Analysis of Other Endpoints 120
4.3.5 Tertiary/Exploratory Endpoints 120
4.3.5.1 Definition 121
4.3.5.2 Primary Analysis of Tertiary/Exploratory Endpoints 121
4.3.6 12-Hour PFT Sub-Study Endpoints 124
4.3.6.1 Derivations 124
4.3.6.2 Primary Analysis of the 12-Hour PFT Sub-Study Endpoints 125
4.3.7 Integrated Pooled Analyses for Summary of Clinical Efficacy 127
4.3.7.1 Study Population 127
4.3.7.2 Endpoint Analyses 130
4.4 Pharmacodynamics 137
4.5 Pharmacokinetics Endpoints 137
4.5.1 PK Sampling 137
4.5.2 Calculation or Derivation of PK Parameters 138
4.5.3 Presentation of Pharmacokinetic Data 138
4.6 Immunogenicity 139
4.7 Safety Analyses 139
4.7.1 Exposure 139
4.7.1.1 Definitions and Derivations 139
4.7.1.2 Presentation 139
4.7.2 Adverse Events 140
4.7.2.1 Definitions and Derivations 140
4.7.2.2 Presentation 143
4.7.3 Clinical Laboratory 145
4.7.3.1 Definitions and Derivations 145
4.7.3.2 Presentations 147
4.7.4 Vital Signs 147
4.7.4.1 Definitions and Derivations 147
4.7.4.2 Presentations 148
4.7.5 Electrocardiogram 148
4.7.5.1 Definitions and Derivations 148
4.7.5.2 Presentations 149
4.7.6 24-Hour Holter Monitoring 150
4.7.6.1 Definitions and Derivations 150

4.7.6.2 Presentations 150
4.7.7 Physical Examination 152
4.7.7.1 Definitions and Derivations 152
4.7.7.2 Presentations 152
4.7.8 Consistency Analyses for Safety 152
5 ANALYSIS OF DATA FROM CCI AND CCI 152
5.1 Definition of CCI and CCI Cohorts 153
5.2 Analysis Considerations for CCI and CCI Cohorts 153
6 INTERIM ANALYSIS 154
7 STATISTICAL SOFTWARE 154
8 REFERENCES 154
9 APPENDIX 157
9.1 DATA HANDLING RULES 157
9.2 DETAILS OF STATISTICAL METHODS 166
9.2.1 Assumption Checks and Removal of Outliers in Sensitivity Analyses 166
9.2.2 Sensitivity Analysis Using a Tipping Point Analysis Under a MNAR Assumption for FEV_1 AUC_{0-3} and Morning Pre-dose Trough FEV_1 167
9.2.2.1 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 167
9.2.2.2 Estimation for the Tipping Point Analysis for FEV_1 AUC_{0-3} and Morning Pre-dose Trough FEV_1 169
9.2.2.3 The Choices of δ in the Tipping Point Analysis 169
9.2.3 Setup and Notation for Negative Binomial Modelling/Analysis of Severe Asthma Exacerbations 170
9.2.4 Sensitivity Analyses Using a Tipping Point Analysis Under a MNAR Assumption for Severe Asthma Exacerbations 171
9.2.4.1 Imputation for the Tipping Point Analysis for Severe Asthma Exacerbations: the Primary Strategy for Handling ICEs 172
9.2.4.2 Estimation for the Tipping Point Analysis for Severe Asthma Exacerbations 173
9.2.4.3 The Choices of δ in the Tipping Point Analysis 173
9.3 ASTRAZENECA SCORING GUIDELINE FOR LOGIC ITEMS OF THE SGRQ 174
9.4 ADDITIONAL REPORTING TO ASSESS THE IMPACT OF STUDY DISRUPTIONS DUE TO CASES OF CIVIL CRISIS, NATURAL DISASTER, OR PUBLIC HEALTH CRISIS 176
9.4.1 Protocol Deviations 176
9.4.2 Disposition due to global/country situation 176
9.4.3 Summary of global/country situation study disruptions 177
9.4.4 Summary of AEs 177

LIST OF ABBREVIATIONS

The table below provides a list of abbreviations and definitions of specialized or unusual terms, measurements, or units.

Refer to Section 4.5 for PK parameter abbreviations for the KALOS study.

Abbreviation or Specialized Term	**Definition**
ACQ	Asthma Control Questionnaire
AE	Adverse Event
AIR	Anti-Inflammatory Reliever
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
AQLQ(s) +12	Asthma Quality of Life Questionnaire for 12 years and older
ATC	Anatomic Therapeutic Class
AUC_{0-3}	Area Under the Curve 0 to 3 hours
BFF	Budesonide and Formoterol Fumarate
BGF	Budesonide, Glycopyrronium, and Formoterol Fumarate
BMI	Body Mass Index
BootMI	Bootstrap Multiple Imputation
BP	Blood Pressure
BSSR	Blinded Sample Size Re-estimation
CCV	Cardio- and Cerebro-vascular
CCU	Coronary Care Units
CI	Confidence Interval
CID	Clinically Important Deterioration
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CCI [redacted]	CCI [redacted]
COVID-19	Coronavirus Disease 2019
CrCl	Creatinine Clearance
CRF	Case Report Form
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CSRHLD	Clinical Study Report or Higher Level Document
CTCAE	Common Terminology Criteria for Adverse Events
DF	Degrees of Freedom
DPI	Dry Powder Inhaler
ECG	Electrocardiogram
eCRF	electronic Case Report Form
eDiary	electronic Diary
eGFR	Estimated Glomerular Filtration Rate
EQ-5D	European Quality-of-Life-5 Dimensions Questionnaire

Abbreviation or Specialized Term	**Definition**
ER	Emergency Room
ERT	eResearch Technology, Inc
CCI	CCI [redacted]
FEF_{25-75}	Forced Expiratory Flow at 25-75%
FeNO	Fractional Exhaled Nitric Oxide
FEV_1	Forced Expiratory Volume in 1 second
FVC	Forced Vital Capacity
GAM	Generalized Additive Model
HCRU	Healthcare Resource Utilization
HFA	Hydrofluoroalkane (propellant)
HLGT	High-Level Group Term
HLT	High-Level Term
HR	Heart rate
IA	Independent Adjudication
ICE	Intercurrent Event
ICF	Informed Consent/Assent Form
ICS	Inhaled Corticosteroid
ICS/BA	Inhaled Corticosteroid together with either Long-Acting β2-Agonist or Short-Acting Beta-Agonists
ICU	Intensive Care Unit
ID	Identification Number
IP	Investigational Product
IPD	Important Protocol Deviation
IQR	Interquartile Range
ITT	Intent-to-Treat
IVRS	Interactive Voice Response Technology
KALOS	Study D5982C00007
LABA	Long-Acting β_2-Agonist
LAMA	Long-Acting Muscarinic Antagonist
LLN	Lower Limit of Normal
LLOQ	Lower Limit of Quantification
LOGOS	Study D5982C00008
LS	Least Squares
MACE	Major Adverse Cardiovascular Event
MAR	Missing at Random

Abbreviation or Specialized Term	Definition
MCAR	Missing Completely at Random
MCMC	Monte Carlo Markov Chain
MedDRA	Medical Dictionary for Regulatory Activities
MDI	Metered-Dose Inhaler
MI	Multiple Imputation
mITT	modified Intent-to-Treat
MLE	Maximum Likelihood Estimate
MHLW	Ministry of Health Labor and Welfare
MNAR	Missing Not at Random
MTP	Multiple Testing Procedure
NI	Non-Inferiority
OCS	Oral Corticosteroids
OEQ	Onset of Effect Questionnaire
PD	Protocol Deviation
PCP	Primary Care Physician
PEFR	Peak Expiratory Flow Rate
PFT	Pulmonary Function Test
PGIC	Patient Global Impression of Change
PK	Pharmacokinetics
pMDI	pressurized Metered-Dose Inhaler
PP	Per-Protocol
PRN	Pro re Nata (taken as needed)
PRO	Patient Reported Outcome
PT	Preferred Term
PVC	Premature Ventricular Contractions
QEMT	Quality Event Monitoring Team
QTcF	QT interval corrected by Fridericia's formula
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDTM	Study Data Tabulation Model Datasets
SGRQ	St. George's Respiratory Questionnaire
SMO	Site Management Organisation
SMQ	Standardized MedDRA Queries

Abbreviation or Specialized Term	**Definition**
SOC	System Organ Class
ULN	Upper Limit of Normal
ULOQ	Upper Limit of Quantification
CCI	CCI
VAS	Visual Analogue Scale
WHO-DD	World Health Organization Drug Dictionary

AMENDMENT HISTORY

CATEGORY Change refers to:	**Date**	**Description of change**	**In line with CSP?**	**Rationale**
N/A	18-Jun-2021	Initial approved SAP	N/A	N/A
Secondary endpoint(s)	08-Jul-2022	A NI comparison of BFF MDI vs Symbicort pMDI added to KALOS.	Yes, v4.0.	NI testing was already included in LOGOS. The strategy was updated to also include KALOS [redacted]
Secondary endpoint(s)	08-Jul-2022	Timepoints for secondary endpoints included in the MTP for the NI comparison of BFF MDI vs Symbicort pMDI were updated, i.e. evaluating endpoints over 24 weeks rather than at Week 24.	Yes, v4.0.	NI comparison supports [redacted] Authority submission and timepoints of analyses were amended to reflect [redacted] authority requirements and to align with superiority analyses.
Secondary endpoint(s)	08-Jul-2022	The Hybrid estimand was added as supportive estimand for the primary and secondary endpoints.	Yes, v4.0.	The Hybrid estimand is deemed to answer an important clinical question of the treatment effect regardless of non-attributable ICEs, where an occurrence of an attributable ICE is considered an unfavourable outcome.
Secondary endpoint(s)	08-Jul-2022	The estimand used for the analysis of Onset of action on Day 1 for [redacted] was changed from While on Treatment.to Treatment Policy.	Yes, v4.0.	Change was done in order to achieve consistency with the testing of the primary and other secondary endpoints for [redacted] The analysis is expected to be equivalent between the two estimands.
Secondary endpoint(s)	08-Jul-2022	HRU endpoints were moved from the safety section to the efficacy section for consistency with CSP v4.0. Subsequently, the Efficacy Analysis Set will be used for those analyses.	Yes, v4.0.	Consistent with CSP v4.0
Secondary endpoint(s)	08-Jul-2022	Safety objectives were updated to include an assessment of the safety of BFF MDI relative to Symbicort pMDI.	Yes, v4.0.	Comparison supports [redacted]

Tertiary/exploratory endpoint	08-Jul-2022	Peak Change from Baseline in FEV_1 will be analyzed by visit, not over each 4-week interval.	Yes, v4.0	This was updated as this data are collected by visit, not daily.
Tertiary/exploratory endpoint	08-Jul-2022	Change from Baseline in Evening Pre-Dose PEFR will be analyzed over each 4-week interval using eDiary data, not by visit.	Yes, v4.0.	This was updated as this data are collected by eDiary, not assessed at clinic visit.
Tertiary/exploratory endpoint	08-Jul-2022	European Quality of Life-5 Dimension Questionnaire presentations will be split by adult and adolescent populations.	Yes, v4.0.	Practical considerations in mapping questions from the 2 questionnaires (adults and adolescents).
Tertiary/exploratory endpoint and PFT sub-study endpoints	08-Jul-2022	The following efficacy endpoints have been added: • The change from baseline in PEFR evaluated using AUC_{0-3} • PEFR evaluated using AUC_{0-12} from the PFT sub-study endpoint.	Yes, v4.0.	These endpoints are measured and considered clinically relevant. Change is aligned with CSP v4.0.
Safety objectives	08-Jul-2022	The While on Treatment ICE strategy will not be used for the analysis of Safety.	Yes, v4.0.	The only ICE of interest for those analyses is IP discontinuation. Instead of defining estimand for safety analyses, an on-treatment, and/or on-study periods for analysis are defined for safety.
24-Hour Holter Monitoring endpoints	08-Jul-2022	Evaluation of the QTcF values and increases from baseline were added for the Holter Monitoring population.	Yes, v4.0.	QTcF evaluations added to be consistent with CSP v4.0.
Statistical analysis method for secondary endpoint(s)	08-Jul-2022	The estimand used for analyses in the 12-Hour PK Sub-Study and 24-Hour Holter Monitor Sub-Study was changed to While on Treatment	Yes, v4.0.	The While on Treatment ICE strategy addresses the objective for these endpoints.

Statistical analysis method for secondary endpoint(s)	08-Jul-2022	For the composite estimand, participants that discontinued from randomized study intervention for reasons related to current global/country situation will not automatically be considered non-responders. Data will be imputed under MAR assumption following such ICEs and responder/non-responder status will be determined from the imputed data	Yes, v4.0.	Missing data following an ICE due to the current global/country situation is expected to occur at random (i.e., irrespective of randomized treatment).
Statistical analysis method for primary and secondary endpoints	08-Jul-2022	The categories (0, 1, ≥2) are added for the covariate baseline severe asthma exacerbation history.	Yes, v4.0.	Due to changes in the studies' inclusion criteria.
Statistical analysis method for primary and secondary endpoints	08-Jul-2022	Covariates for analyses were updated to include baseline trough FEV_1 and percent reversibility. Baseline blood eosinophil count was excluded as a covariate from models.	Yes, v4.0.	Additional covariates were added to control for more confounders that are relevant to the analysis. Baseline blood eosinophil count was excluded from the analyses given lesser relevance and potential impact of missing data.
Statistical analysis method for Tertiary/exploratory endpoint (s)	08-Jul-2022	The While on Treatment ICE strategy will be used for analysis of Time to CID as opposed to a Composite estimand.	Yes, v4.0.	The estimand was updated to align with the analysis of other tertiary time to event endpoints.
Subgroup analyses	08-Jul-2022	Subgroup analyses were added.	Yes, v4.0.	Subgroup analyses were added to explore the uniformity of the overall treatment effect.
PK analyses	08-Jul-2022	PK analyses terminology and outputs were updated.	Yes, v4.0.	PK analyses terminology and outputs were updated to reflect corporate standards.
Data presentation	08-Jul-2022	Removed ITT and mITT Analysis Sets. Added Efficacy Analysis Set, Randomized Analysis Set, and RAU Analysis Set.	Yes, v4.0.	The terms "ITT Analysis Set" and "mITT Analysis Set" replaced with "Efficacy Analysis Set" to align better with the estimand framework. The RAU Analysis Set was added for conducting the analysis on rescue medication use as this analysis set is more appropriate to identify treatment effects on rescue medication use.

Sample size	08-Jul-2022	Holter sub-study sample size was updated.	Yes, v4.0.	Reflects the change in sample size for the studies.
BSSR	08-Jul-2022	The wording for conducting a BSSR was changed from "will be conducted" to "may be conducted".	Yes, v4.0.	Change reflects the possibility of not conducting a BSSR.
Multiple testing procedure Secondary endpoint(s)	18-Jul-2023	**All regions:** MTP strategy was updated to a sequential testing of doses, where BGF high dose will be tested first, followed by BGF low dose. Tests on pooled severe exacerbation rate for participants with percent predicted FEV_1 less than or equal to 55% as well as for those with one or more severe exacerbations in the 12 months prior to Visit 1 were added. CCI MTP strategy was updated to compare BGF versus combined inhaled corticosteroid/long-acting beta2-agonist (pooled BFF and Symbicort) comparator arms. CCI For BFF NI comparisons, assay sensitivity gate requirement was removed, and order of analyses for BFF NI comparisons was updated.	Yes, v4.0.	CCI [redacted]
Statistical analysis method for primary and secondary endpoints	18-Jul-2023	For the repeated measures analysis of covariance model, the variance-covariance structure will be modified in the following order until the model converges: UN, TOEPH, ARH(1), TOEP and AR(1).	NA	This was modified to align with AZ therapeutic area guidance and to deal with possible imputation challenge.

Tertiary/exploratory endpoint	18-Jul-2023	For CCI endpoint: • CCI was renamed CCI CCI • CCI threshold for criteria assessing CCI was updated. • Event count and duration of event were clarified.	NA	These were updated to align with AZ standard in Respiratory & Immunology therapeutic area.
Safety analyses	18-Jul-2023	For AE comparison, the risk difference will be presented based on exposure adjusted incidence rate.	NA	For the comparison of risk difference, exposure adjusted incidence rate was applied due to the variable length of study design.
Safety analyses	18-Jul-2023	For vital sign, shift tables were added for baseline values vs maximum and minimum on-treatment observation values.	NA	Shift tables for vital sign were added to align with AZ corporate standard.
Safety analyses	18-Jul-2023	For ECG, calculations of baseline and post-baseline measurements were added for ECG data from main study and from Holter Monitoring sub-study.	NA	The difference in definition is due to the study design: there is one ECG reading scheduled per timepoint for main study, and there are 6 ECG readings taken pre-dose and triplicate ECG readings taken post-dose for Holter Monitoring sub-study.
Safety analyses	18-Jul-2023	Imputation rules were added for partial/missing AE start date.	NA	Imputation rules were added per AZ corporate standard.
Safety analyses	18-Jul-2023	For adjudicated MACE events, cardiovascular death was added as one sub-category.	NA	Cardiovascular death will be adjudicated under death events. It is considered as one important category of MACE events and added as sub-category for the summary of adjudicated MACE events.
Data presentation	18-Jul-2023	Adjusted analysis-defined visit windows have been defined such that data from repeated visits can be used for visit-based analyses.	Yes, v4.0.	Allows use of data closest to the scheduled visits.

Data presentation	18-Jul-2023	For disease characteristics, the following summary was added: • Categorical summary was added for baseline blood eosinophil count. • Category "low" was defined and added for Prior ICS dose.	NA	Those additional summaries help us better characterize study population.
Data presentation	18-Jul-2023	Reference table for laboratory test criteria was removed. Reference table for eGFR Grade was added.	NA	Centralized lab was applied for lab data collection. The reference range and abnormality were identified by central lab and reported. Grades for eGFR were not identified by centralized lab.
Throughout	18-Jul-2023	Minor editorial revisions.	Yes, v4.0.	Minor, therefore, not summarized
Data presentation	16-Apr-2024	Data from participants at sites using CCI CCI be excluded from all analysis sets.	NA	This was added due to the GCP violations at sites using CCI
Data presentation	16-Apr-2024	Column added in tables 3 and 5 to clarify for exploratory endpoints which are to be reported in the CSR versus outside of CSR.	NA	To provide clarity as to what would be reported in CSR prior to unblinding data.
Data presentation	16-Apr-2024	Rescue Albuterol User (RAU) analysis set was removed. Enrolled Analysis set was changed to "Screened Analysis Set"	No	RAU analysis set was removed due to low number of participants for this analysis set. Clarification re nomenclature for screened.
Data presentation	16-Apr-2024	For participant with overlapping participations, all such participations will be included for the safety analysis of individual study.	NA	For participant with overlapping participations, all such participations are deemed as important for the assessment of individual study safety.
Data presentation	16-Apr-2024	Removed a number of listings	NA	Streamline to what is required per Health Authority requirements
Data presentation	16-Apr-2024	Reasons of exclusion from sub-study were updated to add one summary row for participants who didn't consent.	NA	Participants who didn't consent to participate in the sub-study were summarized.
Data presentation	16-Apr-2024	Updated the definition of countries for CCI .	NA	Updated to reflect the latest recruitment in CCI

Data presentation	16-Apr-2024	Data handling rule for partial/missing concomitant medication start or end date was added.	NA	This was not included in previous version and important for assigning the medications to different phases.
Data presentation	16-Apr-2024	Updated start of treatment period/time at risk derivations to use date of first dose of IP after randomization instead of date of randomization.	NA	Clarified for derivation purpose as a few participants do not have first dose of IP on the same day as date of randomization.
Statistical analysis method for primary and secondary endpoints	16-Apr-2024	Baseline for reversibility was updated: we will use Visit 2 for its baseline value. If the Visit 2 value is missing, then the Visit 3 value will be used. If the Visit 2 and Visit 3 values are both missing, then the historical reversibility value will be used.	NA	The longer in screening period participants are, the higher their reversibility would be, so to have the same baseline criteria for all participants (especially when this is used as covariate), we should use the same Visit 2 as priority (even if we have more recent data for some participants).
Statistical analysis method for primary and secondary endpoints	16-Apr-2024	The simplification to planned last visit and day.	Yes, v5.0.	Clarification of text.
Statistical analysis method for primary and secondary endpoints	16-Apr-2024	For ICEs: • Clarified ICE descriptor to decrease list of prohibited medications to align with CSP and that certain reasons are attributable pending review. • Handling of ICEs revised to focus on first ICE only	Yes, v5.0. NA	• Align with CSP and focus list of treatments to LAMA, LABA and biologics/monoclonal antibodies. • Simplification of approach for Attributable and Hybrid handling of ICEs.
Statistical analysis method for primary and secondary endpoints	16-Apr-2024	For NI analysis, CIs are updated.	No	It was clarified to present the two-sided 95% CIs.
Statistical analysis method for primary and secondary endpoints	16-Apr-2024	Time window was added for spirometry endpoints for main study beside PFT sub-study.	NA	Time window applies for main study spirometry endpoints, same as for PFT sub-study.

Statistical analysis method for primary and secondary endpoints	16-Apr-2024	For onset of action, CIs are updated.	No	It was clarified to present the two-sided 95% CIs.
Statistical analysis method for primary and secondary endpoints	16-Apr-2024	The covariance structure modification approach was updated.	NA	Updated to simplify the approach.
Statistical analysis method for primary and secondary endpoints	16-Apr-2024	For onset of action, it was clarified that results from While on Treatment ICE strategy are the same as the results from Treatment Policy estimand.	NA	Updated for clarification purpose.
Statistical analysis method for primary and secondary endpoints	16-Apr-2024	Added "study" as one covariate into the models for all pooled analyses.	No	"Study" is considered as one important covariate for pooled analyses.
Statistical analysis method for primary and secondary endpoints	16-Apr-2024	Updated the derivation of time at risk for asthma exacerbation for different estimands.	NA	This was updated to reflect the impact of ICEs to time at risk
Tertiary/exploratory endpoint	16-Apr-2024	Baseline for daily eDiary metrics was updated.	NA	This was updated to align with AZ TA standard.
Tertiary/exploratory endpoint	16-Apr-2024	For reversibility subgroup analysis, the categories were updated with ">=20%" "<20%". For baseline pre-bronchodilator percent predicted FEV_1 subgroup, it was updated with "<=55%" and ">55%.	NA	Low number of participants with reversibility < CCI . For baseline pre-bronchodilator percent predicted FEV_1 subgroup analysis, this was updated to be consistent with the subgroup analysis specified in MTP.

Tertiary/exploratory endpoint	16-Apr-2024	For subgroup analysis: • The model was updated to add subgroup and interaction terms instead of subsetting data based on subgroup. • Lower number needed within a subgroup to provide estimates.	NA	• Updated to assess the p-value for treatment-by-subgroup interaction. • Aligning across program.
Tertiary/exploratory endpoint	16-Apr-2024	For EQ-5D comparison model, "Prior ICS dose (Medium vs High)" was added as one covariate.	No	"Prior ICS dose (Medium vs High)" is considered as one important covariate for EQ-5D, and consistent with use in other statistical models in study.
Tertiary/exploratory endpoint	16-Apr-2024	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.	NA	This approach was applied for efficiency purpose.
Safety analyses	16-Apr-2024	Added the data handling rule for concomitant medications/prohibited medications' partial/missing date.	NA	Clear rules to be applied programmatically
Safety analyses	16-Apr-2024	For summary of frequent SAEs table, the cutoff was updated from ">=2% participants in either BGF group" to ">=2 participants in total treatment group".	NA	A majority of the SAE PTs are just reported by one or two subjects across all treatment groups, applying ">=2% participants in either BGF group" would exclude too many SAEs.
Other	16-Apr-2024	Estimand descriptions were clarified, and repetitive text was removed.	Yes	To remove repetitive text and streamline descriptions.
Throughout	16-Apr-2024	Minor editorial revisions.	NA	Minor, therefore, not summarized

Statistical analysis methods for primary endpoint(s) Statistical analysis method for secondary endpoint(s)	22-Nov-2024	ICE strategies aligned with the clinical question. Treatment Policy estimand strategy replaced with Primary strategy for handling ICEs and specified as primary strategy for superiority analysis of primary and secondary endpoints and supportive strategy of NI analyses as well as selected tertiary endpoints for every Healthy Authority CCI CCI While on Treatment strategy specified as a supportive strategy for superiority analysis of all primary and secondary endpoints.	Yes, v6.0	CCI [redacted]
Statistical analysis methods for primary endpoint(s) Statistical analysis method for secondary endpoint(s)	22-Nov-2024	3.3.5 ICE Estimand Strategies: Removal of Hybrid and Attributable supportive estimand strategies for handling of ICEs.	Yes, v6.0	Simplification as new Primary strategy for ICE's mostly addresses the clinical question meant to be answered with the Hybrid and Attributable strategies.
Statistical analysis methods for primary endpoint(s) Statistical analysis method for secondary endpoint(s)	22-Nov-2024	3.3.1.2 Intercurrent events: Update to list of ICEs to remove distinction between attributable and non-attributable ICEs	Yes, v6.0	To align with removal of hybrid and attributable supportive strategies for ICEs.
Statistical analysis methods for primary endpoint(s) Statistical analysis method for secondary endpoint(s)	22-Nov-2024	3.3.1.2 Intercurrent events: Update to the ICE definitions: 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.	Yes, v6.0	Simplification as key medications identified as biological therapy/ monoclonal antibodies, LABA, LAMA, LTRA, maintenance ICS, or ICS/BA PRN (to capture AIR)

Statistical analysis methods for primary endpoint(s) Statistical analysis method for secondary endpoint(s)	22-Nov-2024	3.3.5 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	NA	To provide clarity for programming the analysis
Other	22-Nov-2024	3.3.1.2 Intercurrent events: Holter Monitoring sub-study (for KALOS study only): List of prohibited medications thought to impact interpretation of the Holter data added PFT sub-study (KALOS and LOGOS) clarification added that this sub-study will use the same permanent and temporary ICEs as defined for the main study.	NA	To provide clarification on the ICEs for the sub-studies.
Other	22-Nov-2024	3.3.1 General Study Level Definitions Clarification added that stratification factors covariates as well as disease characteristics parameters will be derived based on the data collected via eCRF and not though the IVRS.	NA	To provide clarity for programming the analysis
Other	22-Nov-2024	3.3.2.1 Hypothesis Testing for Individual Studies Removed comparability test performed prior to pooling BFF MDI and Symbicort pMDI arms.	Yes, v6.0	To align with CSP
Statistical analysis methods for primary endpoint(s) Statistical analysis method for secondary endpoint(s)	22-Nov-2024	3.3.4 Impact of Variable Length of the Study on the Analysis: Updated planned last visit definition to be within the planned treatment period (excludes follow up visits).	NA	To provide clarity for programming data imputations

Multiple testing procedure Secondary endpoint(s)	22-Nov-2024	• For CCI Approach clarified that testing of onset of action on Day 1 will commence only if the test for the pooled severe exacerbation rate and FEV_1 AUC_{0-3} are both statistically significant. • For CCI Approach, replaced the strategy for ICEs for testing rate of severe exacerbations within each study in the MTP from Attributable to Primary strategy	Yes, v6.0	• To correct text. • To align with updated strategies for ICEs.
Statistical analysis method for primary pooled endpoint(s)	22-Nov2024	Removed sensitivity analysis for the NI test on pooled rate of severe exacerbations	NA	Simplification
Other	22-Nov-2024	Table 3 full definition of PK parameters added.	NA	Definitions changed to be in line with AZ PK guidance document
Data presentation	22-Nov-2024	Participants randomized at site 7822 will be removed from all analysis sets. Safety data from this site and those using Medipharma SMO will be listed.	NA	Suspected serious breach of GCP and data fabrication at site.
Statistical analysis method for secondary endpoint(s)	22-Nov-2024	PP Analysis Set amended to exclude those only with an IPD impacting efficacy at baseline and not all IPDs at baseline	Yes, v6.0	To select only IPDs expected to impact the efficacy analysis
Data presentations	22-Nov-2024	P-values, where necessary, will be presented to four decimal places added	NA	To provide clarity for programming the analysis
Data presentations	22-Nov-2024	Removal of demographic summaries for screen-failures; clarification that for disease characteristics will be presented by age not all subgroups as described.	NA	Streamlining number demographic and disease characteristic summaries to key analyses sets/subgroups

Data presentations	22-Nov-2024	Population used for medication summaries changed from safety to efficacy set.	NA	To align with the population used for the efficacy analysis
Other	22-Nov-2024	Added additional details to the definitions for end of treatment period/ time at risk/ for different estimands/ endpoints.	NA	To provide clarity for the endpoint derivations
Other	22-Nov-2024	Removal of concomitant listing, ECG listing (including holter monitoring), physical examination, and vital signs listings; added listing of IP overdosing to AE section	NA	To streamline the number of listings to be generated
Other	22-Nov-2024	Tables 6 to 12 Visit time windows: Adjusted defined window visit for "Follow-up" was removed	NA	No efficacy data collected during follow-up for data presentation.
Other	22-Nov-2024	Upper time limit for post dose 5 mins spirometry assessments changed from 7 to 10 minutes in Table 13.	NA	The window has been extended to reduce the amount of clinically relevant missing data.
Other	22-Nov-2024	Clarified that sensitivity analyses on the primary endpoint in the individual as well as the pooled studies will be performed for the CCI and CCI approaches. Sensitivity analyses for the key secondary endpoint will be performed for CCI only.	NA	Clarification and simplification due to extended computational time required for conducting the analyses.
Derivation of secondary endpoint(s)	22-Nov-2024	Section 4.2.3.2 Clarification that the mean score for ACQ-7 will be calculated prior to assigning visit windows to the data. Additionally, if question 7 is missing then the answer will be derived from the spirometry data on the same date.	NA	Due to Q7 often being entered at a later time by site. Derivations on Q7 will be done to decrease amount of missing data.

Other	22-Nov-2024	Tertiary/ exploratory endpoint: It was clarified that evening PEFR recorded between 00a.m and 03a.m will be considered for the analysis of evening PEFR on the day before the recorded date	NA	To provide clarity for programming the analysis.
Other	22-Nov-2024	Tertiary/ exploratory endpoint: CCI [redacted] CCI [redacted] removed from CCI [redacted] criteria	NA	To align with company standards.
Statistical analysis method for secondary endpoint(s)	22-Nov-2024	Section 4.2.6.1: NI Change from baseline in FEV1 AUC0-3 over 24 weeks moved from a primary endpoint status for the NI tests to secondary.	Yes, v4.0	To correct text to follow the sequential testing order specified in CSP.
Tertiary/exploratory endpoint	22-Nov-2024	Updated rate calculation of endpoint “Rate of Severe Asthma Exacerbation Resulting in a Temporary Course of Systemic Corticosteroids for At Least 3 Consecutive Days” to number of exacerbations and not number of days in the numerator	NA	To correct definition
Other	22-Nov-2024	Clarification added to definition of Time to First Hospitalization for Asthma Exacerbation (Tertiary/ Exploratory endpoint) that the time period starts at the time from the first dose of study medication after randomisation.	NA	To align with first dose date
Tertiary/exploratory endpoint	22-Nov-2024	Removed endpoint: “Time in days to permanent discontinuation of study intervention due to asthma exacerbation”	Yes, v6.0	Insufficient amount of data expected to perform the analysis

Other	22-Nov-2024	Sections 4.7.2 and 9.1: 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.	NA	Clarified for derivation purposes. Definition added in line with the AE reporting on-treatment period
Other	22-Nov-2024	Appendix Data handling rules AEs of worsening severity removed from the treatment emergent definition.	NA	Treatment emergent AEs identified programmatically from onset date within defined study periods.
Other	22-Nov-2024	Appendix Data handling rules definition for treatment period for efficacy removed	NA	Contained within body of the SAP.
Other	22-Nov-2024	Appendix Data handling rules reference to first dose of study drug changed to first dose of randomized IP in imputation methods for handling missing start dates. Similarly for definitions of concomitant medications.	NA	Clarified for derivation purposes
Other	22-Nov-2024	Section 4.7.3 Added definition for a treatment emergent kidney function abnormalities and a summary of number of participants with a treatment emergent kidney abnormality	NA	To allow more comprehensive summary and interpretation of kidney function safety data
Other	22-Nov-2024	Section 5 Added clarification on CCI cohort and analyses for CCI submission	NA	To provide clarity on analyses produced for CCI population
Other	22-Nov-2024	Section 9.2.1 Clarified that model fit of rate of severe asthma exacerbations and rate of CCI will be checked	NA	To provide clarity on the assumptions checks for negative binomial analyses

Other	22-Nov-2024	Section 4.2.16 and Section 9.2.2 For the tipping point analyses of the primary and key secondary endpoints in the individual studies: • "between-within" method for computing the degrees of freedom will be used instead of Kenward-Roger approximation. • The tipping point may be shown to a precision of 10mL. 100 mL precision will be used otherwise.	NA	Simplification due to extended computational time required for conducting the analyses.
Other	22-Nov-2024	Section 9.2.4.3 Added clarifications on the square region of the (δ_1, δ_2) space and for conducting the tipping point analysis on severe asthma exacerbations.	NA	To provide clarity of the of the (δ_1, δ_2) space and its likelihood
Other	22-Nov-2024	Minor editorial revisions	Yes, v6.0.	Minor, therefore, not summarized
Multiple Participation	6-Mar-2025	Section 3.2.10 Clarify multiple participation is counted over all 4 studies KALOS, LOGOS, LITHOS, VATHOS. PFT and PK set to follow handling rules of Efficacy and PP sets. Holter set to follow handling rules of Safety set.	NA	All studies are relevant
Multiple Testing Procedures	6-Mar-2025	Section 3.3.8.4 Update CCI multiple testing procedure and graphic.	Local CSP only	For purposes of CCI approach only, to prioritize lung function tests comparing BGF MDI 320/14.4/9.6 µg versus BFF MDI 320/9.6 µg over pooled severe exacerbations.
Analysis Set Exclusion	6-Mar-2025	Section 4.1.2.1 Clarify that every analysis set excludes multiple participants, not just Efficacy and Safety.	NA	Clarification for programming
ICE strategy/missing data	6-Mar-2025	Section 4.2.3.3 Clarify for Supportive Composite Strategy of PROs, intermittent missing data will be classified as non-response, except due to global/country situation.	Yes	Clarification for programming

Tertiary/Exploratory Endpoint	6-Mar-2025	Section 4.2.9.2 Update definition of Percentage of Rescue-Free and Symptom-Free Days to be clear about how to handle half days, and thus how to calculate numerator and denominator.	NA	Clarification for programming
Tertiary/Exploratory Endpoint	6-Mar-2025	Section 4.3.5.2 More applicable directions for how to program asthma deteriorations versus the definition given in Section 4.3.1.1	NA	Clarification for programming
Pooled analysis	6-Mar-2025	New Section 4.3.7 added to describe integrated pooled analyses to be conducted either to support CSR or High Level Submission Documents (not reported in CSR).	No	Decision to consolidate into main study SAP
Data handling	6-Mar-2025	Appendix 9.1 For Spirometry data processing, all data is mapped to SDTM, not just best effort, and the variable RETREFID is used to map best efforts from SDTM to ADAM data sets.	NA	Correction of previous instructions
Data presentation	10-Mar-2025	Section 3.2 Efficacy data from participants at site 5712 (KALOS) will be excluded from all analysis. An additional set of specified individuals will be excluded from analysis. This additional set will not be excluded from the entire efficacy set, but be excluded from the number of patients used in the analysis: ‘n’ for the endpoints utilizing eDiary data collected at home.	NA	Site-wide GCP compliance issue and QEMT investigations.

1 INTRODUCTION

The purpose of this document is to give details for the statistical analyses of two replicate studies D5982C00007 (KALOS) and D5982C00008 (LOGOS) supporting their respective CSRs. All primary and secondary endpoint analyses will be reported in the CSR. Most tertiary/exploratory analyses and some supportive analyses will be reported outside of the CSR. For details, refer to last column of Table 3 and Table 5. The reader is referred to the CSP Version 6.0 and the CRF for details of study conduct and data collection. The analyses in this document apply to both studies, unless specified otherwise. This SAP is for the individual studies as well as the pooled analysis of both studies.

2 CHANGES TO PROTOCOL PLANNED ANALYSES

To address an error in CSP v6.0, the SAP provides details that censoring for the analysis of time to first CCI in the individual studies, KALOS and LOGOS, will be identical to that in the analysis of time to first CCI performed on the pooled studies data. For those analyses, participants not having any CCI event or any ICE will be censored at the minimum of (their Week 12 visit date, date of last dose +1 day) for the analysis including data up to and including Visit 8 (Week 12). For the analysis including all observed data, those participants will be censored at the date of their last dose + 1 day.

3 DATA ANALYSIS CONSIDERATIONS

3.1 Timing of Analyses

The primary analysis will be performed for each individual study after the respective clinical data lock. CSP-specified pooled analyses will be performed after the clinical data lock of the study that completes last (of the two replicate studies KALOS and LOGOS). Both the individual study analyses and the pooled analyses will be presented in the individual CSRs.

A BSSR may be conducted approximately three months prior to last-participant-in in the earlier completing of the two replicate studies. BSSR will consider the information combined from each study. The operating characteristics of the BSSR will be fully detailed in the BSSR SAP, if it is decided to conduct a BSSR.

3.2 Analysis Populations

The definitions of the following analysis sets are based on participant selection.

Data from participants at sites using CCI will be excluded from all analysis sets except Screened Analysis Set in line with MHLW guidance. This is all participants at sites: CCI
Data from participants at site CCI and siteCCI 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.

Additionally, the following list of participants will be excluded from analyses of selected efficacy endpoints in line with QEMT investigation:

- **KALOS:** CCI [redacted]
- **LOGOS:** CCI [redacted]

Those participants will not be excluded from the efficacy set, but will be excluded from the number of patients used in the analysis: 'n' for the following endpoints utilizing eDiary data collected at home:

- Percentage of responders in SGRQ
- Change from baseline in the mean number of puffs of rescue medication use (puffs/day)
- Percentage of rescue/symptom-free days (24-hour period without rescue medication use)
- Change from baseline in morning/evening pre-dose PEFR
- CCI [redacted]
- CCI [redacted]
- Percentage of perceivers and non-perceivers for weekly OEQ 5-item PRO at home (those patients will be classified to category 'Missing' for this endpoint).

3.2.1 Screened Analysis Set

The Screened Analysis Set is defined as all participants who sign the ICF.

3.2.2 Randomized Analysis Set

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

3.2.3 Efficacy Analysis Set

The Efficacy Analysis 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 study intervention assigned at randomization, regardless of the actual intervention received.

3.2.4 Per-Protocol Analysis Set

The PP Analysis Set is defined as all participants in the Efficacy Analysis Set without an IPD impacting efficacy at randomization. Since receiving the wrong treatment will be an IPD, participants in the PP Analysis Set will be analyzed as randomized (which for this analysis set is identical to analysis by the actual study intervention received).

3.2.5 Safety Analysis Set

The Safety Analysis 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 study intervention received rather than randomized. The actual study intervention is defined as the study intervention that the participant received the most based on number of puffs.

3.2.6 Pulmonary Function Test Sub-Study Analysis Set

The 12-hour PFT Sub-Study Analysis Set is defined as all participants in the Efficacy Analysis Set who consented for PFT sub-study and have at least one post-baseline spirometry assessment (after the first dose of study medication).

3.2.7 Pharmacokinetic Analysis Set

The 12-hour PK Analysis Set is defined as all participants in the Efficacy Analysis Set who consented for PK sub-study, who have at least one post dose PK measurement which is assumed not to be affected by factors such as protocol deviations or AEs (see Section 4.5.2) and who have correctly self-administered the last 3 doses of study intervention (6 inhalations) in order to have achieved steady-state by Visit 8. Participants will be analyzed according to the actual study intervention received rather than randomized.

Note: The PK Analysis Set only applies to KALOS study.

3.2.8 Holter Monitoring Analysis Set

The 24-hour Holter Monitoring Analysis Set is defined as all participants in the Safety Analysis Set who consented for the Holter Monitoring sub-study, had no IPD impacting the data prior to receiving study intervention, and had at least 18 hours of acceptable quality Holter monitoring data at both Visit 4 (Holter baseline) and at least one of Visit 6 (Week 4) and Visit 11 (Week 24).

Note: The Holter Monitoring Analysis Set only applies to KALOS study.

3.2.9 Analysis Sets for Pooled Analyses

The analysis sets for the pooled analyses will be defined as the union of the respective analysis sets of the individual KALOS and LOGOS studies, with the additional considerations for exclusion of participants as summarized in Table 1.

3.2.10 Handling of Participants with Multiple Participation

Participants who participated more than once in the studies (KALOS, LOGOS, LITHOS, VATHOS)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 IP. Overlapping participation refers to multiple participation (at the same or different sites within the KALOS, LOGOS, VATHOS, and LITHOS 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 Set	Individual Studies	Pooled Analysis
Overlapping participations	Efficacy, PP, PFT, PK	Exclude all such participations	Exclude all such participations
Overlapping participations	Safety, Holter	Include all such participations	NA
Non-overlapping participations	Efficacy, PP, PFT, PK	Include the first such participation within the study	Include the first such participation across either of the studies
Non-overlapping participations	Safety, Holter	Include all such participations	NA

3.3 General Considerations

3.3.1 General Study Level Definitions

Stratification factors included in statistical analysis models as covariates, such as baseline severe asthma exacerbation history (0, 1, ≥2) and prior ICS dose (medium vs. high), will be derived based on the data collected via eCRF and not though the IVRS. Similarly, disease

characteristics parameters on stratification factors will be derived based on eCRF data (as per Section 4.1.5.1).

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. 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, baseline is defined as the average of the pre-bronchodilator/pre-dose measurements (at -60 and -30 minutes) at Visit 4 and Visit 5 (scheduled or repeated).
- For onset of action on Day 1 and percentage of peak FEV_1 improvement achieved at 5 minutes on Day 1, baseline is defined as the average of the pre-bronchodilator/pre-dose FEV_1 assessments (at -60 and -30 minutes) at Visit 5 (scheduled or repeated).
- 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.
- For daily eDiary metrics (asthma symptoms scores, rescue medication, awakenings, and PEFR), baseline is defined as the mean of non-missing values from the diary data collected during last 7 days before the first dose of randomized IP, starting the evening 7 days prior to the first dose of randomized IP (Day -7) and ending the morning of the first dose of randomized IP (Day 1). Also, participant needs to have a minimum of 5 days of non-missing morning assessments and 5 days of non-missing evening assessments for the variable in order for the baselines to be calculated.
    - For eDiary metrics measured in the morning, 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).
    - For eDiary metrics measured in the evening, 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).

- Note: an evening PEFR recorded between 00a.m and 03a.m will be considered as an evening PEFR on the day before the recorded date.

- For ICS prior to Visit 1, this covariate is defined as medium dose or high dose according to Table 8 of CSP Version 6.0. In case of multiple concurrent ICS treatments, the rules in Section 4.1.5.1 will be used to determine the dose. For data analysis modelling purposes, prior ICS dose category of low dose will be included in the category for medium dose.

- 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. If the Visit 2 and Visit 3 values are both missing, then the historical reversibility value will be used.

- For ECG measurements (Mean heart rate, RR interval, PR interval, QRS duration, QT interval, QTcB interval, QTcF interval) in the main study, baseline is defined as the last non-missing measurements prior to the start of treatment at Visit 5.

- For ECG measurements (Mean heart rate, RR interval, PR interval, QRS duration, QT interval, QTcB interval, QTcF interval) in the Holter Monitoring sub-study, baseline is defined as the mean of the six pre-dose measurements taken prior to the start of treatment at Visit 5.

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. The following are identified as ICEs for the main study and sub-studies:

Superiority analyses in main study and for PFT sub-study:

- Premature discontinuations from randomized study intervention
- Prolonged exposure to systemic corticosteroids or increased ICS dose for greater than 28 days consecutive 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 ≤28 consecutive days will be considered a temporary ICE only for concurrent lung function assessments (or lung function assessments performed within 7 days following exposure to SCS 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 first dose of randomized IP either

- 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).
  else
- prior to IP discontinuation/completion.

Holter Monitoring sub-study (for KALOS study only):

- Discontinuations from randomized study intervention
- Administration of any prohibited medications thought to impact interpretation of the Holter data

The listing of prohibited medications thought to impact interpretation of the Holter data is a subset of the CSP Table 10. This list includes Long-acting muscarinic antagonist (LAMA), if used as maintenance therapy during the study (not if used for short durations (2 weeks) to treat exacerbations), any drug with the potential to significantly prolong the QT interval, non-selective non-ocular beta-blocking agents (except carvedilol), and Systemic anticholinergics.

PK sub-study (for KALOS study only):

- Premature discontinuations from randomized study intervention
- Administration of the following prohibited medications thought to impact interpretation of the PK data: Systemic treatment with strong CYP3A4-inhibitors (eg, ketoconazole, itraconazole, and ritonavir)
- Dosing errors

Principal Stratum estimand with Per-Protocol Analysis Set (for NI analyses):

- Any ICEs listed for the superiority analyses
- Important protocol deviations thought to impact efficacy. For details on IPDs, refer to Section 3.3.9.

As time is not collected for all ICEs/IPDs, data collected on the same day as ICE or IPD will be assumed to be post-ICE or IPD.

Any prohibited medications initiated prior to first dose of randomized IP, or on the day of or after IP discontinuation are not considered as ICEs.

For temporary ICEs, only assessments within the impact window will be excluded.

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). The start date of the ICE "Initiation of new asthma therapy or administration of prohibited medications thought to impact efficacy following first dose of randomized IP in conjunction with permanent discontinuation of randomized study intervention" is defined by the start date of relevant additional therapy or medication. The date of an IPD will be determined by either manual data review or programming prior to clinical data lock and will be based on the following rules:

- For any IPD with category "Inclusion criteria" or "Exclusion criteria", the date of randomization will be used.
- For any IPD with category "Discontinuation criteria for study product met but participant not withdrawn from study treatment", the date of the first dosing following the development of an exclusion criteria will be used.
- For an IPD with category "Discontinuation criteria for overall study withdrawal met but participant not withdrawn from study", the date when those criteria were met will be used.
- For an IPD with category "IP deviation" – the date of the first deviating dose administration will be used.
- For an IPD with category "Excluded medications taken" – the date of the first receipt of an excluded medication will be used.
- For an IPD with category "Excluded medications taken" or "Other IPDs" – as determined by the manual data review.

Detailed logic for determining the start date of each IPD is provided in the KALOS and LOGOS Intercurrent Event Process document.

3.3.2 Hypothesis Testing

3.3.2.1 Hypothesis Testing for Individual Study

The primary null (H_0) and alternative (H_1) hypotheses are specified below for different regions. P-values, where necessary, will be presented to four decimal places.

CCI

Analysis of the primary endpoint, change from baseline in FEV_1 AUC_{0-3} at Week 24, and any subsequent analyses (except the within-group test on onset of action) will compare each dose of BGF MDI to BFF MDI as follows, where λ represents the mean of change from baseline in FEV_1 AUC_{0-3}.

- H_0: $\lambda_{BGF320/28.8/9.6} = \lambda_{BFF}$
- H_1: $\lambda_{BGF320/28.8/9.6} \neq \lambda_{BFF}$

- H_0: $\lambda_{BGF320/14.4/9.6} = \lambda_{BFF}$

- H_1: $\lambda_{BGF320/14.4/9.6} \neq \lambda_{BFF}$

For CCI

Analysis of the primary endpoint, change from baseline in morning pre-dose trough FEV_1 over 24 weeks, and any subsequent analyses (except the within-group test on onset of action) will compare each dose of BGF MDI to the pooled BFF MDI and Symbicort pMDI control groups as follows, where λ represents the mean of change from baseline in morning pre-dose trough FEV_1.

- H_0: $\lambda_{BGF320/28.8/9.6} = \lambda_{\text{pooled Symbicort and BFF}}$
- H_1: $\lambda_{BGF320/28.8/9.6} \neq \lambda_{\text{pooled Symbicort and BFF}}$

- H_0: $\lambda_{BGF320/14.4/9.6} = \lambda_{\text{pooled Symbicort and BFF}}$
- H_1: $\lambda_{BGF320/14.4/9.6} \neq \lambda_{\text{pooled Symbicort and BFF}}$

For CCI

Analysis of the primary endpoint, change from baseline in morning pre-dose trough FEV_1 over 24 weeks, and any subsequent analyses (except the within-group test on onset of action) testing for superiority will compare each dose of BGF MDI to Symbicort pMDI as follows, where λ represents the mean of change from baseline in morning pre-dose trough FEV_1.

- H_0: $\lambda_{BGF320/28.8/9.6} = \lambda_{Symbicort}$
- H_1: $\lambda_{BGF320/28.8/9.6} \neq \lambda_{Symbicort}$

- H_0: $\lambda_{BGF320/14.4/9.6} = \lambda_{Symbicort}$
- H_1: $\lambda_{BGF320/14.4/9.6} \neq \lambda_{Symbicort}$

For CCI

Analysis of the primary endpoint, change from baseline in morning pre-dose trough FEV_1 over 12 to 24 weeks, and any subsequent analyses (except the within-group test on onset of action) will compare each dose of BGF MDI to BFF MDI as follows, where λ represents the mean of change from baseline in morning pre-dose trough FEV_1.

- H_0: $\lambda_{BGF320/28.8/9.6} = \lambda_{BFF}$
- H_1: $\lambda_{BGF320/28.8/9.6} \neq \lambda_{BFF}$

- H_0: $\lambda_{BGF320/14.4/9.6} = \lambda_{BFF}$
- H_1: $\lambda_{BGF320/14.4/9.6} \neq \lambda_{BFF}$

3.3.2.2 Hypothesis Testing of Non-Inferiority for Individual Study

In addition, NI comparisons of BFF MDI versus Symbicort pMDI will be conducted to CCI The NI assessment for morning pre-dose trough FEV_1 will use a NI margin of CCI and the NI assessment for FEV_1 AUC_{0-3} will apply a NI margin of 125 mL. These margins are consistent with those CCI For these comparisons, the null hypothesis for each pair-wise comparison will be that the mean treatment difference (λ_{BFF} - $\lambda_{Symbicort}$) is less than or equal to the NI margin. The alternative hypothesis is that the mean treatment difference is greater than the NI margin. The null hypothesis will be rejected if the lower bound of the two-sided 95% CI for the mean treatment difference is greater than the NI margin. All CIs will be two-sided with 95% confidence and p-values (presented to four decimal places) will reflect the one-sided test for NI analysis.

For change from baseline in morning pre-dose trough FEV_1 over 24 Weeks

- H_0: λ_{BFF} - $\lambda_{Symbicort} \leq$ CCI
- H_1: λ_{BFF} - $\lambda_{Symbicort} >$ CCI

For change from baseline in FEV_1 AUC_{0-3} over 24 Weeks

- H_0: λ_{BFF} - $\lambda_{Symbicort} \leq$ CCI
- H_1: λ_{BFF} - $\lambda_{Symbicort} >$ CCI

Secondary and other efficacy analyses will involve the above hypotheses applied to secondary efficacy endpoints. The NI assessment for responder analysis will apply to the odds ratio with a NI margin of 0.8.

For percentage of responders in ACQ-7, ACQ-5, AQLQ(s) +12 and SGRQ analyses over 24 Weeks

- H_0: $\lambda_{BFF} / \lambda_{Symbicort} \leq 0.8$
  H_1: $\lambda_{BFF} / \lambda_{Symbicort} > 0.8$

For onset of action on Day 1, it will be within-group superiority testing

- H_0: $\lambda_{BFF} \leq$ CCI
- H_1: $\lambda_{BFF} >$ CCI

3.3.2.3 Hypothesis Testing for Pooled Analysis

For the pooled analysis, the primary endpoint is rate of severe asthma exacerbations. The hypothesis testing of the pooled analysis for each region will follow the same approach for the hypothesis testing of the individual study for the same region.

3.3.2.4 Hypothesis Testing of NI for Pooled Analysis

NI comparisons of BFF MDI versus Symbicort pMDI on severe asthma exacerbation will be conducted for pooled analysis of these two studies[redacted] The NI margin for the pooled assessment of the severe exacerbation rate will be set at 1.20 as this margin preserves more than 50% of the observed severe rate reduction when comparing a medium daily dose of budesonide versus a low daily dose of budesonide with or without formoterol [redacted] For these comparisons, the null hypothesis for each pair-wise comparison will be that the ratio of two treatment means is in excess of the NI margin. The alternative hypothesis is that the ratio of two treatment means is within the NI margin. All CIs will be two-sided with 95% confidence and p-values (presented to four decimal places) will reflect the one-sided test for NI analysis.

- H_0: $\lambda_{BFF} / \lambda_{Symbicort} \geq 1.2$
  H_1: $\lambda_{BFF} / \lambda_{Symbicort} < 1.2$

Analyses of secondary and other efficacy endpoints will involve the above hypotheses applied to secondary efficacy endpoints. Similarly, the NI margin for time to first severe asthma exacerbation will be set at 1.20.

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. These analyses will be conducted if warranted to demonstrate the robustness of the results.

3.3.4 Impact of Variable Length of the Study on the Analyses

Per CSP Version 6.0, both studies will end when the last remaining randomized participant in each study completes Week 24 Visit and subsequent 2-week follow-up phone call. However, no follow-up phone call is expected in the case that the last remaining randomized participant discontinues study intervention prior to the Week 24 Visit. In that case, the study will end at the completion of the participant's Week 24 Visit.

Given the variable length nature of the study, the distinction between "actual last visit" and "planned last visit" will be important for the analyses where the imputation of missing values is required.

The planned last visit is determined by the actual last visit of the participant and the projected study completion date. The projected study completion date is 26 weeks following the last remaining participant's first dose of randomized IP (or 24 weeks in case

study intervention was discontinued). Upon study completion, the projected study completion date will be the actual completion date of the study.

- For participants who discontinued from the study, their planned last (treatment period) visit should be a planned visit to occur before but closest to the projected study completion date. If such projection is a visit prior to Week 24, then Week 24 will be used as the planned last visit instead.
- For participants who did not discontinue from the study, their planned last (treatment period) visit should be the actual last scheduled visit during the treatment period (i.e. excluding follow up call).

The planned last visit day during the treatment period is the study day of the planned last (treatment period) visit. For participants who completed the study, their planned last visit day during the treatment period will be their actual date of last (treatment period) visit. For participants who discontinued from the study, their planned last visit day during the treatment period is the nominal study day of their planned last visit during the treatment period.

When required for an analysis, imputation of missing data will only be performed up to and including the participant's "planned last visit" or "planned last visit day" during the treatment period. There will be no imputation of data beyond the participant's "planned last visit" or "planned last visit day," since those data were not expected to be collected during treatment per protocol. For analysis purpose, those data are not considered missing.

3.3.5 ICE Estimand Strategies

3.3.5.1 Primary strategy 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 subsequent asthma medication is taken in conjunction with premature discontinuation of therapy (which will be considered an unfavourable outcome). For participants with such ICE, a Composite strategy will be utilized, where the participant will be imputed as having a treatment failure from the start of the relevant ICE until planned last visit date in planned treatment period. Treatment failure will be imputed as follows:

- For analysis of change from baseline in $FEV_{1,}$ AUC_{0-3}, morning pre-dose trough FEV_1, onset of action at 5 mins on Day 1, and change from baseline in FEV_1 AUC_{0-12} at Day 1 and Week 12 (PFT sub-study): impute respective parameter with the worst of (12% decrease from participant's baseline value, participant's worst post baseline observed value from scheduled or repeated measures for the respective parameter).

- For analysis of change from baseline in ACQ-7, ACQ-5, ACQ-6 scores: impute respective parameter with the worst of (change from participant's baseline score of 0.5, participant's worst, i.e. highest, post baseline observed score).

- For analysis of change from baseline in AQLQ(s)+12 total and domain scores: impute with the worst of (change from participant's baseline score of -0.5, participant's worst, i.e. lowest, post baseline observed score).

- For analysis of change from baseline in SGRQ total and domain scores: impute with the worst of (change from participant's baseline score of 4, participant's worst, i.e. highest, post baseline observed score).

- For analysis of percentage of responders (ACQ-7, ACQ-5, ACQ-6, AQLQ(s)+12, SGRQ): impute with non-responder status.

- For analysis of 'rate of' or 'time to' severe or moderate/severe exacerbations, any exacerbation with a start date on or after the start date + 2 days of the ICE handled as composite will be ignored and not used for the analysis. A severe exacerbation will be imputed midway (imputation date) between the start date +2 days of this ICE and planned last visit date during treatment period. In case that an exacerbation is already ongoing at the time of this ICE + 1 day and the imputation date falls within the duration of that exacerbation or the 7 days following it, then an exacerbation will instead be imputed at the 8th day following the end of the observed exacerbation. The time at risk for those participants will continue until their planned last visit date during treatment period. 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 prior to the planned last visit date during the treatment period. 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).

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 the Primary strategy for ICEs will be conducted in the Efficacy Set.

3.3.5.2 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 analysis for the estimands applying a While on Treatment strategy for ICEs will be conducted using the Efficacy Set with only data obtained from the first dose of randomized

IP to the day prior to the occurrence of first ICE (for exacerbations this will be the day after the occurrence of the ICE). For participants that complete the planned treatment in the absence of an ICE, data until date of last dose (date of last dose + 1 day for exacerbations) will be utilized.

3.3.5.3 Supportive Composite strategy applied to responder endpoints

This estimand 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.

The analysis of the estimands applying a Composite strategy for ICEs will be conducted using the Efficacy Set. Similar ICEs as considered for the While on Treatment ICE strategy will be utilized. All observed data from the date of first dose of randomized IP to the day prior to the first ICE will be utilized, and data will be set to a non-responder status from the day of the ICE. 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.

3.3.5.4 Principal Stratum

This estimand 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).

The analysis of the estimands applying a Principal Stratum strategy for ICEs will use the observed treatment difference estimator in the PP Set, and this will be used for all NI analyses. All data from and including the day of the first occurrence of an ICE or IPD impacting efficacy or safety (or day after the first occurrence of first ICE/ IPD for exacerbations) will not be included in the analysis.

For participants that complete the planned treatment in the absence of an ICE/IPD, data until the date of last dose (date of last dose +1 day for exacerbations) will be utilized.

For the binary responder endpoints a mix of Principal Stratum and Composite will be used, in that all data from and including the day of the first occurrence of an ICE or IPD impacting efficacy will not be included in the analysis, and timepoints following ICE/IPD due to lack of efficacy will be set to a non-responder status until planned last visit date during treatment period.

3.3.5.5 Objectives and Estimand Strategies for Individual Studies

Table 2 and Table 3 summarizes the objectives and estimand strategies for each individual study.

3.3.5.6 Objectives and Estimand Strategies for Pooled Studies

Table 4 and Table 5 summarizes the objectives and estimand strategies for pooled studies.

Table 2 Primary/Secondary Objectives and Estimand Strategies for Individual Studies

Objective	**Estimand**	
Primary	CCI **approach**[a]	CCI **approach**[a]
To assess the effect of BGF MDI relative to BFF MDI, Symbicort pMDI or the pooled BFF MDI and Symbicort pMDI arms on lung function in participants with inadequately controlled asthma.	• **Treatment**: CCI BGF MDI 320/28.8/9.6 µg, BGF MDI 320/14.4/9.6 µg, or BFF MDI 320/9.6 µg CCI: BGF MDI 320/28.8/9.6 µg, BGF MDI 320/14.4/9.6 µg, or Symbicort pMDI 320/9 µg CCI BGF MDI 320/28.8/9.6 µg, BGF MDI 320/14.4/9.6 µg, or ICS/LABA (pooled BFF MDI 320/9.6 µg and Symbicort pMDI 320/9 µg) • **Population:** adults and adolescents with inadequately controlled asthma • **Endpoint:** CCI Change from baseline in FEV_1 AUC_{0-3} at Week 24 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 • **Population summary measure:** Difference in mean change from baseline • **Handling ICEs:** **Primary strategy:** – Premature discontinuations from randomized study intervention: Treatment Policy[b], i.e., all observed data used regardless of ICE. – Prolonged exposure to systemic corticosteroids or increased ICS dose for greater than 28 days consecutive or a single depot corticosteroid injection: Treatment Policy[b], i.e., all observed data used regardless of ICE. – Initiation of new asthma therapy or administration of prohibited medications thought to impact efficacy: Composite (data following ICE will be imputed as treatment failures) if in conjunction with premature IP discontinuation, else Treatment Policy. **Supportive strategy:** – Premature discontinuations from randomized study intervention: While on Treatment, i.e., data after ICE will not be used. – Prolonged exposure to systemic corticosteroids or increased ICS dose for greater than 28 days consecutive or a single 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.
Secondary	
To assess the effect of BGF MDI relative to BFF MDI, Symbicort pMDI or the pooled BFF MDI and Symbicort pMDI arms on lung function in participants with inadequately controlled asthma.	• **Key Endpoint:** CCI Change from baseline in morning pre-dose trough FEV_1 at Week 24 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 ICEs:** Same as for primary endpoint
To assess the effect of BGF MDI relative to BFF MDI, Symbicort pMDI or the pooled BFF MDI and Symbicort pMDI arms on lung function, PROs, and symptoms in participants with inadequately controlled asthma.	• **Endpoint:** CCI Percentage of responders in ACQ-7 (≥0.5 decrease equals response) at Week 24 CCI : Percentage of responders in ACQ-7 (≥0.5 decrease equals response) over 24 weeks CCI Percentage of responders in ACQ-7 (≥0.5 decrease equals response) over 12 to 24 weeks • **Population summary measure:** Odds ratio • **Handling of ICEs:** **Primary strategy:** – Premature discontinuations from randomized study intervention: Treatment Policy[b], i.e., all observed data used regardless of ICE. – Prolonged exposure to systemic corticosteroids or increased ICS dose for greater than 28 days consecutive or a single depot corticosteroid injection: Treatment Policy[b], i.e., all observed data used regardless of ICE. – Initiation of new asthma therapy or administration of prohibited medications thought to impact efficacy: Composite if in conjunction with IP discontinuation, non-responder status will be assumed for participants from (and including) day of ICE, else Treatment Policy.

	Supportive Composite: – Premature discontinuations from randomized study intervention: o For reasons related to global/country situation, data following such ICE will be considered missing and will not be imputed. o For other reasons, non-responder status will be assumed for participants from (and including) the day of first ICE (Composite strategy). – Prolonged exposure to systemic corticosteroids or increased ICS dose for greater than 28 days consecutive or a single depot corticosteroid injection: Non-responder status will be assumed for participants from (and including) day of first ICE (Composite strategy) – Initiation of new asthma therapy or administration of prohibited medications thought to impact efficacy following first dose of randomized IP: Non-responder status will be assumed for participants from (and including) day of first ICE (Composite strategy)
	• **Endpoint:** CCI Percentage of responders in ACQ-5 (≥0.5 decrease equals response) at Week 24 CCI Percentage of responders in ACQ-5 (≥0.5 decrease equals response) over 24 weeks CCI Percentage of responders in ACQ-5 (≥0.5 decrease equals response) over 12 to 24 weeks • **Population summary measure:** Odds ratio • **Handling of ICEs:** Same as for percentage of responders in ACQ-7
	• **Endpoint:** CCI Percentage of responders in AQLQ(s) +12 (≥0.5 increase equals response) at Week 24 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:** Same as for percentage of responders in ACQ-7

	• **Endpoint:** CCI Percentage of responders in SGRQ (≥4.0 unit decrease equals response) at Week 24 CCI Percentage of responders in SGRQ (≥4.0 unit decrease equals response) over 24 weeks CCI Percentage of responders in SGRQ (≥4.0 unit decrease equals response) at Week 24 • **Population summary measure**: Odds ratio • **Handling of ICEs:** Same as for percentage of responders in ACQ-7	
	• **Endpoint:** Onset of action on Day 1: Absolute change in FEV_1 at 5 minutes on Day 1 • **Population Summary Measure:** Mean change from baseline (Within treatment) • **Handling of ICEs:** Same as primary strategy for primary endpoint	
		• **Endpoint:** CCI Rate of severe asthma exacerbations over the Treatment Period • **Population Summary Measure:** Rate ratio • **Handling of ICEs**: Same as primary strategy for primary endpoint
Non-inferiority (NI)		
CCI only: To assess the effect of BFF MDI relative to Symbicort pMDI on lung function, PROs,	**N/A**	• **Treatment**: CCI: BFF MDI 320/9.6 µg or Symbicort pMDI 320/9 µg • **Population:** adults and adolescents with inadequately controlled asthma

and symptoms in participants with inadequately controlled asthma [NI][c].		• **Endpoint:** Change from baseline in FEV_1 AUC_{0-3} over 24 weeks Change from baseline in morning pre-dose trough FEV_1 over 24 weeks • **Population summary measure:** Difference in mean change from baseline • **Handling ICEs:** Primary: Principal Stratum: All data following an ICE (including data on the same day of the event) will be excluded. – Any ICEs listed for the superiority analyses. – Important protocol deviations impacting efficacy. Supportive #1: Same as primary strategy for handling ICEs for the primary endpoint Supportive #2: While on Treatment (per supportive strategy for the primary endpoint)
		• **Endpoint:** Percentage of responders in ACQ-7 (≥0.5 decrease equals response) over 24 weeks Percentage of responders in ACQ-5 (≥0.5 decrease equals response) over 24 weeks Percentage of responders in the AQLQ(s)+12 (≥0.5 increase equals response) over 24 weeks Percentage of responders in the SGRQ (≥4.0 unit decrease equals response) over 24 weeks • **Population summary measure**: Odds ratio

		• **Handling of ICEs:** Mix of Principal Stratum and Composite; – All data following a permanent ICE or an IPD **impacting** efficacy (including data on the same day of the event) will be excluded: Principal Stratum. – All data following a permanent ICE or an IPD **due to** efficacy (including data on the same day of the event) will then be imputed to a non-responder status: Composite. – Discontinuations from randomized study intervention for reasons related to global/country situation: Data following such ICE will be considered missing and will not be imputed.
		• **Endpoint:** Onset of action on Day 1: Absolute change in FEV_1 at 5 minutes on Day 1 • **Population summary measure**: Mean change from baseline (within treatment) • **Handling of ICEs:** Principal Stratum: Same as for primary strategy for change from baseline in FEV_1 AUC_{0-3} over 24 weeks of NI analysis

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

b. The Treatment Policy strategy assesses the effect of BGF MDI plus subsequent therapies relative to BFF MDI, Symbicort pMDI or ICS/LABA plus subsequent therapies on treatment effects in participants with inadequately controlled asthma.

c. CCI [redacted]

Table 3 Other Objectives and Estimand Strategies for Individual Studies

	Estimand				
Objective	**Population**	**Endpoint**	**Population Summary Measure**	**Strategy for Intercurrent Events**	**Reported in CSR?**
Safety					
To assess the safety of BGF MDI relative to BFF MDI or Symbicort pMDI in participants with inadequately controlled asthma. To assess the safety of BFF MDI relative to Symbicort pMDI in participants with inadequately controlled asthma	Participants with inadequately controlled asthma (symptomatic on medium to high-dose ICS with LABA)	AEs	Percentage Exposure adjusted incidence rate (EAIR)	All events per study periods defined in Section 4.7.2.1 will be included in the analysis.	CSR
		Vital signs	Mean absolute value and mean change from baseline	Only on-treatment observations will be included in the analysis.	CSR
		Clinical laboratory values	Mean absolute value and mean change from baseline	Only on-treatment observations will be included in the analysis.	CSR
		ECGs	Mean absolute value and mean change from baseline	Only on-treatment observations will be included in the analysis.	CSR
Tertiary/Exploratory					
To further assess the effect of BGF MDI relative to BFF MDI, Symbicort pMDI on lung function,	Participants with inadequately controlled asthma	Change from baseline in the mean number of puffs of rescue medication use (puffs/day) over 24 weeks or over 12 to 24 weeks	Difference in mean change from baseline	While on Treatment	Outside of CSR

PROs, time to event, and symptoms in participants with inadequately controlled asthma.	(symptomatic on medium to high-dose ICS with LABA)	Percentage of rescue-free days (24-hour period without rescue medication use)	Difference in mean percentage	While on Treatment	Outside of CSR
		Percentage of symptom-free days (24-hour period without symptoms)	Difference in mean percentage	While on Treatment	Outside of CSR
		Peak change from baseline in FEV_1 at each visit	Mean difference	While on Treatment	Outside of CSR
		Time to peak FEV_1 on Day 1	Mean difference	While on Treatment	Outside of CSR
		FVC, PEFR, and FEF_{25-75} evaluated using AUC_{0-3}	Difference in mean change from baseline	While on Treatment	Outside of CSR
		Change from baseline in morning pre-dose PEFR	Difference in mean change from baseline	While on Treatment	Outside of CSR
		Change from baseline in evening pre-dose PEFR	Difference in mean change from baseline	While on Treatment	Outside of CSR
		Percentage of responders in ACQ-6 (≥0.5 decrease equals response)	Odds ratio	Same as primary strategy for ACQ-7	Outside of CSR
		Change from baseline in ACQ-5, ACQ-7 total scores and AQLQ(s)+12, SGRQ total and domain scores	Difference in mean change from baseline	Same as primary strategy for the primary endpoint	CSR
		Change from baseline in ACQ-6 total score	Difference in mean change from baseline	Same as primary strategy for the primary endpoint	Outside of CSR

		Time to CID	Hazard ratio	While on Treatment	Outside of CSR
		CCI [redacted]	Hazard ratio	While on Treatment	Outside of CSR
		CCI [redacted]	Rate ratio	While on Treatment	Outside of CSR
		Time to first ICE	Hazard ratio	While on Treatment	CSR
		Time to first ICE of initiation of new asthma therapy or prohibited medications thought to impact efficacy in conjunction with discontinuation from study intervention	Hazard ratio	Same as primary strategy for the primary endpoint	CSR
		PGIC	Percentage	While on Treatment	Outside of CSR
		EQ-5D Questionnaire index score and VAS Questionnaire score at each post-randomization visit and end of study visit	Mean absolute value and mean change from baseline	While on Treatment	Outside of CSR
		The percentage of participant's categorical responses to each of the 5-dimensions in EQ-5D	Percentage	While on Treatment	Outside of CSR
		Percentage of participants with FeNO less than 25 ppb, between 25 ppb and less than 50 ppb, and at least 50 ppb	Percentage	While on Treatment	Outside of CSR

		Percentage of peak FEV_1 improvement achieved at 5 minutes on Day 1	Percentage	While on Treatment	CSR
Healthcare Resource Utilization					
To assess the overall and asthma specific HCRU of BGF MDI relative to BFF MDI, Symbicort pMDI in participants with inadequately controlled asthma.	Participants with inadequately controlled asthma (symptomatic on medium to high-dose ICS with LABA)	Days missed school/work per patient-year	Mean Annualized Rate	While on Treatment	Outside of CSR
		Days that primary caregivers of participants missed from work as a result of the participant's asthma per patient year	Mean Annualized Rate	While on Treatment	Outside of CSR
		Percentage of participants with telephone calls to healthcare providers - Calls to PCP - Calls to specialist - Calls to other healthcare providers	Percentage	While on Treatment	Outside of CSR
		Number of telephone calls to healthcare providers per patient-year - Calls to PCP - Calls to specialist - Calls to other healthcare providers	Mean Annualized Rate	While on Treatment	Outside of CSR
		Percentage of participants with visits to healthcare providers - Visits to PCP - Visits to specialist	Percentage	While on Treatment	Outside of CSR

		- Visits to other healthcare providers			
		Number of visits to healthcare providers per patient-year - Visits to PCP - Visits to specialist - Visits to other healthcare providers	Mean Annualized Rate	While on Treatment	Outside of CSR
		Percentage of participants with ER visits	Percentage	While on Treatment	Outside of CSR
		Number of visits to ERs per patient-year	Mean Annualized Rate	While on Treatment	Outside of CSR
		Percentage of participants hospitalized	Percentage	While on Treatment	Outside of CSR
		Number of participant hospitalizations per patient-year	Mean Annualized Rate	While on Treatment	Outside of CSR
		Number of days in the hospital per patient-year	Mean Annualized Rate	While on Treatment	Outside of CSR
		Number of days in ICU per patient-year	Mean Annualized Rate	While on Treatment	Outside of CSR
		Percentage of participants in the ICU	Percentage	While on Treatment	Outside of CSR
		Number of days in CCU per patient-year	Mean Annualized Rate	While on Treatment	Outside of CSR

		Percentage of participants in CCU	Percentage	While on Treatment	Outside of CSR
		Percentage of participants who required ambulance transport	Percentage	While on Treatment	Outside of CSR
		Number of times ambulance transport was required per patient-year	Mean Annualized Rate	While on Treatment	Outside of CSR
12-Hour Pharmacokinetic Sub-Study (KALOS Study Only)					
To characterize the steady state PK of budesonide, glycopyrronium, and formoterol fumarate based on PK assessments in participants with inadequately controlled asthma.	Participants with inadequately controlled asthma (symptomatic on medium to high-dose ICS with LABA) who consent to PK Sub-study	Steady-state partial area under the concentration-time curve from 0 to 12 hours post dose AUC_{0-12}	Mean	While on Treatment	CSR
		Steady-state area under concentration-time curve from time 0 to the last quantifiable concentration AUC_{last}	Mean	While on Treatment	CSR
		Steady-state maximum observed concentration (C_{max})	Mean	While on Treatment	CSR
		Steady-state average concentration over a dosing interval (C_{avg})	Mean	While on Treatment	CSR
		Steady-state time to reach Cmax (T_{max})	Mean	While on Treatment	CSR
		Observed lowest concentration before the next dose is administered (C_{trough})	Mean	While on Treatment	CSR

24-Hour Holter Monitor Sub-Study (KALOS Study Only)					
To assess the cardiovascular safety of BGF MDI relative to BFF MDI or Symbicort pMDI as evaluated by 24-hour Holter monitoring	Participants with inadequately controlled asthma (symptomatic on medium to high-dose ICS with LABA) who consent to Holter Monitor Sub-study	Change from baseline in mean heart rate (HR) over 24 hours	Difference in mean change from baseline	While on Treatment	CSR
		Change from baseline in nighttime (2200 to 0600) and daytime (0600 to 2200) HR	Difference in mean change from baseline	While on Treatment	CSR
		Change from baseline in the maximum 24-hour HR	Difference in mean change from baseline	While on Treatment	CSR
		Change from baseline in the minimum 24-hour HR	Difference in mean change from baseline	While on Treatment	CSR
		Change from baseline in the frequency of isolated ventricular events (PVCs)	Difference in mean change from baseline	While on Treatment	CSR
		Change from baseline in the frequency of ventricular couplets (defined as 2 PVCs preceded or followed by regular beats)	Difference in mean change from baseline	While on Treatment	CSR
		Change from baseline in the frequency of ventricular runs (defined as 3 or more PVCs preceded or followed by regular beats)	Difference in mean change from baseline	While on Treatment	CSR
		Change from baseline in the frequency of supraventricular couplets	Difference in mean change from baseline	While on Treatment	CSR

		Change from baseline in the frequency of isolated supraventricular events	Difference in mean change from baseline	While on Treatment	CSR
		Change from baseline in the frequency of supraventricular ectopic beats	Difference in mean change from baseline	While on Treatment	CSR
		Change from baseline in the frequency of supraventricular runs	Difference in mean change from baseline	While on Treatment	CSR
		Incidence of atrial fibrillation with rapid ventricular response (>100 bpm)	Incidence	While on Treatment	CSR
		Proportion of participants with maximum HR >180, >160 to 180, >140 to 160, >120 to 140, >100 to 120, and 100 bpm or less	Percentage	While on Treatment	CSR
		Proportion of participants with minimum HR >60, >50 to 60, >40 to 50, and <40 bpm	Percentage	While on Treatment	CSR
		Proportion of participants in each category of change from baseline in the number of PVCs per hour (no change; increase of >0 to <60, 60 to <120, and ≥120; and decrease of >0 to <60, 60 to <120, and ≥120)	Percentage	While on Treatment	CSR
		Number of cases and percentages in each	Percentage	While on Treatment	CSR

		category of QTcF ≥450 msec, QTcF ≥480 msec, and QTcF ≥500 msec; Change from baseline QTcF ≥30 msec, QTcF ≥60 msec, value >500 msec or change from baseline ≥60 msec			

Table 4 Primary/Secondary Objectives and Estimand Strategies for Pooled Studies

Objective	**Estimand**	
Primary	CCI **approach**[a]	CCI **approach**[a]
To assess the effect of BGF MDI relative to BFF MDI, Symbicort pMDI or the pooled BFF MDI and Symbicort pMDI arms on asthma exacerbations in participants with inadequately controlled asthma.	• **Treatment**: CCI BGF MDI 320/28.8/9.6 µg, BGF MDI 320/14.4/9.6 µg or BFF MDI 320/9.6 µg CCI BGF MDI 320/28.8/9.6 µg, BGF MDI 320/14.4/9.6 µg or Symbicort pMDI 320/9 µg CCI BGF MDI 320/28.8/9.6 µg, BGF MDI 320/14.4/9.6 µg, or ICS/LABA (pooled BFF MDI 320/9.6 µg and Symbicort pMDI 320/9 µg) • **Population:** adults and adolescents with inadequately controlled asthma	
	• **Endpoint**: Rate of severe asthma exacerbations • **Population summary measure**: Rate ratio • **Handling ICEs:** Same as primary and supportive strategies for primary endpoint for individual studies	
Secondary		
To assess the effect of BGF MDI relative to BFF MDI,	• **Endpoint:** Rate of severe asthma exacerbations for participants with percent predicted $FEV_1 \leq 55\%$ at baseline • **Population summary measure**: Rate ratio • **Handling of ICEs:** Same as primary and supportive strategies for primary endpoint for individual studies	

Symbicort pMDI or the pooled BFF MDI and Symbicort pMDI arms on asthma exacerbations, PROs, and symptoms in participants with inadequately controlled asthma.	• **Endpoint:** Rate of severe asthma exacerbations for participants with ≥ 1 severe exacerbation in the 12 months prior to Visit 1 • **Population summary measure**: Rate ratio • **Handling of ICEs:** Same as primary and supportive strategies for primary endpoint for individual studies
	• **Endpoint:** Time to first severe asthma exacerbation • **Population summary measure**: Hazard ratio • **Handling of ICEs:** Same as primary and supportive strategies for primary endpoint for individual studies
	• **Endpoint:** Rate of moderate/severe asthma exacerbations • **Population summary measure**: Rate ratio • **Handling of ICEs:** Same as primary and supportive strategies for primary endpoint for individual studies
	• **Endpoint:** Time to first moderate/severe asthma exacerbation • **Population summary measure**: Hazard ratio • **Handling of ICEs:** Same as primary and supportive strategies for primary endpoint for individual studies
	• **Endpoint:** CCI Percentage of responders in ACQ-7 (≥0.5 decrease equals response) at Week 24 CCI Percentage of responders in ACQ-7 (≥0.5 decrease equals response) over 24 weeks CCI Percentage of responders in ACQ-7 (≥0.5 decrease equals response) over 12 to 24 weeks • **Population summary measure**: Odds ratio • **Handling of ICEs:** Same as for percentage of responders in ACQ-7 for individual studies
	• **Endpoint:** CCI Percentage of responders in ACQ-5 (≥0.5 decrease equals response) at Week 24 CCI Percentage of responders in ACQ-5 (≥0.5 decrease equals response) over 24 weeks CCI Percentage of responders in ACQ-5 (≥0.5 decrease equals response) over 12 to 24 weeks • **Population summary measure**: Odds ratio • **Handling of ICEs:** Same as for percentage of responders in ACQ-7 for individual studies

		• **Endpoint:** CCI Percentage of responders in AQLQ(s) +12 (≥0.5 increase equals response) at Week 24 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:** Same as for percentage of responders in ACQ-7 for individual studies
Non-inferiority (NI)		
CCI : To assess the effect of BFF MDI relative to Symbicort pMDI on asthma exacerbations in participants with inadequately controlled asthma [NI][b].	**N/A**	• **Treatment**: CCI BFF MDI 320/9.6 µg or Symbicort pMDI 320/9 µg • **Population:** adults and adolescents with inadequately controlled asthma
		• **Endpoint:** Rate of severe asthma exacerbations over the Treatment Period • **Population summary measure:** Rate ratio • **Handling ICEs:** • Primary: Principal Stratum. All data following an ICE (including data on the same day of the event) will be excluded: – Any ICEs listed for the superiority analyses. – Important protocol deviations impacting efficacy. Supportive #1: Same as primary strategy for handling ICEs for the primary endpoint Supportive #2: While on Treatment (per supportive strategy for the primary endpoint)

		• **Endpoints:** Time to first severe asthma exacerbation (assessed over the Treatment Period only) Time to first moderate/severe asthma exacerbation (assessed over the Treatment Period only) • **Population summary measure**: Hazard ratio • **Handling of ICEs:** Principal Stratum, same as primary non-inferiority strategy for rate of severe asthma exacerbations over the Treatment Period
		• **Endpoint:** Rate of moderate/severe asthma exacerbations over the Treatment Period • **Population summary measure**: Rate ratio **Handling of ICEs:** Principal Stratum, same as primary strategy for rate of severe asthma exacerbations over the Treatment Period

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

b. CCI [redacted].

Table 5 Other Objectives and Estimand Strategies for Pooled Analyses

	Estimand				
Objective	**Population**	**Endpoint**	**Population Summary Measure**	**Strategy for Intercurrent Events**	**Reported in CSR**
Tertiary/Exploratory Pooled Analysis Objective					
To further assess the effect of BGF MDI relative to BFF MDI or Symbicort pMDI on asthma exacerbations in participants with inadequately controlled asthma.	Participants with inadequately controlled asthma (symptomatic on medium to high-dose ICS with LABA)	Time to first hospitalization for asthma exacerbation	Hazard ratio	While on Treatment	Outside of CSR
		Rate of hospitalization for severe asthma exacerbations	Rate ratio	While on Treatment	CSR
		Rate of severe asthma exacerbations resulting in a temporary course of systemic corticosteroids for at least 3 consecutive days	Rate ratio	While on Treatment	Outside of CSR
		Time to first CID	Hazard ratio	While on Treatment	Outside of CSR
		CCI [redacted]	Hazard ratio	While on Treatment	Outside of CSR
		CCI [redacted]	Rate ratio	While on Treatment	Outside of CSR
		Time to first ICE	Hazard ratio	While on Treatment	CSR

		Time to first ICE of initiation of new asthma therapy or prohibited medications thought to impact efficacy in conjunction with discontinuation from study intervention	Hazard ratio	Same as Primary strategy for primary endpoint	CSR
		Percentage of participants who permanently discontinued study intervention due to asthma exacerbation	Percentage	While on Treatment	Outside of CSR
		Total number of days on systemic corticosteroids to treat asthma exacerbations	Mean	While on Treatment	Outside of CSR
		Rate of severe asthma exacerbations treated with systemic corticosteroids only (assessed over the Treatment Period only)	Rate ratio	While on Treatment	Outside of CSR
		Rate of asthma deteriorations treated with ICS and/or antibiotics (assessed over the Treatment Period only)	Rate ratio	While on Treatment	Outside of CSR
		Rate of asthma deteriorations treated with antibiotics (assessed over the Treatment Period only)	Rate ratio	While on Treatment	Outside of CSR
		Time to first severe asthma exacerbation treated with systemic corticosteroids only (assessed over the Treatment Period only)	Hazard ratio	While on Treatment	Outside of CSR

		Time to first asthma deterioration treated with ICS and/or antibiotics (assessed over the Treatment Period only)	Hazard ratio	While on Treatment	Outside of CSR
		Time to first asthma deterioration treated with antibiotics (assessed over the Treatment Period only)	Hazard ratio	While on Treatment	Outside of CSR
12-Hour Pulmonary Function Test Pooled Sub-Study Objective					
To assess the effect of BGF MDI relative to BFF MDI or Symbicort pMDI on PFT parameters over 12-hours in participants with inadequately controlled asthma.	Participants with inadequately controlled asthma (symptomatic on medium to high-dose ICS with LABA) who consent to PFT Sub-study	FEV_1 AUC_{0-12} at Day 1 and Week 12	Difference in mean change from baseline	Same as for primary endpoint	CSR
		FEV_1 at each timepoint at Day 1 and Week 12	Mean absolute value and mean change from baseline	While on Treatment	CSR
		FEV_1 AUC_{0-6}, FEV_1 AUC_{6-12}, and peak FEV_1	Difference in mean change from baseline	While on Treatment	CSR
		FVC, PEFR, and FEF_{25-75} evaluated using AUC_{0-12}	Difference in mean change from baseline	While on Treatment	CSR
		Percentage of perceivers and non-perceivers for weekly OEQ 5-item PRO at home	Percentage	While on Treatment	CSR

		Percentage of perceivers and non-perceivers for repeat OEQ item in clinic (post-dose)	Percentage	While on Treatment	CSR
		Time for the participant to first perceive the medication as working	Hazard ratio	While on Treatment	CSR

3.3.6 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 visit's label numbering. The adjusted analysis-defined windows are summarized in Table 6 to Table 12 , where study day is defined in Appendix 9.1.

Table 6 Visit windows for Spirometry[a] (main study and 12-hour spirometry sub-study[b]), ACQ, EQ-5D and Healthcare Resource Utilization

Adjusted Defined Windows Visit	Scheduled Study Day	Maximum Windows
Baseline	1	Study Day ≤1[a]
Week 4	29	2≤ Study Day ≤42
Week 8	57	43≤ Study Day ≤70
Week 12	85	71≤ Study Days ≤98
Week 16	113	99≤ Study Day ≤126
Week 20	141	127≤ Study Day ≤154
Week 24	169	155≤ Study Day ≤182
Week 28	197	183≤ Study Day ≤ 224
Week 36	253	225≤ Study Day ≤280
Week 44	309	281≤ Study Day ≤336
Week 52	365	337≤ Study Day ≤378

[a] For calculating the baseline spirometry endpoints, as well as pre-bronchodilator percent predicted FEV1 that are based on observations from Visit 4 and Visit 5, the observations from the latest scheduled or repeat respective visits (with labels indicating Visit 4 and Visit 5) that are prior to first dose of IP will be used.

[b] For 12-hour spirometry sub-study, only Baseline and Week 12 visits are defined.

Table 7 Visit windows for AQLQ(s)+12

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
Week 28	197	183≤ Study Day ≤ 224
Week 36	253	225≤ Study Day ≤280
Week 44	309	281≤ Study Day ≤336
Week 52	365	337≤ Study Day ≤378

Table 8 Visit windows for SGRQ

Adjusted Defined Windows Visit	Scheduled Study Day	Maximum Windows
Baseline	1	Study Day ≤1
Week 4	29	2≤ Study Day ≤98
Week 24	169	99≤ Study Day ≤182

Table 9 Visit windows for PGIC

Adjusted Defined Windows Visit	Scheduled Study Day	Maximum Windows
Week 12	85	43≤ Study Days ≤126
Week 24	169	127≤ Study Day ≤266
Week 52	365	267≤ Study Day ≤378

Table 10 Visit windows for PK

Adjusted Defined Windows Visit	Scheduled Study Day	Maximum Windows
Week 12	85	43≤ Study Days ≤126

Table 11 Visit windows for Vital Signs, Laboratory Assessments, Height/Weight, and Physical Examination

Adjusted Defined Windows Visit	Scheduled Study Day	Maximum Windows
Baseline	1	Study Day ≤1
Week 4 [a]	29	2≤ Study Day ≤98
Week 24	169	99≤ Study Day ≤266
Week 52	365	267≤ Study Day ≤378

[a] Week 4 is only defined for vital signs.

Table 12 Visit windows for ECGs (Main Study and Holter Monitoring Sub-study)

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 ≤126
Week 24	169	127≤ Study Day ≤210
Week 36 [a]	253	211≤ Study Day ≤308
Week 52	365	309≤ Study Day ≤378

[a] Week 36 is only defined for Holter Monitoring Sub-study.

[b] Follow-up is only defined for main study.

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 0.

- 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 (or 12-hour spirometry is planned) per Table of Activities (Table 1) and Timing of Spirometry Table (Table 2) in CSP, then the closest scheduled or repeat visit that also has pre- and post- dose assessments collected (or 12-hour spirometry for the 12-hour spirometry analyses) 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 (or 12-hour spirometry is planned) per Table of Activities (Table 1) and Timing of Spirometry Table (Table 2) in CSP, then the earliest scheduled or repeat visit that also has pre- and post- dose assessments collected (or 12-hour spirometry for the 12-hour spirometry analyses) 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. spirometry), then the observation with the earliest collection time within the respective time window (as defined in Table 13) will be used.

Scheduled or repeated visits, including premature discontinuation visits that occurred at a date later than the date of the last dose, will be mapped to an adjusted window in the same

manner as described above, but the date of the intercurrent event of IP discontinuation will be the date of the last IP dose. The data collected at those visits may be ignored for some estimands as described in Section 3.3.5.

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 13.

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

Table 13 Analysis Study Time Window 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
Post-dose 6 hrs.[b]	4.5 to <7.5 hrs. post-dose
Post-dose 9 hrs.[b]	7.5 to <10.5 hrs. post-dose
Post-dose 12 hrs.[b]	10.5 to <13.5 hrs. post-dose

[a] Visit 5 only.

[b] At Visit 8, for 12-hour serial spirometry sub-study participants 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.

Also, 4-Week intervals will be defined by study day as specified in Table 14. Study day is defined in Appendix 9.1. This will be applied for efficacy endpoints that utilize a repeated measures analysis of covariance model, i.e., endpoints that are recorded by the participants on a daily basis (e.g. rescue medication use in puffs/day, morning and evening PEFR). The daily data for each participant will be averaged over the respective interval. Note that

depending on the estimand strategy utilized, not all data from the respective period may be used for averaging for participants with ICEs.

Table 14 Definition of 4-Week Intervals

Interval	Label	Time Period
1	1-4 Weeks	Day 1 to Day 28
2	5-8 Weeks	Day 29 to Day 56
3	9-12 Weeks	Day 57 to Day 84
4	13-16 Weeks	Day 85 to Day 112
5	17-20 Weeks	Day 113 to Day 140
6	21-24 Weeks	Day 141 to Day 168
7	25-28 Weeks	Day 169 to Day 196
8	29-32 Weeks	Day 197 to Day 224
9	33-36 Weeks	Day 225 to Day 252
10	37-40 Weeks	Day 253 to Day 280
11	41-44 Weeks	Day 281 to Day 308
12	45-48 Weeks	Day 309 to Day 336
13	49-52 Weeks	Day 337 to Day 364

3.3.7 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.

If a visit for an efficacy assessment or non-efficacy assessment is labelled as "Unscheduled" but is actually the same as the date of premature discontinuation visit, then the visit label for that assessment will be relabelled to "Premature Discontinuation" Visit and will also be used in any visit-based analyses.

3.3.8 Multiplicity/Multiple Comparisons

The change from baseline in FEV1 AUC0-3 will be the primary endpoint for CCI and a key secondary endpoint CCI [redacted]. The change from baseline in morning pre-dose trough FEV1 will be the primary endpoint for CCI [redacted] and the key secondary endpoint for CCI Each region has a specific approach, which refers to the submission to their Health Authorities. Lung function parameters will be evaluated in studies D5982C00007 (KALOS) and D5982C00008 (LOGOS) to provide replicate results for regions requiring this approach.

Data from the 2 studies will be combined to analyze the rate of severe exacerbations. In the multiple testing procedure, the Type I error for the analysis of the primary and secondary

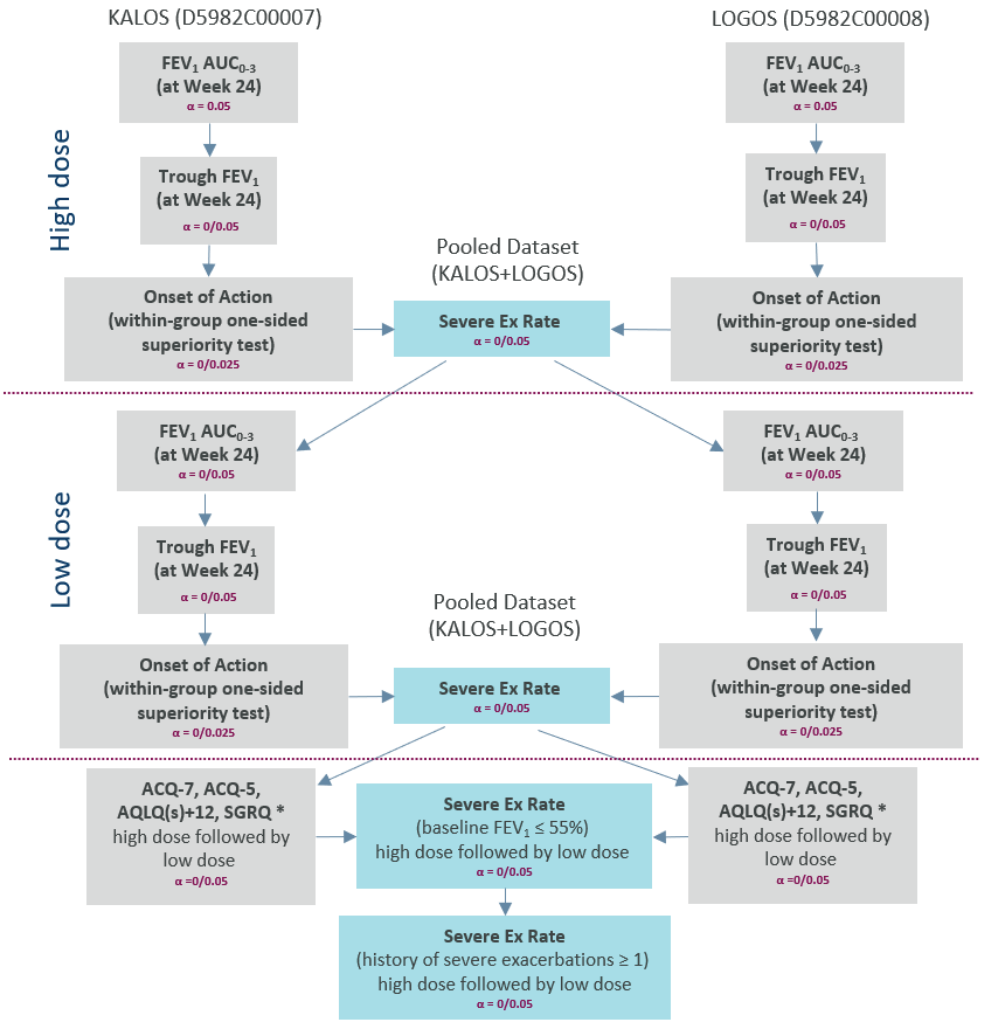
endpoints will be strongly controlled and will include the pooled analysis. As such, both studies D5982C00007 and D5982C00008 are included in the description of the procedure.

Due to variation in the CCI l requirements, the MTP will be different depending on the region.

3.3.8.1 CCI Approach

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

Figure 1 CCI Type I Error Control Procedure
BGF MDI (28.8 or 14.4 µg GP) vs BFF MDI



* After testing the rate of severe exacerbations for low dose, the secondary endpoints on PROs (percentage of responders in ACQ-7, ACQ-5, AQLQ(s)+12, and SGRQ) will be strongly controlled using a Hochberg procedure (Gou et al. 2014).

The procedure starts by comparing BGF MDI 320/28.8/9.6 µg versus BFF MDI 320/9.6 µg,

testing the primary endpoint, change from baseline in FEV_1 AUC_{0-3}, within each of the two studies (Study D5982C00007 and Study D5982C00008). If these results are statistically significant (alpha = 0.05, two-sided) within a study, change from baseline in trough FEV_1 will be tested at 2-sided alpha of 0.05 for that study. If these results are statistically significant within a study, the onset of action on Day 1 (within-group superiority test for the BGF MDI 320/28.8/9.6 µg arm) will be tested at alpha = 0.025 (one-sided) for that study. If the test for onset of action on Day 1 is statistically significant in at least one study, the pooled severe exacerbation rate will be tested at alpha = 0.05 (two-sided).

If the test for the pooled severe exacerbation rate is statistically significant for BGF MDI 320/28.8/9.6 µg versus BFF 320/9.6 µg, the change from baseline in FEV_1 AUC_{0-3}, change from baseline in trough FEV_1, and onset of action on Day 1 (within-group one-sided superiority test) and pooled severe exacerbation rate will be tested comparing BGF MDI 320/14.4/9.6 µg versus BFF MDI 320/9.6 µg, in the same manner as described above at alpha = 0.05 (two-sided).

If the test for pooled severe exacerbation rate comparing BGF MDI 320/14.4/9.6 µg versus BFF MDI 320/9.6 µg is statistically significant, the secondary endpoints (percentage of responders in ACQ-7, ACQ-5, AQLQ(s)+12, and SGRQ) will be simultaneously tested by study (alpha=0.05, two-sided) with a Hochberg procedure [Gou 2014] comparing BGF MDI 320/28.8/9.6 µg versus BFF MDI 320/9.6 µg. If all the tests for those secondary endpoints are statistically significant by study, the same Hochberg approach will be applied for those endpoints comparing BGF MDI 320/14.4/9.6 µg versus BFF MDI 320/9.6 µg in the respective study.

If all the tests for the secondary endpoints in the Hochberg procedure are statistically significant in at least one of the studies, the pooled severe exacerbation rate for participants with baseline percent predicted $FEV_1 \leq 55\%$ will be tested at alpha = 0.05 (two-sided) comparing BGF MDI 320/28.8/9.6 µg versus BFF MDI 320/9.6 µg. In case of a statistically significant result, the same test will be performed comparing BGF MDI 320/14.4/9.6 µg versus BFF MDI 320/9.6 µg. If the test in the subgroup is statistically significant, the pooled severe exacerbation rate for participants with ≥ 1 severe exacerbation in the 12 months prior to Visit 1 will be tested at alpha = 0.05 comparing BGF MDI 320/28.8/9.6 µg versus BFF MDI 320/9.6 µg. In case of a statistically significant result, the same test will be performed comparing BGF MDI 320/14.4/9.6 µg versus BFF MDI 320/9.6 µg.

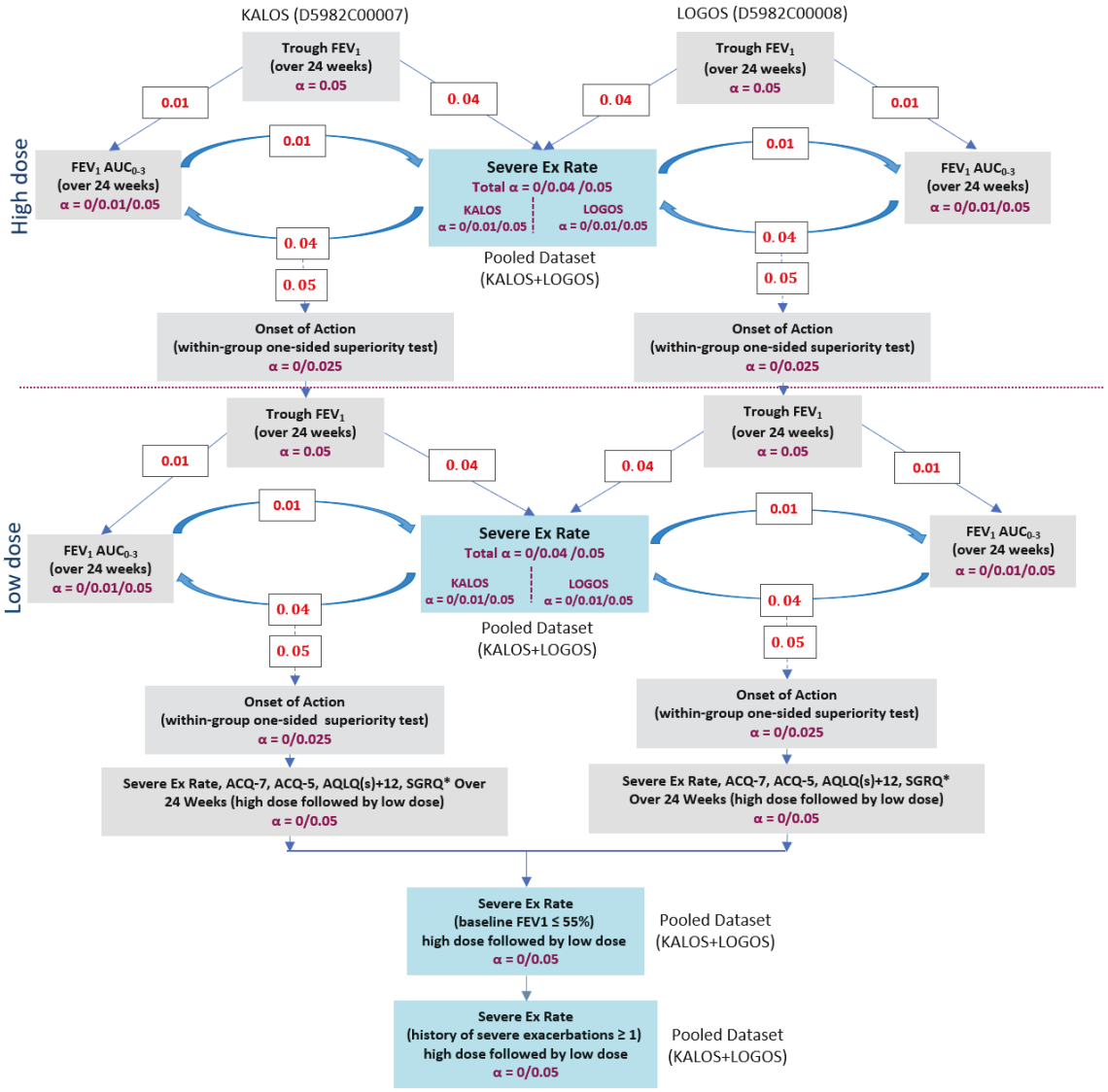
Endpoints evaluated at individual study level (i.e. any endpoint other than severe exacerbation rate) will only be tested if the tests for all preceding endpoints performed within the respective study were statistically significant.

3.3.8.2 CCI Approach

The Type I error control procedure for CCI is described graphically in Figure 2.

Figure 2 CCI Type I Error Control Procedure

BGF MDI (28.8 or 14.4 µg GP) vs ICS/LABA (pooled BFF MDI and Symbicort pMDI)



* Onset of action can only be tested if both FEV_1 $AUC_{0\text{-}3}$ for the respective study and the pooled severe exacerbation rate are statistically significant. After onset of action for low dose, the testing of the severe exacerbation rate and the secondary endpoints on PROs (percentage of responders in ACQ-7, ACQ-5, AQLQ(s)+12, and SGRQ) will be strongly controlled using a Hochberg procedure (Gou et al. 2014).

The procedure starts by comparing BGF MDI 320/28.8/9.6 µg versus ICS/LABA, testing the primary endpoint, change from baseline in trough FEV_1, within each of the two studies (Study D5982C00007 and Study D5982C00008). If these results are statistically significant (alpha = 0.05, two-sided) within a study, the alpha is further split with 0.04 allocated to the

test of the pooled severe exacerbation rate and 0.01 allocated to the test of change from baseline in FEV_1 AUC_{0-3} within the respective study.

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

If the test for the pooled severe exacerbation rate and FEV_1 AUC_{0-3} are both statistically significant, the onset of action on Day 1 (within-group superiority test for BGF MDI 320/28.8/9.6 µg) will be tested at alpha = 0.025 (one-sided).

If the test for onset of action is then statistically significant, change from baseline in trough FEV_1 and change from baseline in FEV_1 AUC_{0-3}, pooled severe exacerbation rate comparing BGF MDI 320/14.4/9.6 µg versus ICS/LABA, and onset of action Day 1 (within-group one-sided superiority test for the BGF MDI 320/14.4/9.6 µg), will be tested in the same manner as described above.

If the test for onset of action is then statistically significant within a study, the secondary endpoints (severe exacerbation rate in the individual studies and percentage responders in ACQ-7, ACQ-5, AQLQ(s)+12, and SGRQ) will be simultaneously tested (alpha = 0.05, two-sided) for the respective study with a Hochberg procedure [Gou et al. 2014] comparing BGF MDI 320/28.8/9.6 µg versus ICS/LABA. If all the tests for those secondary endpoints are statistically significant within a study, the same Hochberg approach will be applied for those endpoints comparing BGF MDI 320/14.4/9.6 µg versus ICS/LABA in the respective study.

If all the tests for the secondary endpoints in the Hochberg procedure are statistically significant in at least one of the studies, the pooled severe exacerbation rate for participants with percent predicted $FEV_1 \leq 55\%$ will be tested at alpha = 0.05 (two-sided) comparing BGF MDI 320/28.8/9.6 µg versus ICS/LABA. In case of a statistically significant result, the same test will be performed comparing BGF MDI 320/14.4/9.6 µg versus ICS/LABA. If the test in this subgroup is statistically significant, the pooled severe exacerbation rate for participants with ≥ 1 severe exacerbation in the 12 months prior to Visit 1 will be tested at alpha = 0.05 comparing BGF MDI 320/28.8/9.6 µg versus ICS/LABA. In case of a statistically significant result, the same test will be performed comparing BGF 320/14.4/9.6 µg versus ICS/LABA.

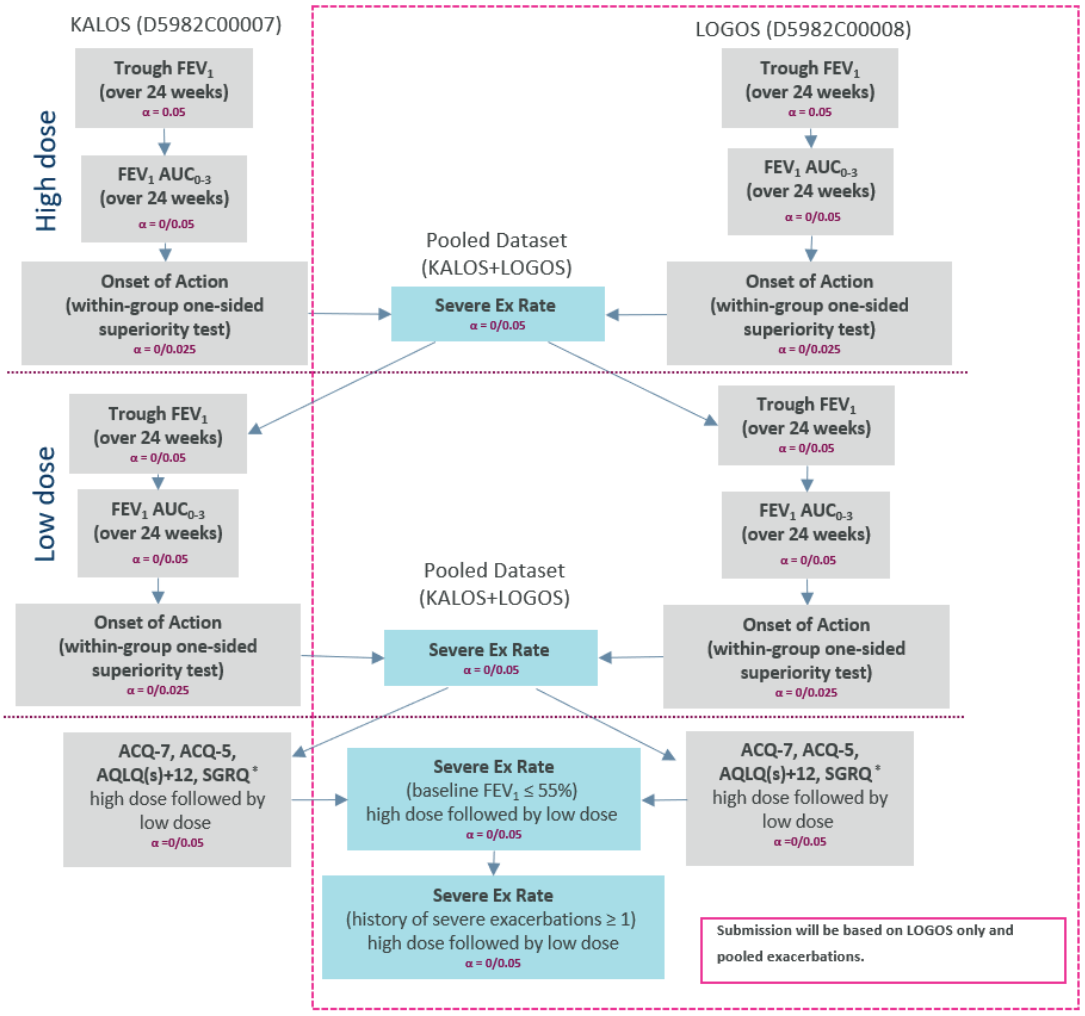
Endpoints evaluated at individual study level (ie, any endpoint other than severe exacerbation rate) will only be tested if the tests for all preceding endpoints performed within the respective study were statistically significant.

3.3.8.3 CCI Approach

The Type I error control procedure for CCI is described graphically in Figure 3. The procedure will apply a sequential testing method.

Figure 3 CCI Type I Error Control Procedure

BGF MDI (28.8 or 14.4 µg GP) vs Symbicort pMDI



* The secondary endpoints on PROs (percentage of responders in ACQ-7, ACQ-5, AQLQ(s)+12, and SGRQ) will be strongly controlled using a Hochberg procedure (Gou et al. 2014).

The procedure starts by comparing BGF MDI 320/28.8/9.6 µg versus Symbicort pMDI 320/9.6 µg, testing the primary endpoint, change from baseline in trough FEV_1, within each

of the two studies (Study D5982C00007 and Study D5982C00008). If these results are statistically significant (alpha = 0.05, two-sided) within a study, change from baseline in FEV_1 AUC_{0-3} will be tested (alpha = 0.05, two-sided) for that study. If these results are statistically significant within a study, the onset of action on Day 1 (within-group superiority test for the BGF MDI 320/28.8/9.6 µg arm) will be tested at alpha = 0.025 (one-sided) for that study. If the test for onset of action on Day 1 is statistically significant in at least one study, the pooled severe exacerbation rate will be tested at alpha = 0.05 (two-sided).

If the test for the pooled severe exacerbation rate is statistically significant, change from baseline in trough FEV_1, change from baseline in FEV_1 AUC_{0-3}, and onset of action on Day 1 (within-group one-sided superiority test for the BGF MDI 320/14.4/9.6 µg) and pooled severe exacerbation rate will be tested comparing BGF MDI 320/14.4/9.6 µg versus Symbicort pMDI 320/9.6 µg, in the same manner as described above at alpha = 0.05 (two-sided).

If the test for the pooled severe exacerbation rate comparing BGF MDI 320/14.4/9.6 µg versus Symbicort pMDI 320/9.6 µg is statistically significant, the secondary endpoints (percentage of responders in ACQ-7, ACQ-5, AQLQ(s)+12, and SGRQ) will be simultaneously tested for each study (alpha = 0.05, two-sided) with a Hochberg procedure [Gou et al. 2014] comparing BGF MDI 320/28.8/9.6 µg versus Symbicort pMDI 320/9.6 µg. If all of the tests for those secondary endpoints are statistically significant within a study, the same Hochberg approach will be applied for those endpoints comparing BGF MDI 320/14.4/9.6 µg versus Symbicort pMDI 320/9.6 µg in the respective study.

If all of the tests for the secondary endpoints in the Hochberg procedure are statistically significant in at least one of the studies, the pooled severe exacerbation rate for participants with percent predicted $FEV_1 \leq 55\%$ will be tested at alpha = 0.05 (two-sided) comparing BGF MDI 320/28.8/9.6 µg versus Symbicort pMDI 320/9.6 µg. In case of a statistically significant result, the same test will be performed comparing BGF MDI 320/14.4/9.6 µg versus Symbicort pMDI 320/9.6 µg. If the test in this subgroup is statistically significant, the pooled severe exacerbation rate for participants with ≥ 1 severe exacerbation in the 12 months prior to Visit 1 will be tested at alpha=0.05 comparing BGF MDI 320/28.8/9.6 µg versus Symbicort pMDI 320/9.6 µg. In case of a statistically significant result, the same test will be performed comparing BGF MDI 320/14.4/9.6 µg versus Symbicort pMDI 320/9.6 µg.

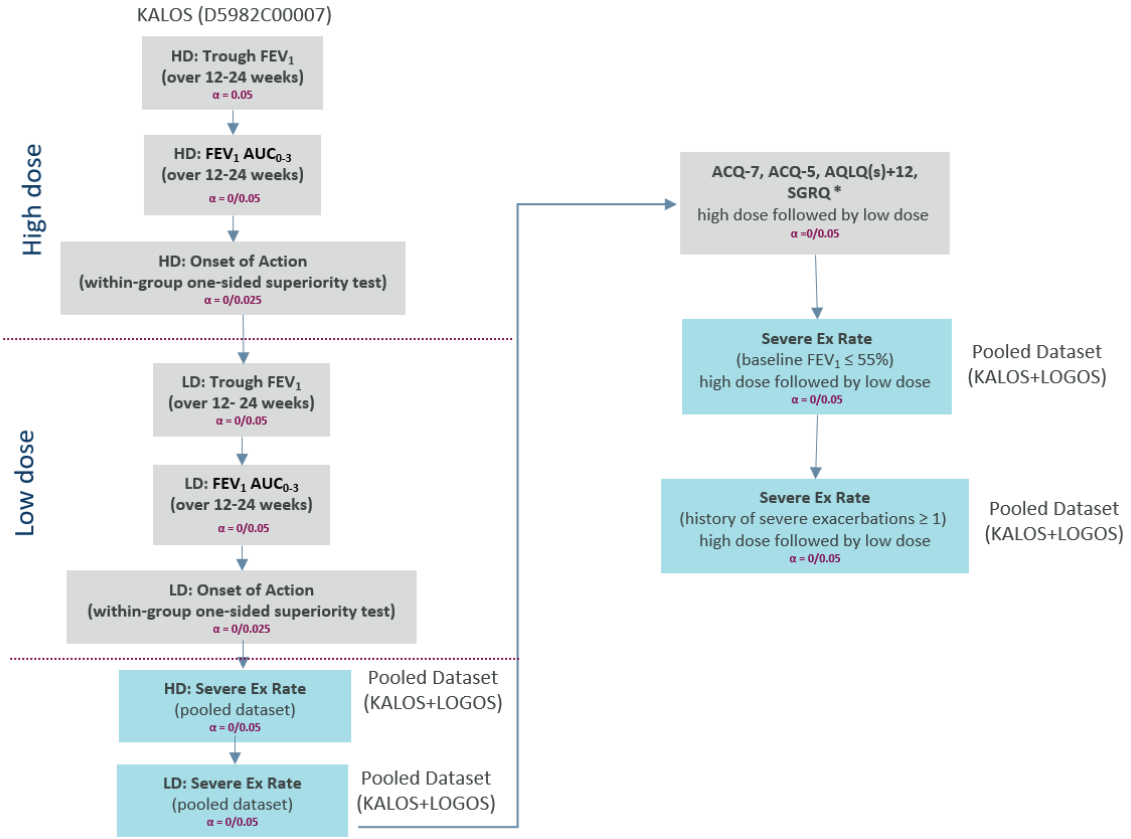
Endpoints evaluated at individual study level (i.e., any endpoint other than severe exacerbation rate) will only be tested if the tests for all preceding endpoints performed within the respective study were statistically significant.

3.3.8.4 CCI Approach

The Type I error control procedure for CCI is described graphically in Figure 4. The procedure will apply with sequential testing method.

Figure 4 CCI Type I Error Control Procedure

BGF MDI (28.8 or 14.4 µg GP) vs BFF MDI



HD = High Dose, LD = Low Dose

* After testing the pooled severe exacerbation rate for low dose, the secondary endpoints on PROs (ACQ-7, ACQ5, AQLQ(s)+12, and SGRQ) will be strongly controlled using a Hochberg-type procedure (Gou et al. 2014).

The procedure starts by comparing BGF MDI 320/28.8/9.6 µg versus BFF MDI 320/9.6 µg, testing the primary endpoint, change from baseline in trough FEV_1. If this result is statistically significant (alpha = 0.05, two-sided), change from baseline in FEV_1 AUC_{0-3} will be tested (alpha = 0.05, two-sided). If this result is statistically significant, the onset of action on Day 1 (within-group superiority test for the BGF MDI 320/28.8/9.6 µg arm) will be tested at alpha = 0.025 (one-sided).

If the test for onset of action on Day 1 (within-group superiority test for the BGF MDI 320/28.8/9.6 µg arm) is statistically significant, change from baseline in trough FEV_1, and

then change from baseline in FEV_1 AUC_{0-3} will be tested sequentially comparing BGF MDI 320/14.4/9.6 µg versus BFF MDI 320/9.6 µg at alpha = 0.05 (two-sided). If significant, the onset of action on Day 1 (within-group test for the BGF MDI 320/14.4/9.6 µg) will be tested alpha = 0.025 (one-sided).

If the test of the onset of action on Day 1 (within-group test for the BGF MDI 320/14.4/9.6 µg) is statistically significant, the pooled (Study D5982C00007 and Study D5982C00008) severe exacerbation rate comparing BGF MDI 320/28.8/9.6 µg versus BFF MDI 320/9.6 µg will be tested at alpha = 0.05 (two-sided). If the test is statistically significant, the pooled severe exacerbation rate comparing BGF MDI 320/14.4/9.6 µg versus BFF MDI 320/9.6 µg will be tested at alpha = 0.05 (two-sided).

If the test for the pooled severe exacerbation rate comparing BGF MDI 320/14.4/9.6 µg versus BFF MDI 320/9.6 µg is statistically significant, the secondary endpoints (percentage of responders in ACQ-7, ACQ-5, AQLQ(s)+12, and SGRQ) will be simultaneously tested (alpha = 0.05, two-sided) with a Hochberg procedure [Gou et al. 2014] comparing BGF MDI 320/28.8/9.6 µg versus BFF MDI 320/9.6 µg. If all the tests for those secondary endpoints are statistically significant, the same Hochberg approach will be applied for those endpoints comparing BGF MDI 320/14.4/9.6 µg versus BFF MDI 320/9.6 µg.

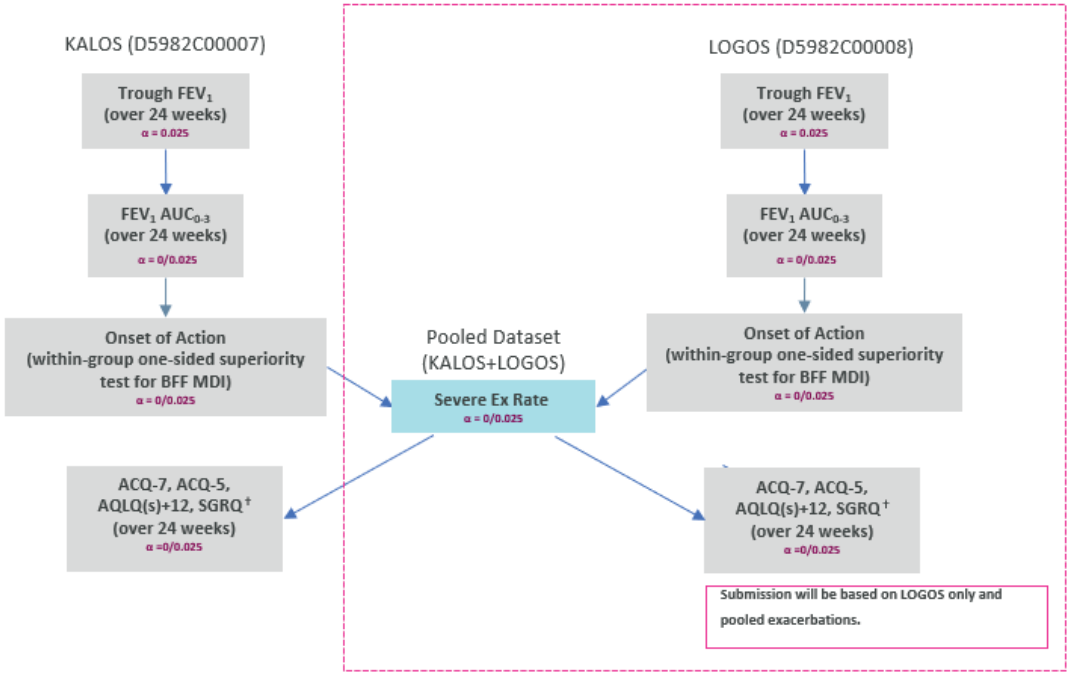
If all the tests for the secondary endpoints in the Hochberg procedure are statistically significant, the pooled severe exacerbation rate for participants with percent predicted FEV_1 ≤ 55% will be tested at alpha = 0.05 (two-sided) comparing BGF MDI 320/28.8/9.6 µg versus BFF MDI 320/9.6 µg. In case of a statistically significant result, the same test will be performed comparing BGF MDI 320/14.4/9.6 µg versus BFF MDI 320/9.6 µg. If the test in this subgroup is statistically significant, the pooled severe exacerbation rate for participants with ≥ 1 severe exacerbation in the 12 months prior to Visit 1 will be tested at alpha=0.05 comparing BGF MDI 320/28.8/9.6 µg versus BFF MDI 320/9.6 µg. In case of a statistically significant result, the same test will be performed comparing BGF MDI 320/14.4/9.6 µg versus BFF MDI 320/9.6 µg.

3.3.8.5 CCI NI Tests

Additionally, NI tests of BFF MDI vs Symbicort pMDI will be conducted as described in Figure 5 toCCI [redacted]

Figure 5 CCI **Type I Error Control for NI**

BFF MDI vs Symbicort pMDI



* After testing pooled severe exacerbation rate, the remaining secondary endpoints will be strongly controlled using a Hochberg-type procedure (Gou et al. 2014).

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

3.3.9 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 CSR for all 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
- Exclusion criteria
- Discontinuation criteria for study product met but participant not withdrawn from study treatment
- Discontinuation criteria for overall study withdrawal met but participant not withdrawn from study
- IP deviation
- Excluded medications taken
- Deviation related to study procedure
- Other IPDs

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, 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).

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 treatment compliance.

4.1.1 Subject Disposition and Completion Status

4.1.1.1 Definitions and Derivations

Subject disposition will be summarized using the Screened Set. The number of screened participants will be summarized. The number and percentage of participants within each treatment group will be presented by the following categories: screened, screen failures (and reason), randomized, randomized but not treated (and reason), started treatment, completed treatment, discontinued treatment early, as well as discontinued treatment prior to Week 24 (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, as well as withdrawn from study prior to Week 24. For screened and randomized categories, the number and percentage will be summarized separately for participants at sites using Medipharma SMO and participants excluding those sites using Medipharma SMO. Disposition summaries will also be produced for the age subgroups at study entry: adults (≥18) and adolescents (≥12 to <18).

Participant recruitment by region, country and site will also be summarized by treatment group. The following regions are defined: US & Canada, Asia, Europe, Mexico & Central America & South America, Australia & New Zealand & South Africa.

4.1.1.2 Presentation

A disposition table for all participants will be provided. Disposition table by age subgroup (adults and adolescents) will be provided. Discontinued participants and participants completing the study will be listed. The numbers of participants randomized will be summarized by region, country, site, and treatment.

Time to premature IP discontinuation and time to study withdrawal will be presented using Kaplan-Meier curves by treatment group for the Efficacy Set.

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 by the following analysis sets: Efficacy, PP, Safety, PFT, PK (for KALOS only) and Holter Monitoring (for KALOS only).

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

For the Efficacy and Safety Sets:

- Participant did not receive study intervention
- Participant randomised multiple times at sites or studies

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 study intervention
- Participant had an IPD impacting efficacy at the day of first dose of randomized IP
- Participant randomised multiple times at sites or studies

For the PFT Set the first condition met according to the following priority order will be defined as the reason for exclusion:

- Participant did not consent to participate in PFT sub-study
- Participant did not receive study intervention
- Participant did not have at least 1 post baseline spirometry assessment following the first dose of study intervention
- Participant randomised multiple times at sites or studies

For the PK Set the first condition from the list below will define the reason for exclusion for each participant:

- Participant did not consent to participate in PK sub-study
- Participant did not receive study intervention
- Participant did not have at least one post-dose PK measurement
- Participant had not correctly self-administered the last 3 doses of IP (6 inhalations), i.e., participant has recorded in e-Diary correct administration for the morning dose of Visit 8, and morning and evening of day before Visit 8.
- Participant randomised multiple times at sites or studies

For the Holter Monitoring Set the first condition from the list below will define the reason for exclusion for each participant:

- Participant did not consent to participate in Holter Monitoring sub-study

- Participant did not receive study intervention
- Participant had an IPD impacting data prior to receiving study intervention
- Participant did not have at least 18 hours of acceptable quality Holter monitoring data at both Visit 4 (Holter baseline) and at least one of Visit 6 (Week 4) and Visit 11 (Week 24)
- Participant randomised multiple times at sites or studies

4.1.2.2 Presentation

A summary of all analysis sets will be provided. Participants excluded from any analysis set will be listed.

4.1.3 Protocol Deviations

4.1.3.1 Definitions and Derivations

Important PD categories are specified in Section 3.3.9 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 Protocol Deviations 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 important PD 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)
- Sex
- Race
- Ethnic group
- Country

4.1.4.2 Presentation

Demographics will be summarized for the Efficacy, Safety, PFT Sub-study, PP and Holter Monitoring analysis sets.

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 FEV1 - 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, ≥2) 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 to < 450, >=450)
- Baseline pre-bronchodilator percent predicted FEV_1 (%)
- Pre-bronchodilator FEV_1 (L)

- Baseline ACQ-5 score
- Baseline ACQ-7 score
- Prior ICS dose (Low, Medium, High)
- Smoking status (former smoker, non-smoker)
- Number of Pack Years Smoked
- PEFR stability limit at Visit 5 (L/min)
- FeNO at Visit 1 (ppb)
- FeNO at Visit 5 (ppb)

Characterization of Reversibility:

Reversibility to albuterol will be evaluated for participant qualification purposes and characterization. For participants who did not meet albuterol reversibility criterion at Visit 2 (including those with documented historical reversibility to albuterol within 12 months prior to Visit 1), albuterol reversibility testing must be repeated at Visit 3.

Reversibility will be a comparison of the average best FEV1 effort obtained at 60- and 30-minutes pre-bronchodilator to the best FEV1 effort obtained at 30 minutes (or up to 60 minutes, if repeated) post-bronchodilator following administration of albuterol. A participant ≥18 years of age is considered reversible if the improvement in FEV1 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 FEV1 at 30 minutes (or at 60 minutes) post-dose is ≥12%.

Prior ICS dose:

The classification of the prior ICS total daily dose (defined as a stable dose for at least 4 weeks prior to Visit 1) as medium or high is according to Table 8 of the CSP Version 6.0. In case of multiple concurrent ICS treatments, the following rules will be applied:

- In case of any combination of Medium and High dose, the total daily dose will be classified as High.
- In case of any combination of two or more Medium doses, the total daily dose will be classified as High.
- In case of any combination of Medium and Low doses and two or more Low doses, the total daily dose will be calculated by converting the dose of each ICS treatment to a Fluticasone propionate equivalent dose and summing those doses. The total dose will be classified as Medium or High per Table 8 of the CSP Version 6.0. The conversion factors in Table 15 will be used to derive the

Fluticasone propionate equivalent dose for each ICS treatment – the recorded daily dose of each ICS treatment will be multiplied by the conversion factor.

If the prior ICS total daily dose is non-missing and doesn't belong to medium or high, it will be classified as low.

Table 15 ICS Equivalency Conversion Factors

Inhaled Corticosteroid	**Conversion factor**
Beclomethasone dipropionate (pMDI, standard particle, HFA)	0.5000
Beclomethasone dipropionate (pMDI, extrafine particle, HFA)	1.2500
Budesonide (DPI)[a]	0.6250
Budesonide as delivered dose, e.g. Symbicort	0.7813
Ciclesonide (pMDI, extrafine particle, HFA)	1.5625
Fluticasone furoate (DPI)	2.5000
Fluticasone propionate (DPI)	1.0000
Fluticasone propionate (pMDI, standard particle, HFA)	1.0000
Mometasone furoate (DPI)	Due to complexity around dosing in different devices/formulations, this will be discussed with physician ahead of clinical data lock to agree conversion factor and will be documented
Mometasone furoate (pMDI, standard particle, HFA)	1.2500
Mometasone furoate as metered dose in Atectura Breezhaler	1.5625

HFA = Hydrofluoroalkane (propellant), DPI = Dry Powder Inhaler

[a] Include pMDI, standard particle, HFA.

Baselines for Blood Eosinophil Count and Pre-bronchodilator Percent Predicted FEV_1:

Baselines for these two variables are defined in Section 0.

PEFR Stability Limit:

At Visit 5, a PEFR baseline will be calculated to define a stability limit. The stability limit is defined as the average of the available morning PEFR eDiary recordings during the last 7 days before Visit 5 (i.e., the baseline PEFR), multiplied by 0.8.

FeNO:

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

4.1.5.2 Presentation

Disease characteristics will be summarized for the Efficacy, Safety, PFT Sub-study, PP and Holter Monitoring analysis sets. Baseline disease characteristics will also be summarized by adults (>= 18 years) and adolescents (>= 12 to <18 years) for 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. As the BFF MDI product administered during the run-in period is not registered, only events that occurred before the enrolment or were ongoing at enrolment should be captured and presented as medical and surgical history.

Medical history related to asthma will be recorded on a separate respiratory disease history 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 (0, 1, >=2)
- 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 MedDRA primary SOC, and for each MedDRA PT within a SOC for the Safety Set.

Asthma characteristics at study entry will be summarized for the Efficacy, Safety, PFT Sub-study, PP and Holter Monitoring analysis sets.

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 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 treatment 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 first dose of randomized IP and the date that is one day before discontinuation from or completion of study treatment.

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 (screening period or treatment period), or Post-Treatment will be considered as being in each of the categories that are possible from the available information.

Separate tables will be presented for participants who took disallowed concomitant medications or disallowed post-treatment medications. Disallowed medications include medications defined as prohibited according to Section 6.5.5 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) or post-treatment asthma related medication will be tabulated separately for the Efficacy Set by the following categories: 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).

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 or disallowed post-treatment medication (by ATC classification system codes and generic term) will be presented separately 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)
- BMI (kg/m²)
- BMI categories (kg/m2) (<18.5, >=18.5 to <25, >=25 to <30 and >=30)

BMI is calculated as:

BMI = Weight (kg) / [Height (m)]^2].

Weight/Height/BMI:

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

Stratification factors recorded at randomisation by IVRS will also be summarized. For adults, randomization is stratified by country, baseline pre-bronchodilator percent predicted FEV1 (≤55% vs. >55%), severe exacerbation history in the 12 months prior to Visit 1 (0, 1, ≥2), and ICS dose (medium vs. high). For adolescents, randomization will be stratified by country and baseline pre-bronchodilator percent predicted FEV1 (≤75% vs. >75%).

4.1.8.2 Presentation

Baseline characteristics will be summarized for the Efficacy, Safety, PP, PFT Sub-study, and Holter Monitoring analysis sets.

The number of participants within each stratum recorded at randomisation by IVRS will be tabulated for randomized adults and adolescents separately, across all regions and by region.

4.1.9 Study Treatment Compliance

4.1.9.1 Definitions and Derivations

Percent compliance with study treatment is defined as (total number of puffs of study treatment 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 treatment and last day on study treatment 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 (n, mean, SD, median, minimum and maximum) for percent compliance with study treatment will be summarized and study treatment compliance will be categorized into different groups depending on the degree of compliance: 0 – < 20%, ≥ 20 – < 40%, ≥ 40 – < 60%, ≥ 60 – < 80%, ≥ 80 – ≤ 100%, > 100 – ≤ 120%, and > 120% for Safety, PFT Sub-study and Holter Monitoring analysis sets.

Exposure of IP will be listed.

4.2 Endpoint Analyses for Individual Study

This section covers details related to the endpoint analyses for individual study such as primary, secondary, exploratory endpoints including sensitivity and supportive analyses.

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 CCI Change from Baseline in Morning Pre-dose Trough FEV_1 over 12 to 24 weeks is the primary endpoint.

Treatment comparisons are different for different regions and 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 measurement occurring within 4.5 hours post-dose, i.e., the upper limit of the "post-dose 3 hours" analysis study time window as defined in Table 13 (the last measurement is targeted 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.

4.2.1.3 Handling of Dropouts and Missing Data

Missing data not handled by imputations as per Section 3.3.5.1 will be assumed to be missing at random in either the Primary strategy for handling ICEs or for the While on Treatment strategy for ICEs. However, under the Primary strategy to ICEs, data following the initiation of new asthma therapy or administration of prohibited medications thought to impact efficacy in conjunction with premature discontinuation of study invention will be imputed as treatment failures (see Section 3.3.5.1 for further details).

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

4.2.1.4 Primary Analysis of Primary Endpoint

The primary analysis of the primary endpoint will utilize the Primary strategy for handling ICEs as per Section 3.3.5.1. The Efficacy Set will be used for the analysis and only participants with baseline and at least one post randomization measurement will be included.

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

Change from baseline in FEV_1 AUC_{0-3} will be analyzed using a repeated measures analysis of covariance model. The model will include treatment, visit, prior ICS dose (medium vs. high), and treatment-by-visit interaction as categorical covariates and baseline trough FEV_1 and percent reversibility (as 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. Contrasts will be used to obtain estimates of the treatment differences at Week 24 for CCI Two-sided p-values and point estimates with 95% CIs will be produced for each treatment difference.

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

Change from baseline in morning pre-dose trough FEV_1 will be analyzed using a repeated measures analysis of covariance model. The model will be similar to the one used for FEV_1 AUC_{0-3}.

Contrasts will be used to obtain estimates of the treatment differences over 24 weeks for CCI and over 12 to 24 weeks for CCI [20] Two-sided p-values and point estimates with 95% CIs will be produced for each treatment difference.

4.2.1.5 Supportive Analyses of the Primary Endpoint

As supportive analysis, the primary endpoint will be analyzed using a While on Treatment strategy for all ICEs. The Efficacy Set will be used for theses analyses and only participants with baseline and at least one post randomization measurement will be included.

4.2.1.6 Sensitivity Analyses of the Primary Endpoint

For the primary endpoint, sensitivity analyses will be conducted at Week 24 CCI approach), over 12-24 weeks CCI approach), and over 24 weeks CCI approach) on the Primary strategy for handling ICEs to evaluate the robustness of the analysis findings to missing data. For the Primary strategy for handling ICEs, the primary analyses of FEV_1 AUC_{0-3} and morning pre-dose trough FEV_1 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 missing data following study withdrawal/Lost To Follow Up are 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 the p-value for the primary analysis is below or equal to 0.05.

All missing data since study withdrawal and until the last planned study day in the treatment period (unless already imputed under the Primary strategy for handling ICEs) will be imputed. For these imputations, the missing data are considered MNAR and imputed with a two-dimensional decrementing method. 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, or until the p-value for the comparison is no longer significant per MTP. Imputed values may not be impossible values i.e., changes from baseline that would imply a negative FEV_1 value. Thus, the values will be imputed from a truncated distribution. Details of the sensitivity analyses are described in Section 9.2.2.

4.2.1.7 Subgroup and Consistency Analyses of the Primary Endpoint

To explore the uniformity of the overall treatment effect, subgroup analyses based on the primary analysis for each respective region will be performed for the following factors:

- Age with following categories:
  - ≥12 and <18
  - ≥18 and <65
  - ≥65
- 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 specifying multiple racial groups.
- Baseline severe asthma exacerbation history (0, ≥1)
- Baseline pre-bronchodilator percent predicted FEV_1 (≤55%, >55%)
- Prior ICS dose (Medium, High)
- Reversibility (<20%, >=20%)
- Region with the following categories
  - US & Canada
  - Asia
  - Europe
  - Mexico & Central America & South America
  - Australia & New Zealand & South Africa

To investigate the interaction effect between subgroup and treatment, 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, allows the 2-way interaction between treatment and subgroup to vary 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 within each subgroup category. Point estimates with two-sided P-value and 95% confidence interval (CI) will be produced for each treatment difference.

A Heterogeneous Toeplitz (TOEPH) correlation matrix will be used to model the variance-covariance structure for subgroup analysis. If this model fails to converge, the following hierarchical approach is proposed to select a simpler covariance structure if the preceding covariance structure fails to converge: Heterogeneous Toeplitz -> Toeplitz -> Compound Symmetry. 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, a similar model to the one used for FEV_1 AUC_{0-}

$_3$ will be used. A contrast will be computed over 24 weeks and over 12-24 weeks 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 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 then 10 participants, then model estimates will not be presented for that treatment group of the subgroup category.

A forest plot will be used to summarize the estimates of the treatment effect for the above applicable subgroups and the overall result from the primary analysis.

Furthermore, subgroup analyses will be conducted for the primary endpoint to support local registration requirements including by-country and by-region assessments of consistency. Subgroups on regions are defined as CCI and CCI Subgroup analysis on regions will be performed for the Primary estimand strategy for all ICEs.

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 key secondary endpoint is change from baseline in FEV_1 AUC_{0-3} over 12 to 24 weeks. The key secondary endpoint CCI secondary for CCI is change from baseline in FEV_1 AUC_{0-3} over 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 specified in Section 4.2.1.3.

4.2.2.4 Primary Analysis of Secondary Endpoint

The primary analysis of secondary endpoint will utilize the Primary strategy for handling ICEs as per Section 3.3.5.1. The Efficacy Set will be used for the analysis and only participants with baseline and at least one post randomization measurement will be included. For details, refer to Section 4.2.1.4.

4.2.2.5 Supportive Analyses of the Secondary Endpoint

As supportive analyses, the secondary endpoint will be analyzed with the While on Treatment ICE strategy for all ICEs. The Efficacy Set will be used for the analyses. For details, refer to Section 3.3.5.2.

4.2.2.6 Sensitivity Analyses of the Secondary Endpoint

The sensitivity analysis of the secondary endpoint is similar as the sensitivity analyses of the primary endpoint specified in Section 4.2.1.6 and will be conducted at Week 24 CCI approach) only in the case where a statistically significant effect was observed for the primary analysis for the key secondary endpoint.

4.2.2.7 Subgroup and Consistency Analyses of the Secondary Endpoint

The subgroup analyses, including subgroup analyses on regions to support local registration requirements are similar as the subgroup analyses for the primary endpoint specified in Section 4.2.1.7.

4.2.3 Other Secondary Endpoints: PROs

4.2.3.1 Definition

The 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. 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

The SGRQ is a 50-item questionnaire developed to measure the health status of participants with respiratory diseases (Jones, 1991). The questionnaire is divided into two parts: part 1 consists of 8 items pertaining to the severity of respiratory symptoms in the preceding 4 weeks; part 2 consists of 42 items related to the daily activity and psychosocial impacts of the individual's respiratory condition.

The SGRQ comprises three domains: "Symptoms" concerned with respiratory symptoms, their frequency, and severity; "Activity" concerned with activities that cause or are limited by breathlessness; and "Impacts" which covers a range of aspects concerned with social functioning and psychological disturbances resulting from airway disease. A score will be calculated for each component and a "Total" score will be calculated. In each case, the lowest possible value is zero and the highest is 100. Higher values correspond to greater impairment of QoL.

The SGRQ will be administered and completed on the eDiary by the participant on the evening before specific site visits throughout the treatment period.

4.2.3.2 Derivations

The ACQ-5 score is the mean of the responses to the relevant 5 items. ACQ-6 and ACQ-7 are calculated similarly. 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 score will be assigned to the earliest date and time of all 7 items. Scores of ≤0.75 indicate well-controlled asthma, scores between 0.75 and <1.5 indicate partly controlled asthma, and a score ≥1.5 indicates not well-controlled asthma (Juniper, 2006). Individual changes of at least 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 change ≥0.5 increases are considered clinically meaningful; higher scores indicate better health status.

The SGRQ yields a total score (range 0 to 100) and three domain scores (symptoms, activity, and impacts). The total score indicates the impact of disease on overall health status. This total score is expressed as a percentage of overall impairment, in which higher scores indicate worse health status. Likewise, the domain scores range from 0 to 100, with higher scores indicative of greater impairment. SGRQ score changes of at least a 4-point

decrease on the total score and in each domain are considered clinically meaningful. Specific details on the scoring algorithms are provided in St George's Respiratory Questionnaire Manual (Jones 2009) and Appendix 9.3.

4.2.3.3 Primary Analysis of Other Secondary Endpoint: PROs

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 and for SGRQ at Week 24 and over 24 weeks with the Primary strategy for handling ICEs and supportive Composite strategy for ICEs. Analysis is in the Efficacy Set. For CCI SGRQ will be tested at Week 24 due to the schedule of data collection of that endpoint (data is not collected from Week 8 through Week 20).

Responders are defined as participants with an improvement of ≥0.5 points over baseline (decrease in ACQ scores, increase in AQLQ(s)+12 score). For SGRQ, responders are defined as participants with an improvement (≥4.0 points decrease) over baseline. For the Primary strategy for ICEs, participants who experience initiation of new asthma therapy or administration of prohibited medications thought to impact efficacy following first dose of randomised IP in conjunction with premature discontinuation of randomized study intervention will be classified as non-responders from the date of this ICE. For the supportive Composite strategy for ICEs, non-responder status will be imputed for all ICEs from the date of occurrence, except for data following premature IP discontinuation for reasons related to global/country situation, which will be considered missing and will not be imputed. Additionally, for the supportive Composite strategy, intermittently missing data will be classified as non-response, except due to global/country situation. For over 24 weeks and over 12 to 24 weeks, if the participant is considered a responder (i.e., improvement from baseline is observed beyond the pre-specified thresholds above) for at least 50% visits over that period, the participant will be considered responder over that period. Otherwise, the participant will be considered as non-responder.

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

4.2.4 Other Secondary Endpoint: Onset of Action on Day 1

4.2.4.1 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.

4.2.4.2 Derivations

For the onset of action on Day 1, baseline is defined in Section 0.

4.2.4.3 Primary Analysis of Other Secondary Endpoint: Onset of Action on Day 1

Descriptive statistics will be presented by treatment group. A within-group T-test to demonstrate that the mean change from baseline in FEV_1 at 5 minutes post-dose on Day 1 is statistically greater than 100 mL will also be provided with corresponding one-sided p-value and two-sided 95% CIs. The analysis will be performed using the Primary strategy for handling ICEs as per Section 3.3.5.1. Analysis is in the Efficacy Set.

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

Within-group T-test analyses will be performed in the same subgroups as described in Section 4.2.1.7 for the onset of action evaluation using the Primary strategy for handling ICEs, except that no subgroup analyses on regions will be performed.

No subgroup analyses in the individual studies will be performed for CCI for this endpoint, only for the pooled data.

4.2.5 Other Secondary Endpoint: Rate of Severe Exacerbations CCI

4.2.5.1 Definition

For the definition of severe asthma exacerbation, refer to Section 4.3.1.1.

4.2.5.2 Derivations

For the derivation related to severe asthma exacerbation, refer to Section 4.3.1.2.

4.2.5.3 Primary Analysis of Other Secondary Endpoint: Rate of Severe Asthma Exacerbations CCI

For CCI approach, rate of severe asthma exacerbations will be analyzed in the individual studies in the same way as indicated in the primary pooled analysis (Section 4.3.1.4) utilizing the Primary strategy for handling ICEs as per Section 3.3.5.1. Analysis is in the Efficacy Set. Note the model for the individual study analysis contains no term for the study effect.

The severe asthma exacerbation rates, and rate ratios comparing treatments will be summarized for the given estimand based on the Efficacy Set.

4.2.6 Non-Inferiority Test Endpoints (CCI Only)

CCI NI tests of BFF MDI vs Symbicort pMDI will be conducted. For the NI hypothesis testing, refer to Section 3.3.2.2. For MTP, refer to Section 3.3.8.5. 95% two-sided CIs and one-sided p-values will be reported for NI analysis.

4.2.6.1 Definition

The primary endpoint for NI test is change from baseline in morning pre-dose trough FEV_1 over 24 weeks. Other endpoints for NI tests include: change from baseline in FEV_1 AUC_{0-3} over 24 weeks, Onset of Action on Day 1 (within group superiority test), Percentage of responders in ACQ-7 (≥0.5 decrease equals response), ACQ-5 (≥0.5 decrease equals response), and AQLQ(s)+12 (≥0.5 increase equals response) over 24 weeks; Percentage of responders in the SGRQ (≥4.0 unit decrease equals response) over 24 weeks.

4.2.6.2 Derivations

For the derivation of NI for the primary endpoints, refer to Section 4.2.1.2. For the derivations of NI for other endpoints, refer to Section 4.2.3.2 and 4.2.4.2.

4.2.6.3 Analysis of NI Primary Endpoint

The primary analysis will utilize the Principal Stratum estimand with the PP Analysis Set, including only on-treatment data unaffected by ICEs (Section 3.3.9). Supportive analyses will be performed using the Primary strategy for ICEs and While on Treatment strategy for all ICEs in the Efficacy Analysis Set. The analysis models are the same as models specified in Section 4.2.1.4.

4.2.6.4 Analysis of NI Other Endpoints

The analysis of NI other endpoints will be performed for the Principal Stratum estimand with PP Analysis Set. The analysis models are the same specified in Section 4.2.3.3 for responder analysis and Section 4.2.4.3 for Onset of Action.

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
- FVC, PEFR, and 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 strategy for all ICEs in the Efficacy Set.

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

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

Change from baseline in FVC, PEFR, and FEF_{25-75} evaluated using AUC_{0-3} will be analyzed over 24 weeks, over 12 to 24 weeks, and by visit using a repeated measures analysis of covariance model. The model will be similar as the one used for the primary endpoint analysis except that the covariate baseline trough FEV_1 will be replaced with the relevant baseline value for the respective parameter (Section 4.2.1.4).

Change from Baseline in Morning Pre-Dose PEFR

Change from baseline in morning pre-dose PEFR 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 13), prior ICS dose (medium vs. high), and treatment by 4-week interval interaction as categorical covariates and baseline morning pre-dose PEFR, and percent reversibility as continuous covariates. An unstructured (UN) correlation matrix will be used to model the variance-covariance structure. If this model fails to converge, 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.

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 PEFR

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

Note: an evening PEFR recorded between 00a.m and 03a.m will be considered for the analysis of evening PEFR on the day before the recorded date.

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 of randomization.

4.2.8 Tertiary/Exploratory Endpoints: PROs and Time to Event

4.2.8.1 Definition

Exploratory PROs and time to event 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 total scores and AQLQ(s)+12 total and domain scores
- Change from baseline in SGRQ total and domain scores
- PGIC
- EQ-5D Questionnaire index score and VAS Questionnaire score at each post-randomization visit and end of study visit
- The percentage of participant's categorical responses to each of the 5-dimensions in EQ-5D
- Time to first CID
- Time to first ICE
- Time to first ICE of initiation of new asthma therapy or prohibited medications thought to impact efficacy in conjunction with premature discontinuation from study intervention
- CCI [redacted]
- CCI [redacted]

4.2.8.2 Derivations

ACQ and SGRQ

For the derivation details of ACQ and SGRQ, refer to Section 4.2.3.2.

PGIC

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

The PGIC will be completed on the eDiary by the participant at Visit 8 (Week 12), Visit 11 (Week 24) and Visit 15 (Week 52).

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. If no weight is listed for a specific country, then apply the weight for same region.

The VAS records the respondent's self-rated health on a 20 cm, 0 to 100 vertical scale with endpoints labelled "the best health you can imagine" and "the worst health you can imagine" with higher scores corresponding to a better health state. This information is used as a quantitative measure of health as judged by the individual respondents.

The EQ-5D will be completed on the eDiary by the participant at 11 site visits throughout the treatment period.

Time to First CID

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

- 12% decrease from baseline in pre-bronchodilator FEV_1
- AQLQ(s)+12 decrease of ≥0.5 from baseline
- ACQ-5 increase of ≥0.5 from baseline
- One severe or moderate asthma exacerbation

- Use of antibiotics for respiratory conditions

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

Time to First ICE

For the definition of ICE, refer to Section 3.3.1.2.

Time to first ICE is calculated as time in days from first dose of randomized IP to the earliest date of any ICE.

Time to First ICE of initiation of new asthma therapy or prohibited medications thought to impact efficacy in conjunction with premature discontinuation from study intervention

For the definition of this ICE and its start date, refer to Section 3.3.1.2.

Time to first ICE of interest is calculated as time in days from first dose of randomized IP to the start date of the ICE.

CCI [redacted]

CCI [redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

CCI [redacted]

4.2.8.3 Analysis of Exploratory PRO Endpoints

Unless specified otherwise, analyses of exploratory PROs endpoints will be performed for the While on Treatment strategy for all ICEs in the Efficacy Set.

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 4.2.3.3 utilizing the Primary strategy for ICEs.

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

Change from baseline in ACQ-5, ACQ-6, ACQ-7 total scores and AQLQ(s)+12 total and domain scores will each be analyzed using a repeated measures analysis of covariance model utilizing the Primary strategy for ICEs (see Section 3.3.5.1). The model will include treatment, visit, prior ICS dose (medium vs. high), and treatment-by-visit interaction as categorical covariates and baseline trough FEV_1, percent reversibility, and baseline score for the patient-reported outcome instrument as continuous covariates. Contrasts will be used to obtain estimates of the treatment differences by visit for measures assessed at clinic visits, over 24 weeks, and 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 SGRQ

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

PGIC

For PGIC, the number and percentage of participants defined as responders will be summarized descriptively and presented by treatment group and visit. A responder is defined as a participant with any of those categorized responses: “Much better”, “Moderately better” or “A little better”.

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 index score and VAS will be presented by treatment group and type of questionnaire. The VAS scores at each post-randomization visit, using a While on Treatment strategy, will be analyzed using a repeated measures analysis of covariance model with age and baseline score as continuous covariates and prior ICS dose (medium vs. high), region (as defined in Section 4.1.1.1), sex, treatment, visit and treatment-by-visit as categorical covariates.

Time to First CID

Time to first CID will be analyzed with a Cox regression model to compare the treatment groups, adjusted for baseline severe asthma exacerbation history (0, 1, ≥2), prior ICS dose (medium vs. high), region (as defined in Section 4.1.1.1), baseline trough FEV_1, and percent reversibility.

For the While on Treatment ICE strategy, participants who experience an ICE without any CID will be censored at the time of the ICE + 1 day. Participants not having any CID or any ICE will be censored at 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.

Time to First ICE

Time to first ICE will be analyzed in a manner similar to the analysis of time to first CID. For the While on Treatment ICE strategy, participants not having any ICE will be censored at their last dosing date.

This analysis answers the clinical question of whether participants receiving BGF MDI are more likely to adhere to the treatment without any ICE than those on BFF MDI or Symbicort pMDI.

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

Time to First ICE of initiation of new asthma therapy or prohibited medications thought to impact efficacy in conjunction with premature discontinuation from study intervention

Time to first ICE of this type will be analyzed in a manner similar to the analysis of time to first CID, but utilizing the Primary strategy for ICEs. Under this strategy, participants not having any ICE of interest (new asthma therapy or prohibited medications thought to impact efficacy in conjunction with premature discontinuation from study intervention) will be censored at their last recorded date of (any asthma status assessment in planned treatment period, last visit in planned treatment period).

This analysis answers the clinical question of whether participants receiving BGF MDI are more likely to adhere to the treatment without use of new asthma therapy or prohibited medications than those on BFF MDI or Symbicort pMDI.

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

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

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 will 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.

CCI will be analyzed in a manner similar to the analysis of rate of severe asthma exacerbations in the primary pooled analysis (Section 4.3.1.4).

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

4.2.9 Tertiary/Exploratory Endpoints: Symptoms and Other

4.2.9.1 Definition

Exploratory symptoms and other endpoints include the following:

- Change from baseline in the mean number of puffs of rescue medication use (puffs/day) over 24 weeks or over 12 to 24 weeks
- Percentage of rescue-free days (24-hour period without rescue medication use)
- Percentage of symptom-free days (24-hour period without symptoms)
- Percentage of participants with fractional exhaled nitric oxide (FeNO) less than 25 ppb, between 25 ppb and less than 50 ppb, and at least 50 ppb

4.2.9.2 Analysis of Exploratory Symptoms and Other Endpoints

Analyses of exploratory symptoms endpoints will be performed for the While on Treatment strategy for all ICEs in the Efficacy Set.

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

The mean daily number of puffs of rescue medication use will be calculated over 24 weeks, over 12 to 24 weeks and for each of the 4-week intervals during the 24-Week Treatment Period. For every period of time for which the mean number of puffs of rescue medication will be calculated, missing values will be ignored in both the numerator and denominator.

As such, the denominator will be adjusted based on the number of days (including half days) with non-missing values.

A repeated measures analysis of covariance model will be used to analyze change from baseline in average daily rescue albuterol/salbutamol use. The model will include treatment, the number of the relevant 4-week interval (interval 1 to 13), baseline severe asthma exacerbation history (0, 1, ≥2), prior ICS dose (medium vs. high), and the treatment-by-4-week interval interaction as categorical covariates and baseline daily rescue medication use, baseline trough FEV_1, and percent reversibility as continuous covariates.

An unstructured (UN) correlation matrix will be used to model the variance-covariance structure. If this model fails to converge, 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.

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.

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.

Percentage of Rescue-Free and Symptom-Free Days

A rescue-free or symptom-free day relates to a 24-hour period without rescue medication use or a 24-hour symptom-free period respectively, which consists of daytime + nighttime diary entries, where daytime is on the actual day recorded and nighttime is the night before (e.g., the morning and evening ePRO daily diary entries completed in the morning and evening in a 24-hour day).

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

Handling half days and missing half days for rescue-free days:

- Half days (due to days with only one of am/pm information recorded) are counted as whole days.
- If a subject is missing a whole days' worth of information (ie missing both AM and PM observations) then they will be ignored and not contribute to either the numerator or denominator.
- If a subject has missing record for half a day and they took rescue mediation in non-missing part of the day, the day contributes 0 to the numerator (not a rescue free day) and 1 to the denominator.
- If a subject has missing record for half a day and the observation was rescue free in non-missing part of the day, the day contributes 1 to both the numerator and the denominator.
- All middle intervals are 28 days (unless whole missing days).

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.

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

4.2.10 Healthcare Resource Utilization

4.2.10.1 Definition

Data on HCRU will be collected at baseline and all visits post-baseline and summarized by treatment group. The responses will be tabulated by assigned treatment and relationship to asthma and overall (asthma-related, not asthma-related, and combined).

The following variables will be calculated unadjusted (per participant) and also adjusted (per participant per year) and tabulated by treatment for those participants for whom they or one or more of their family members missed school/work:

- The number of days missed school/work
- The number of days that caregivers of participants missed from work as a result of the participant's asthma

The following variables will be tabulated by treatment. The percentage of participants, mean and mean per person-year will be calculated across all participants in a treatment.

- Ambulance Transport
- In ICU

- In CCU
- Hospitalizations
- ER Visits
- Visits to health care providers: visits to PCP, visits to specialist, visits to other healthcare provider
- Telephone calls to healthcare providers: calls to PCP, calls to specialist, calls to other healthcare provider

The number of days, mean number of days and mean number of days per person-year will be calculated across all participants in a treatment for hospitalizations, ICU and CCU. These variables will be tabulated by actual treatment received.

Analyses will be performed using the Efficacy Set.

4.2.10.2 Analysis of HCRU Endpoints

Analyses of HCRU endpoints will be performed for the While on Treatment strategy for all ICEs in 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.

Descriptive statistics (n, percentage, mean, SD, median, minimum, and maximum) will be provided by treatment and relationship to asthma and overall (asthma-related, not asthma-related, and combined).

Descriptive statistics (n, mean, SD, median, minimum, and maximum) will be provided by treatment for the number of days missed from school/work per year, the number of days that family members of participants missed from work per year overall during the study.

The percentage of participates will be presented by treatment for the following variables: telephone calls to healthcare providers, visits to health care providers, ER Visits, hospitalizations, in ICU, in CCU, used ambulance transport.

Also, descriptive statistics will be provided by treatment for the following variables: the number of telephone calls to health care providers, the number of visits to health care providers, the number of ER visits, the number of participant hospitalizations, the number of days in the hospital, the number of participant in the ICU, the number of days in the ICU, the number of participant in the CCU, the number of days in the CCU and the number of times ambulance transport was required.

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.

4.3 Endpoint Analyses for Pooled Studies

This section covers details related to the endpoint analyses for pooled studies such as primary, secondary, tertiary/exploratory endpoints and 12-hour PFT sub-study endpoints.

4.3.1 Primary Endpoint for Pooled Analyses: Rate of Severe Asthma Exacerbations

4.3.1.1 Definition

An Asthma exacerbation is defined as a worsening of asthma that requires medical intervention.

Worsening of asthma is defined as (at least 1 of the following 3 elements of worsening listed below must be fulfilled for at least 2 consecutive days):

- worsening of asthma signs/symptoms:
  - asthma symptoms (an increase of total asthma symptom score of at least 2 units above the run-in average or the highest possible score of 6)
  - night-time awakening due to asthma (an increase of 2 or more nights with awakenings due to asthma requiring rescue medication use over a 7-day period compared with the average run-in, and/or ≥6 out of the previous 7 nights with awakenings due to asthma requiring rescue medication)
  - physical exam finding consistent with the deterioration of asthma
- increased use of 'as-needed' rescue/reliever medication (an increase of ≥4 inhalations compared with baseline average use)
- deterioration of lung function (decrease in morning PEFR ≥20% as compared with baseline average)

Additionally, the investigator may identify certain events (recorded on the same CRF page) which don't entirely meet the criteria above as exacerbations; the justifications supporting the investigator's judgment will be recorded on the same eCRF page.

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

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

- A temporary course of systemic corticosteroids for at least 3 consecutive days to treat symptoms of asthma worsening (a single depo-injectable dose of corticosteroids will be considered equivalent to a 3-day of oral corticosteroids)
- An ER or urgent care visit (defined as evaluation and treatment for <24 hours in an emergency department or urgent care centre) due to asthma that required treatment with systemic corticosteroids (as per the above)
- An in-patient hospitalization (defined as admission to an in-patient facility and/or evaluation and treatment in a healthcare facility for ≥24 hours) due to asthma

- Death related to asthma

All moderate or severe asthma exacerbations following Visit 1 will be entered in the eCRF by the investigators.

All ER visit/urgent care visit/hospitalization/death will be adjudicated by the IA Committee. When there is discrepancy between IA committee and investigator, the decision by IA committee will prevail in the analysis. Specifically, if the severe exacerbations entered in eCRF associated with ER visit/urgent care visit/hospitalization/death that are adjudicated not to be asthma related, they will not be counted as severe asthma exacerbation in the analysis. If there are ER visit/urgent care visit/hospitalization/death that are adjudicated to be asthma related but not entered in eCRF as severe asthma exacerbations, they will be counted as severe asthma exacerbations in the analysis.

Asthma exacerbations not meeting the criteria for moderate or severe asthma exacerbations will be considered mild asthma exacerbations.

4.3.1.2 Derivations

Onset and Duration of Asthma Exacerbation

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

For severe asthma exacerbations:

- The start date will be defined as the start date of prescribed treatment with a systemic corticosteroid, the hospital/ER admission date, or the date of death (if the exacerbation resulted in death), whichever is earlier.
  - Note: The start date could be the start date of an additional ICS when treatment is switched to at least 3 days of systemic corticosteroids.
- The stop date will be defined as the stop date of prescribed treatment with systemic corticosteroids, or date of emergency visit requiring systemic corticosteroids, or date of hospital/ER discharge due to asthma, 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, or emergency visit date will be used as start/stop dates.

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.

The start and end dates of asthma exacerbations 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 period between ICS or systemic corticosteroid treatments, then separate exacerbations should be recorded in the eCRF.

4.3.1.3 Handling of Dropouts and Missing Data

For any moderate or 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.

4.3.1.4 Primary Analysis of Primary Endpoint for Pooled Analyses

The rate of severe asthma exacerbations will be analyzed using negative binomial regression model as implemented in SAS PROC GENMOD. Treatments will be compared adjusting for baseline trough FEV_1, percent reversibility, baseline severe asthma exacerbation history (0, 1, ≥2), prior ICS dose (medium vs. high), region (as defined in Section 4.1.1.1) and study. The logarithm of time at risk of experiencing a severe exacerbation will be used as an offset variable in the model.

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, prior ICS dose, percent reversibility, baseline trough FEV_1, baseline severe asthma exacerbation history, and study.

Analyses will be conducted in the Efficacy Analysis Set utilizing the Primary strategy for handling ICEs as per Section 3.3.5.1. The While on Treatment strategy for all ICEs will be utilized as a supportive strategy. 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.

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 the 7 days after the exacerbation) 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 While on Treatment and Principal Stratum 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.

For the Primary strategy for handling ICEs, the follow-up time is defined as the total of observed follow up time and imputed follow up time as follows:

- For participants without an ICE of new asthma therapy or use of prohibited medications thought to impact efficacy in conjunction with premature discontinuation from study intervention: the time from first dose of randomized IP up to the last recorded date of (any asthma status assessment in planned treatment period, last visit in planned treatment period) for the participant.

- For participants with such an ICE: time from first dose of randomized IP until planned last visit date during treatment period (see Section 3.3.4). This includes observed data up to the day of ICE (start date of new medication) +1 day and imputed time at risk data from day of ICE +2 days to planned last visit date in treatment period.

The number of exacerbations, the percentage of participants who experience exacerbations, exacerbation rates, the dispersion parameter, and rate ratios comparing treatments will be summarized for severe exacerbations. The time at risk for severe asthma exacerbations will also be summarized for each estimand. Similar analysis will be produced for moderate or severe asthma exacerbations.

An additive-model plot of the rate of severe asthma exacerbations versus baseline eosinophil count will also be provided for each estimand strategy. This analysis will use a generalized additive model (GAM) having a nonparametric regression for the relationship of baseline eosinophil levels to the exacerbation rate with a negative binomial model. Baseline eosinophil count can be log-transformed for this analysis. The graph will plot the predicted yearly “Rate of Severe Asthma Exacerbations (events/year)” and its 95% credibility intervals on the vertical axis.

4.3.1.5 Sensitivity Analyses of the Primary Endpoint for Pooled Analyses

Robustness of results to missing data under the Primary strategy for handling ICEs will be explored using tipping point analyses (Ratitch 2013). Those analyses will be performed only if a statistically significant effect was observed for the primary analysis of rate of severe asthma exacerbations for the CCI and CCI approaches respectively (as per Section 4.3.1.4). The number of asthma exacerbations since study withdrawal and until the last planned study day will be imputed. Those imputations for the sensitivity analysis will not be performed for participants who have had an ICE of new asthma therapy or use of prohibited medications thought to impact efficacy with severe exacerbation imputation under the Primary strategy for handling ICEs. Event rates will be gradually adjusted in the treatment arm (increased by a factor of δ_1) and in the comparator arm (decreased by a factor of δ_2). Rates in the other arms will not be adjusted. δ_1 is varied from 1 (no adjustment) up to 1.5 (worsening of exacerbation rate in the treatment arm by 50%) and δ_2 is varied from 1 (no adjustment) to $\frac{1}{1.5} = 0.67$ (improvement of exacerbation rate in the control arm by up to 33%) as per the grid in Section 9.2.4.3 or until the p-value for the comparison is no longer significant per MTP. The tipping point will be shown to a precision of at least 0.02 exacerbations/year. For details of this method, refer to Section 9.2.

4.3.1.6 Subgroup Analyses of the Primary Endpoint for Pooled Analyses

The same subgroup analyses described in Section 4.2.1.7 will be performed for the pooled analysis of rate of severe asthma exacerbations. Note that the subgroup analysis for rate of severe asthma exacerbation in participants with baseline percent predicted FEV_1 less or equal to 55% as well as participants with ≥1 severe exacerbation in the 12 months prior to Visit 1 will also be analyzed as a secondary endpoint for the pooled analyses as specified in Section 4.3.2.2.

4.3.2 Secondary Endpoints for Pooled Analyses: Asthma Exacerbations

4.3.2.1 Definition

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

4.3.2.2 Primary Analysis of Secondary Endpoints for Pooled Analyses

Rate of Severe Asthma Exacerbation for certain subgroups

Rate of Severe Asthma Exacerbation will be tested for the subgroup of participants with baseline percent predicted FEV_1 less or equal to 55% as well as in the subgroup of participants with ≥1 severe exacerbation in the 12 months prior to Visit 1. The analyses are similar to the analysis of the rate of severe asthma exacerbations in the primary pooled

analysis as in Section 4.2.1.4 utilizing the Primary strategy for handling ICEs and While on Treatment strategy for all ICEs as supportive (see Section 3.3.5.1).

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

Time to first severe asthma exacerbation will be analyzed up to the Week 52 visit with a Cox regression model to compare the treatment groups, adjusted for baseline severe asthma exacerbation history (0, 1, ≥2), prior ICS dose (medium vs. high), region (as defined in Section 4.1.1.1), study, baseline trough FEV_1, and percent reversibility. The Primary strategy for handling ICEs will be utilized (see Section 3.3.5.1) and the While on Treatment strategy for all ICEs will be used as supportive.

Where the Primary strategy for handling ICEs applies, participants that experience no severe asthma exacerbation and no ICE of new asthma therapy or prohibited medication use thought to impact efficacy in conjunction with discontinuation from study intervention will be censored at the latest date of (asthma status assessment, last visit in planned treatment period). For participants experiencing such an ICE, the time to first actual or imputed exacerbation will be utilized.

For the While on Treatment ICE strategy, participants experiencing 1 or more ICEs without any exacerbation of respective severity will be censored on the date of their first ICE + 1 day. Participants who do not experience a severe asthma exacerbation or ICE will be censored at the date of last dose +1 day for the participant.

Estimated adjusted hazard ratios relative to the comparator will be displayed along with the associated Wald two-sided 95% confidence interval (CI) and p-values for all treatment comparisons.

Time to first moderate or severe asthma exacerbation will be displayed graphically for each treatment group using a Kaplan-Meier curve.

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

Rate of Moderate or Severe Asthma Exacerbations

Rate of moderate or severe asthma exacerbations will be analyzed in a manner similar to the analysis of the rate of severe asthma exacerbations in the primary pooled analysis as in Section 4.3.1.4.

4.3.3 Secondary Endpoints for Pooled Analyses: PROs

4.3.3.1 Definition

Responder analyses will be performed for ACQ-7, ACQ-5 and AQLQ(s) +12 at Week 24, over 24 weeks, and over 12 to 24 weeks utilizing the Primary strategy for handling ICEs as well as the supportive Composite strategy (see Section 3.3.5.1 and 3.3.5.3). Analysis is in the Efficacy Set. Responders are defined in Section 4.2.3.3.

4.3.3.2 Primary Analysis of Secondary Endpoints for Pooled Analyses

Percentage of responders will be analyzed similar as percentage of responders in ACQ-7 specified in Section 4.2.3.3. Note: an extra term for the study effect will be included in the logistic regression model.

4.3.4 Non-Inferiority Test Endpoints for Pooled Studies (CCI Only)

CCI [redacted], NI tests of BFF MDI vs Symbicort pMDI will be conducted for pooled data from KALOS and LOGOS studies. For the NI hypothesis testing, refer to Section 3.3.2.4. For MTP, refer to Section 3.3.8.5. 95% two-sided CIs and one-sided p-values will be reported for NI analysis.

4.3.4.1 Definition

The primary endpoint for NI tests from pooled studies is rate of severe asthma exacerbations. Other endpoints for NI tests from pooled studies include: Time to first severe asthma exacerbation; Rate of moderate/severe asthma; Time to first moderate/severe asthma exacerbation.

4.3.4.2 Derivations

For the derivation of NI test endpoints, refer to Section 4.3.1.2.

4.3.4.3 Analysis of NI Primary Endpoints

The primary analysis of NI primary endpoints will be performed for the Principal Stratum estimand with the PP Analysis Set. Supportive analyses of NI primary endpoints will be performed for the Primary strategy as well as the While on Treatment strategy for all ICEs. The analysis model is same as model specified in Section 4.3.1.4.

4.3.4.4 NI Analysis of Other Endpoints

The NI analysis of other endpoints will be performed for the Principal Stratum estimand with the PP Analysis Set. The analysis models are same as models specified in Section 4.3.2.2.

4.3.5 Tertiary/Exploratory Endpoints

Unless specified otherwise, analysis of Tertiary/Exploratory endpoints using the pooled data will be conducted only using the While on Treatment estimand strategy for all ICEs.

4.3.5.1 Definition

Time to First Hospitalization for Asthma Exacerbation is the time from the first dose of randomized study medication to the date of admission of the first hospitalization due to asthma exacerbation. Participants experiencing 1 or more ICEs will be censored on the day of their first ICE + 1 day. Participants who do not experience an event or ICE will be censored on the participant's date of last dose +1 day.

Rate of hospitalization for Severe Asthma Exacerbation is defined as (the number of hospital admissions due to asthma exacerbation) * 365.25 / (time of exposure), where time of exposure is the number of days from the first dose of randomized study medication 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, minus the number of days in hospital (the date of admission is excluded from deduction).

Rate of Severe Asthma Exacerbation Resulting in a Temporary Course of Systemic Corticosteroids for At Least 3 Consecutive Days is defined as (the number of severe asthma exacerbations treated with short course of systemic corticosteroids) * 365.25 / (time of exposure), where time of exposure is the number of days from the first dose of randomized study medication to participant's date of last dose +1 day for participants without an ICE or the date of the first ICE + 1 day, minus the number of days treated with a temporary course(s) of systemic corticosteroids (the first date of each temporary course(s) of systemic corticosteroids is excluded from deduction).

A single depo-injectable dose of corticosteroids will be considered equivalent to a 3-day of oral corticosteroids.

4.3.5.2 Primary Analysis of Tertiary/Exploratory Endpoints

Time to First Hospitalization for Severe Asthma Exacerbation

Time to first hospitalization for severe asthma exacerbation will be analyzed in a manner similar to the analysis of time to first severe asthma exacerbation in the secondary pooled analysis (Section 4.3.2.2) utilizing the While on Treatment strategy for all ICEs.

Rate of Hospitalizations for Severe Asthma Exacerbations and Rate of Severe Asthma Exacerbation Resulting in a Temporary Course of Systemic Corticosteroids for At Least 3 Consecutive Days

Rate of hospitalization for severe asthma exacerbations will be analyzed in a manner similar to the analysis of the rate of severe asthma exacerbations in the primary pooled analysis (Section 4.3.1.4) utilizing the While on Treatment strategy for all ICEs.

Time to First CID

Time to first CID will be analyzed in a manner similar to the analysis of time to first severe asthma exacerbation in the secondary pooled analysis utilizing the While on Treatment strategy for handling ICEs, where CID event can occur from first dose of randomized IP up to date of last dose +1 day.

For this strategy, participants who experience an ICE without any prior CID will be censored at the time of the ICE + 1 day. Participants not having any CID or any ICE will be censored at the participants' date of last dose +1 day.

CCI

There will be two analyses for CCI The first analysis will include only data up to and including Visit 8 (Week 12). Participants who did not have an event or ICE by then will be censored at the minimum of (their Week 12 Visit date +1 day, date of last dose +1 day) or on the date of ICE + 1 day if an ICE occurs before the Week 12 Visit.

The second analysis will include all observed data with censoring at the participant's date of last dose +1 day, if the participant does not experience an event or ICE. Participants who experience an ICE without any CCI event will be censored at the date of the ICE + 1 day.

Both analyses will be analyzed in a manner similar to the analysis of time to first severe asthma exacerbation in the secondary pooled analysis utilizing the While on Treatment strategy for all ICEs.

CCI

CCI events will be analyzed in a manner similar to the analysis of rate of severe asthma exacerbations in the primary pooled analysis utilizing the While on Treatment strategy for all ICEs.

Time to First ICE

Time to first ICE will be analyzed in a manner similar to the analysis of time to first severe asthma exacerbation in the secondary pooled analysis utilizing the While on Treatment strategy for all ICEs. Participants not having any ICE will be censored at their last dosing date.

Time to First ICE of initiation of new asthma therapy or prohibited medications thought to impact efficacy in conjunction with discontinuation from study intervention

Time to first such ICE will be analyzed in a manner similar to the analysis of time to first severe asthma exacerbation in the secondary pooled analysis utilizing the Primary strategy for ICEs. Participants not having the ICE of interest (new asthma therapy or prohibited medications thought to impact efficacy in conjunction with discontinuation from study intervention) will be censored at their last recorded date of (any asthma status assessment in planned treatment period, last visit in planned treatment period).

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

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

Total Number of Days on Systemic Corticosteroids to Treat Asthma Exacerbations

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

Rate of Severe Asthma Exacerbations Treated with Systemic Corticosteroids Only

Rate of severe asthma exacerbations treated solely with systemic corticosteroids will be analyzed in a manner similar to the analysis of the rate of severe asthma exacerbations in the primary pooled analysis utilizing the While on Treatment strategy for all ICEs.

Rate of Asthma Deteriorations Treated with ICS and/or Antibiotics

Asthma deterioration refers to worsening of asthma as specified in Section 4.3.1.1. Programmatically, the following logic can be utilized as a simpler reference for analysis. Any recorded moderate or severe exacerbation is a deterioration. The duration and time of deterioration will be the same as the corresponding exacerbation. If not labelled a moderate or severe exacerbation, any medication of type: Inhaled corticosteroids, ICS/LABA, ICS/LAMA/LABA, ICS/SABA, or Antibiotics, taken for the reason of asthma worsening will be counted as a deterioration. For this type, the medication duration is taken to be the duration of deterioration, with analogous start date as well. If end date is missing, a 5-day deterioration is assumed. For both types of deterioration, if there is less than 7 days between any of those medications for the same patient, it will be assumed that this is the same deterioration event.

Rate of asthma deteriorations treated with ICS and/or antibiotics will be analyzed in a manner similar to the analysis of the rate of severe asthma exacerbations in the primary pooled analysis utilizing the While on Treatment strategy for all ICEs.

Rate of Asthma Deteriorations Treated with Antibiotics

Rate of asthma deteriorations treated with antibiotics will be analyzed in a manner similar to the analysis of the rate of severe asthma exacerbations in the primary pooled analysis utilizing the While on Treatment strategy for all ICEs.

Time to First Severe Asthma Exacerbation Treated with Systemic Corticosteroids Only

Time to first severe asthma exacerbation treated solely with systemic corticosteroids will be analyzed in a manner similar to the analysis of time to first severe asthma exacerbation in the secondary pooled analysis utilizing the While on Treatment strategy for all ICEs.

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

Time to first asthma deterioration treated with ICS and/or antibiotics will be analyzed in a manner similar to the analysis of time to first severe asthma exacerbation in the secondary pooled analysis utilizing the While on Treatment strategy for all ICEs.

Time to First Asthma Deterioration Treated with Antibiotics

Time to first asthma deterioration treated with antibiotics will be analyzed in a manner similar to the analysis of time to first severe asthma exacerbation in the secondary pooled analysis utilizing the While on Treatment strategy for all ICEs.

4.3.6 12-Hour PFT Sub-Study Endpoints

Serial PFTs will be conducted over 12-hours in a subset of participants at Visit 5 (Day 1) and Visit 8 (Week 12). Data from the 2 studies will be combined for the 12-hour PFT sub-study analyses.

4.3.6.1 Derivations

FEV_1 $AUC_{0\text{-}12}$ will be calculated for the change from baseline using the trapezoidal rule and will be normalized into a time weighted average by dividing the time (in hours) from dosing to the last measurement occurring within 13.5 hours post-dose, i.e., the upper limit of the “post-dose 12 hours” analysis defined time window (the last measurement is expected to typically be at 12 hours post-dose). For all estimands, only one non-missing post-dose value is required for the calculation of AUC. Actual time from dosing will be used if available; otherwise, scheduled time will be used.

AUC_{0-12} for FVC, PEFR, and FEF_{27-75} will be calculated similarly using change from baseline in FVC, PEFR, and FEF_{25-75}, respectively.

FEV_1 AUC_{0-6} will be calculated using the trapezoidal rule and will be normalized into a time weighted average by dividing by the time in hours from dosing up to the last measurement within the 6-hour post-dose time window. **FEV_1 AUC_{6-12}** will be calculated using the trapezoidal rule and will be transformed into a time weighted average by dividing the time in hours between the first measurement within the 6-hour post-dose time window and the last available measurement within the 12-hour post-dose window (typically 12-hour post-dose). For both calculations, 1) at least one non-missing value is required; 2) actual time from dosing will be used if available; otherwise, scheduled time will be used.

Peak FEV_1 is defined as the maximum post-dose FEV_1.

4.3.6.2 Primary Analysis of the 12-Hour PFT Sub-Study Endpoints

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

The differences between treatment groups in change from baseline in FEV_1 AUC_{0-12} at Day 1 and Week 12 will be evaluated using a repeated measures analysis of covariance model with baseline trough FEV_1 and percent reversibility as continuous covariates and study, treatment, visit, treatment by visit interaction, and prior ICS dose (medium vs. high) as categorical covariates and an unstructured covariance. Two-sided p-values and point estimates with two-sided 95% CIs will be produced for each treatment difference. The PFT sub-study set will be used for the analyses utilizing the Primary strategy for handling ICEs and the While on Treatment strategy as a supportive approach (see Section 3.3.5.1).

Change from Baseline in FEV_1 at each timepoint at Day 1 and Week 12

Considering only the While on Treatment strategy for all ICEs, the differences between treatment groups in change from baseline in FEV_1 at post-dose timepoints at Day 1 and at Week 12 will be evaluated using a repeated measures analysis of covariance model with baseline trough FEV_1 and percent reversibility as continuous covariates and study, treatment, post-dose time point, treatment by post-dose time point interaction, prior ICS dose (medium vs. high) as categorical covariates and an unstructured covariance. Two-sided p-values and point estimates with two-sided 95% CIs will be produced for each treatment difference.

LS Mean change from baseline in post-dose FEV_1 will be plotted by time point. The same analysis will be implemented for change from baseline in FEV1 at Day 1.

FEV_1 AUC_{0-6}, FEV_1 AUC_{6-12}, and peak FEV_1

Results will be presented using the While on Treatment strategy for all ICEs.

The differences between treatment groups in FEV_1 AUC_{0-6}, FEV_1 AUC_{6-12}, and peak FEV_1 at Week 12 will be evaluated using a repeated measures analysis of covariance model with baseline trough FEV_1 and percent reversibility as continuous covariates and study, treatment, visit, treatment by visit interaction, prior ICS dose (medium vs. high) as categorical covariates and an unstructured covariance. Two-sided p-values and point estimates with two-sided 95% CIs will be produced for each treatment difference.

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

Considering only the While on Treatment strategy for all ICEs, the differences between treatment groups in FVC AUC_{0-12} at Week 12 will be evaluated using a repeated measures analysis of covariance model with baseline FVC, baseline trough FEV_1, and percent reversibility as continuous covariates and study, treatment, visit, treatment by visit interaction, prior ICS dose (medium vs. high) as categorical covariates and an unstructured covariance. Two-sided p-values and point estimates with two-sided 95% CIs will be produced for each treatment difference. The same analysis will be repeated for PEFR AUC_{0-12} and FEF_{25-75} AUC_{0-12} with the baseline covariate for the respective variable to be used instead of baseline FVC.

Weekly 5-Item OEQ

The weekly 5-item OEQ will be completed at home on the eDiary weekly at Weeks 1, 2, 3, 4, and 12 after randomization. For each item of the weekly 5-item OEQ at home, the percentage of perceivers (participants responding, “strongly agree” or “somewhat agree”) and percentage of non-perceivers (participants responding, “neither agree nor disagree,” “somewhat disagree,” or “strongly disagree”) will be summarized for each treatment arm. Pearson chi-square test will be used to compare among pairs of treatment groups. The summary and comparison will be for the While on Treatment strategy for all ICEs only and for each Week 1, 2, 3, 4, and 12. Missing responses to OEQ items will be reported in the summaries and ignored for the chi-square tests.

One Item OEQ in Clinic

One item OEQ will be administered during site Visit 5 and Visit 8 at the scheduled time points (2, 5, 15, 30, 60 min post-dose). For the one item OEQ in the clinic, participants will be asked if they can feel the study medication working after administration.

The percentage of perceivers (participants responding ‘yes’) and percentage of non-perceivers (participants responding ‘no’) will be summarized for each treatment arm. Pearson chi-square test will be used to compare among pairs of treatment groups. The summary and comparison will be for the While on Treatment strategy for all ICEs only and

for Visit 5 and Visit 8 and at each of scheduled time points. Missing responses to the repeat OEQ items will be reported in the summaries and ignored for the chi-square tests.

Considering only the While on Treatment strategy for all ICEs, time to first occurrence that participant feels the medication is working will be analyzed with a Cox regression model to compare the treatment groups, adjusted for severe asthma exacerbation history, prior ICS dose (medium vs. high), study, region, baseline trough FEV_1, and percent reversibility.

The time to event for this endpoint will be counted since the morning dose on Day 1, and in a separate analysis, since the morning dose on Week 12. If the dose was not administered or the participant discontinued treatment, the participant will be excluded from the analysis. Intermittently missing OEQ responses will be treated as 'no' for the purpose of time to event determination. Participants who did not respond 'yes' at any time point during the visit will be censored at minimum of (Week 12 visit, date of last dose +1 day).

4.3.7 Integrated Pooled Analyses for Summary of Clinical Efficacy

4.3.7.1 Study Population

All outputs described in this section will be delivered together with the pooled analysis for the individual study CSRs.

4.3.7.1.1 Subject Disposition and Completion Status

4.3.7.1.1.1 Definitions and Derivations

For details, refer to Section 4.1.1.1 Definitions and Derivations.

4.3.7.1.1.2 Presentation

Disposition tables will be provided for all participants and by age subgroup (adults and adolescents). Discontinued participants and participants completing the study will also be listed. Numbers of participants randomized will be summarized by region, country, site, and treatment.

4.3.7.1.2 Demographic, Disease Characteristics, and Baseline Characteristics

Demographic, disease characteristics, and baseline characteristics will be presented in the pooled analysis of both studies.

Demographic variables summarized will include the following:

- Age (years)
- Age (years) group (>=12 to <18, >=18 with subcategories >=18 to <65 and >=65)
- Sex (female, male)
- Race (Black or African American, Native Hawaiian or Other Pacific Islander, American Indian or Alaska Native, Asian, White, Other, Not reported)
- Ethnic group (Hispanic or Latino, Non-Hispanic or Latino)

- Country
- Region (US & Canada, Asia, Europe, Mexico & Central America & South America, Australia & New Zealand & South Africa)

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 x 100 (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 only, i.e. they did not meet the 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, ≥2) 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 to < 450, >=450)
- Baseline pre-bronchodilator percent predicted FEV_1 (%)
- Average of Pre-bronchodilator FEV_1 (L) at Visit 4 and Visit 5
- Baseline ACQ-5 score
- Baseline ACQ-7 score
- Prior ICS dose (Low, Medium, High)
- Smoking status (former smoker, non-smoker)

- Number of Pack Years Smoked
- PEFR stability limit at Visit 5 (L/min)
- FeNO at Visit 1 (ppb)
- FeNO at Visit 1 (<25 ppb, >=25 and <50 ppb, >=50 ppb)
- FeNO at Visit 5 (ppb)
- FeNO at Visit 5 (<25 ppb, >=25 and <50 ppb, >=50 ppb)

Baseline characteristic variables summarized will include the following:

- Height (cm)
- Weight (kg)
- BMI (kg/m^2)
- BMI categories (kg/m^2) (<18.5, >=18.5 to <25, >=25 to <30 and >=30)

4.3.7.1.2.1 Definitions and Derivations

For details, refer to Section 4.1.4.1, Section 4.1.5.1, and Section 4.1.8.1.

4.3.7.1.2.2 Presentation

Demographic, disease characteristics, and baseline characteristics will be summarized for the Efficacy Analysis Set.

Baseline and disease characteristics will be tabulated for randomized adults (>=18) and adolescents (>=12 to <18) separately.

4.3.7.1.3 Medical and Surgical History

General medical history will not be summarized in the integrated analysis. However, medical and surgical history variables related to asthma will be included. They are:

- 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 (0, 1, >=2)
- Allergies (None, Respiratory allergies, Non-respiratory allergies, Respiratory and non-respiratory allergies)
- Nasal polyps (Yes, No)

4.3.7.1.3.1 Definitions and Derivations

For details, refer to Section 4.1.6.1.

4.3.7.1.3.2 Presentation

Asthma characteristics at study entry will be summarized for the Efficacy Analysis Set.

4.3.7.1.4 Prior, Concomitant, and Post-Treatment Medications

4.3.7.1.4.1 Definitions and Derivations

For details, refer to Section 4.1.7.1.

4.3.7.1.4.2 Presentation

Disallowed concomitant medication will be tabulated by treatment group, ATC classification, and generic drug name for the Efficacy Analysis Set.

4.3.7.2 Endpoint Analyses

Endpoints are summarized below, as well as timing, ICE strategy, and treatment comparisons of interest. All objectives in this section are supportive. These endpoints will be presented only in High Level Documents, not in the Clinical Study Report.

4.3.7.2.1 Change from Baseline in FEV_1 AUC_{0-3} and Change from Baseline in Morning Pre-Dose Trough FEV_1

4.3.7.2.1.1 Definition

For details, refer to Section 4.2.1.1.

4.3.7.2.1.2 Derivations

For details of derivations, refer to Section 4.2.1.2.

4.3.7.2.1.3 Handling of Dropouts and Missing Data

Dropouts and missing data will be handled the same way as mentioned in Section 4.2.1.3.

4.3.7.2.1.4 Pooled KALOS and LOGOS Analysis of Change from Baseline in FEV_1 AUC_{0-3} and Change from Baseline in Morning Pre-Dose Trough FEV_1

The endpoints change from baseline in FEV_1 AUC_{0-3} and change from baseline in morning pre-dose trough FEV_1 will be analyzed using combined KALOS and LOGOS participant level data, using the Primary strategy for handling ICEs.

The Efficacy Analysis Set will be used for these analyses and only participants with baseline and at least one post randomization measurement will be included.

Change from Baseline in FEV_1 AUC_{0-3}

Change from baseline in FEV_1 AUC_{0-3} will be analyzed using a repeated measures analysis of covariance model. The model will include study, treatment, visit, treatment-by-visit interaction, and prior ICS dose (medium vs. high) as categorical covariates and baseline trough FEV_1 and percent reversibility (as defined in Section 4.1.5.1) as continuous covariates.

An unstructured correlation covariance matrix (UN) 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 (UN) -> Heterogeneous Toeplitz (TOEPH) -> Toeplitz (TOEP) -> Compound Symmetry (CS).

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 be used for tests of fixed effects derived from this model.

Contrasts will be used to obtain estimates of the treatment differences at Week 24/over 12-24 weeks/over 24 weeks. Two-sided p-values and point estimates with 95% CI will be generated for each treatment difference.

Change from Baseline in Morning Pre-dose Trough FEV_1

Change from baseline in morning pre-dose trough FEV_1 will be analyzed using a repeated measures analysis of covariance model. The model will be similar to the one used for FEV_1 AUC_{0-3}.

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

4.3.7.2.1.5 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 for both FEV endpoints in the previous section (Best et al 2021).

Difference in mean change from baseline is the population summary measure of interest, which can be approximated by a normal distribution. A Robust Mixture Prior approach is used, first specifying the initial proportion of borrowing w from 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 with mean of null effect (e.g. mean of 0) and large variance but still proper, as the method requires proper distributions. The initial weight w is put on the informative element and $(1 - w)$ is placed on the uninformative element. This weight w is updated during posterior calculation depending on the degree to which the observed adolescent mean difference agrees with the adult mean difference.

The analysis process follows these steps:

1. Standard frequentist regression is fit to the adult data to obtain normal approximation for the adult mean difference (mean and variance). This regression is repeated for the adolescent data.

2. The normal approximation obtained in the previous step for adults 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 mean difference 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 mean difference in adolescents is calculated by assuming an approximate normal likelihood $L(\theta|Y_{adol})$ for the mean difference in adolescents obtained from step 1. This likelihood is combined with the robust mixture prior using the following conjugate model results to obtain the posterior mixture distribution for mean difference in adolescents. Assume the informative prior π_1 has mean m_1 and variance v_1, denoted as $N(m_1, v_1)$ and the vague prior π_2 is $N(m_2, v_2)$. Denote the normal approximation 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:

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

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

Four mean differences are of interest: both dosages of BGF MDI vs. BFF and both dosages of BGF MDI vs. Symbicort. This posterior calculation is done for each treatment comparison, where the data and parameter estimates are comparison specific. The standard frequentist regression referenced above is the MMRM model specified in Section 3.2.1.4. The data from adults and adolescents are subset and two separate MMRM models are fit. Estimated means and variances of mean differences from these regressions are used to

create posteriors for each population. For a given posterior, the treatments are considered significantly different in effect if the 95% credible interval does not contain zero, and treatment effect is concluded to be in the direction of the interval.

The initial weight proposed is $w = 0.25$, which would correspond to approximately 80% of the prior Effective Sample Size (ELIR method, Neuenschwander et al. 2020) in the adolescent posterior being borrowed from the adult population given the assumed treatment effects in each group are the same and true to the Protocol (based on simulation), for both endpoints.

4.3.7.2.2 Onset of Action Day 1

4.3.7.2.2.1 Definition

For details, refer to Section 4.2.4.1.

4.3.7.2.2.2 Derivations

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

4.3.7.2.2.3 Analysis of Onset of Action on Day 1

Descriptive statistics will be displayed by treatment group. The analysis to be performed will be the same as in individual studies. A within-group T-test to demonstrate that the mean change from baseline in FEV1 at 5 minutes post-dose on Day 1 is statistically greater than 100 mL will also be provided with corresponding one-sided p-value and two-sided 95% CIs. The analysis will be performed using the Efficacy Analysis Set. Since this endpoint is defined at 5 minutes post-dose on Day 1, the data selection will be the same for the two ICE handling approaches.

4.3.7.2.3 Severe Asthma Exacerbations

4.3.7.2.3.1 Definition

For details on the definition of Rate of Severe Asthma Exacerbation, refer to Section 4.3.1.1.

4.3.7.2.3.2 Derivations

For the derivation of the onset and duration of asthma exacerbation, refer to Section 4.3.1.2.

4.3.7.2.3.3 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 for Severe Asthma Exacerbations (Best et al 2021).

Rate ratio is the population summary measure of interest, and the log of rate ratio can be approximated by a normal distribution, using a Robust Mixture Prior approach. The analysis process follows the same steps as described in Section 4.3.7.2.1.5. The standard frequentist regression referenced is the negative binomial regression specified in Section

4.3.1.4. The data from adults and adolescents are subset and two separate negative binomial regressions are fit. Estimated means and variances of log rate ratios from these regressions are used to create posteriors for each population. For a given posterior, the treatments are considered significantly different in effect if the 95% credible interval does not contain zero (1 if on rate ratio scale), and treatment effect is concluded to be in the direction of the interval.

The initial weight proposed is $w = 0.25$, which would also correspond to approximately 80% of the prior Effective Sample Size (ELIR method, Neuenschwander et al. 2020) in the adolescent posterior being borrowed from the adult population given the assumed treatment effects in each group are the same and true to the Protocol (based on simulation).

4.3.7.2.4 Subgroup Analyses for Efficacy

The subgroup analyses utilizing the Primary strategy for handling ICEs will be performed for the following factor:

- Age (years) with the following categories:
  - >=12 and <18
  - >=18 and <65
  - >=65

Analytical Approach

Change from Baseline in FEV_1 AUC_{0-3} and Change from Baseline in Morning Pre-dose Trough FEV_1

To investigate the interaction effect between subgroup and treatment, a similar model to the overall analysis 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 CCI over 24 Weeks CCI, and over 12-24 Weeks CCI 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 CCI, over 24 Weeks CCI and over 12-24 Weeks CCI within each subgroup category. Point estimates with two-sided P-value and 95% CI will be produced for each treatment difference.

A Heterogeneous Toeplitz (TOEPH) correlation matrix will be used to model the variance-covariance structure for subgroup analysis. If this model fails to converge, the following hierarchical approach is proposed to select a simpler covariance structure if the preceding

covariance structure fails to converge: Heterogeneous Toeplitz -> Toeplitz -> Compound Symmetry. 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.

If a treatment group within a subgroup category has less than 10 participants, then model estimates will not be presented for that treatment group of the subgroup category.

Onset of Action on Day 1

To investigate the interaction effect between the subgroup and treatment for the onset of action on Day 1, an ANOVA model will be fitted within each treatment group (combined subgroup categories), and the subgroup will be included as a factor.

Estimated mean change from baseline in FEV_1 at 5 minutes post-dose, its 95% CI, and a two-sided p-value for the subgroup effect will be reported within each treatment group and subgroup variable.

If a treatment group within a subgroup category has less than 10 participants, then model estimates will not be presented for that treatment group of the subgroup category.

Graphical Approach

Model estimates will be used to represent treatment effect in the plots described below. Separate plots will be prepared for each comparison of interest:

- BGF MDI 320/28.8/9.6 µg vs BFF MDI 320/9.6 µg
- BGF MDI 320/14.4/9.6 µg vs BFF MDI 320/9.6 µg
- BGF MDI 320/28.8/9.6 µg vs Symbicort pMDI 320/9 µg
- BGF MDI 320/14.4/9.6 µg vs Symbicort pMDI 320/9 µg
- BGF MDI 320/28.8/9.6 µg vs Pooled BFF MDI and Symbicort pMDI Control Groups
- BGF MDI 320/14.4/9.6 µg vs Pooled BFF MDI and Symbicort pMDI Control Groups

For within-group comparison on onset of action, treatment effect will be represented by each dose of BGF MDI and two comparator arms (BFF MDI and Symbicort pMDI).

Forest plots will be provided for the following endpoints and estimands:

- Change from baseline in FEV_1 AUC_{0-3} at Week 24, Primary strategy for handling ICEs

- Change from baseline in FEV_1 AUC_{0-3} over 24 weeks, Primary strategy for handling ICEs
- Change from baseline in FEV_1 AUC_{0-3} over 24 weeks, Primary strategy for handling ICEs CCI approach)
- Change from baseline in FEV_1 AUC_{0-3} over 12-24 weeks, Primary strategy for handling ICEs
- Change from baseline in morning pre-dose trough FEV_1 at Week 24, Primary strategy for handling ICEs
- Change from baseline in morning pre-dose trough FEV_1 over 24 weeks, Primary strategy for handling ICEs
- Change from baseline in morning pre-dose trough FEV_1 over 24 weeks, Primary strategy for handling ICEs CCI approach)
- Change from baseline in morning pre-dose trough FEV_1 over 12-24 weeks, Primary strategy for handling ICEs

Additionally, forest plots will be provided for Onset of Action.

Forest plots will be used to display the point estimates of the treatment effect for each pre-specified subgroup, along with corresponding confidence intervals, as well as the overall result from the primary analysis.

Horizontal line segments will represent the confidence intervals, and a vertical line will be drawn at 1 if the treatment effect is a rate ratio, hazard ratio, or odds ratio and at 0 if it is a mean difference. The direction of the treatment effect will be annotated to indicate whether it favours BGF MDI or the control treatment.

4.3.7.2.5 Non-Inferiority Test Analyses CCI approach Only)

NI tests of BFF MDI vs. Symbicort pMDI will be performed CCI . The NI assessment for morning pre-dose trough FEV_1 will use an NI margin of CCI and the NI assessment for FEV_1 AUC_{0-3} will apply an NI margin of 125 mL. For more details about the NI hypothesis testing, refer to the main SAP Section 3.3.2.2. All CIs will be two-sided with 95% confidence and p-values (presented to four decimal places) will reflect the one-sided test for NI analysis.

4.3.7.2.5.1 Definition

The endpoints of interest for NI test include: Change from baseline in FEV_1 AUC_{0-3} over 24 weeks and change from baseline in morning pre-dose trough FEV_1 over 24 weeks (see Table 1).

4.3.7.2.5.2 Derivation

For details, refer to Section 4.2.1.2.

4.3.7.2.5.3 Analysis of NI Endpoints

The primary analysis will utilize the Principal Stratum estimand with the Per-Protocol Analysis Set – including only on-treatment data unaffected by ICEs (see Section 3.3.9).

4.4 Pharmacodynamics

Not Applicable.

4.5 Pharmacokinetics Endpoints

This section covers details related to PK endpoints and analyses and only applies to the KALOS study.

The PK parameters will be estimated for budesonide, glycopyrronium and formoterol, as appropriate for each treatment, using plasma concentration-time data from Week 12 (Visit 8, Study Day 85) for participants in the 12-hour PK Sub-Study. It is assumed that all of the analytes will have achieved steady state by Week 12.

The following multiple dose PK parameters will be determined for each analyte and treatment where data allow:

C_{max}	Maximum observed concentration
t_{max}	Time to reach maximum observed concentration
$AUC_{(0–12)}$	Partial area under concentration-time curve from 0 to12 hours post dose
AUC_{last}	Area under concentration-time curve from time zero to the time of the last quantifiable concentration
C_{avg}	Average concentration over the dosing interval (calculated as $AUC_{(0-12)}$ divided by 12)
C_{trough}	Observed lowest concentration before next dose is administered (Predose concentration)

Additional PK parameters may be calculated as appropriate.

4.5.1 PK Sampling

Blood samples for provision of plasma will be collected for measurement of plasma concentrations of budesonide, glycopyrronium, and formoterol.

PK assessments will be performed in a subset of adult and adolescent participants who participate in the 12-hour spirometry sub-study who have confirmed to have taken the last 6 inhalations (3 doses) of each study intervention device prior to Visit 8 (Week 12) in the daily eDiary. Approximately CCI randomized participants CCI participants from each treatment group with at least 6 participants per treatment group 12 to <18 years of age) will be assessed at Visit 8 (Week 12). Approximately 10 mL of whole blood will be collected at

Visit 8 within 30 minutes before administration of study intervention and at 2, 5, 20, and 40 minutes, and 1, 2, 4, 8, 10, and 12 hours post-dose.

4.5.2 Calculation or Derivation of PK Parameters

The PK analyses of the plasma concentration data for budesonide, glycopyrronium and formoterol will be performed by Fortrea on behalf of the Clinical Pharmacokinetic Alliance, AstraZeneca R&D and will be calculated according to the AstraZeneca Standards (Guidance for Non-compartmental Pharmacokinetic Evaluations in Clinical Studies, 2022).

PK parameters will be derived using non-compartmental methods with Phoenix® WinNonLin® Version 8.1, or higher.

PK parameters will, where possible, be carried out using actual times recorded in the raw data. If actual times are missing, nominal times may be used.

Any protocol deviations or adverse events that may impact PK and lead to the exclusion of any participants from the PK Set, of any PK concentrations or parameters from the descriptive or inferential statistical analyses, or of any concentration-time points from the PK non-compartmental analysis, will be discussed and agreed by the PK Scientist with the AZ Clinical Pharmacology Scientist prior to the handover of the final PK parameters to programming.

4.5.3 Presentation of Pharmacokinetic Data

PK concentration and parameter data will be presented for the on-treatment period according to the general principals and table templates in the AZ Standard Output Library (for tables presentation) and most recent version of the AstraZeneca Corporate CSRHLD Reporting Standards (for data handling as well as figures and listings presentation), that include applicable descriptive statistics, handling of individual concentrations below the LLOQ for the listings, descriptive statistics and figures, and precision and rounding rules for concentration and parameter data.

Plasma concentrations for each time-point will be summarized for participants in the PK Set (overall as well as separately presented for adults and adolescents) for each analyte by treatment, using protocol scheduled times and appropriate descriptive statistics.

The individual and geometric mean plasma concentration-time data will be plotted for Week 12 (Visit 8) on both the linear and semi-logarithmic scale. The individual plots will contain data from all participants dosed in the 12-hour PK Sub-Study. The geometric mean plots will include only data from participants in the PK Set (overall as well as separately presented for adults and adolescents) i.e., only those participants where the PK data is not excluded due to an important AE or PD that may impact PK, and will present all treatments on the same plot.

Plasma PK parameters will be summarized for the participants in the PK Set (overall as well as separately presented for adults and adolescents) for each analyte by treatment, using descriptive statistics appropriate for each parameter.

Inferential PK statistical analyses

Non-compartmental parameter estimates for budesonide and formoterol C_{max}, $AUC_{(0-12)}$, and AUC_{last} will be natural log transformed and analyzed using ANOVA models in order to estimate the relative bioavailability of budesonide or formoterol for each BGF MDI treatment arm vs BFF MDI, for each BGF MDI treatment arm vs Symbicort pMDI, and for BFF MDI vs Symbicort pMDI. Estimated ratios and their 90% CIs will be presented.

Also, a separate linear ANCOVA model with treatment group, and relevant demographic characteristics as covariates will be used to draw comparisons between BGF MDI vs BFF MDI, between BGF MDI vs Symbicort pMDI, and between BFF MDI vs Symbicort pMDI. Estimated ratios and their 90% CIs will be presented. The following demographic characteristics will be evaluated for inclusion in the model for both analytes separately using backward elimination: age, sex, height, weight, race (white, black, other), and ethnicity.

4.6 Immunogenicity

Not Applicable.

4.7 Safety Analyses

The term safety covers exposure, AEs, clinical laboratory, vital signs, ECG, 24-hour Holter monitoring and physical examination.

Tables and listings will be provided for the Safety Set. Hypothesis testing will not be performed for any safety analyses.

4.7.1 Exposure

4.7.1.1 Definitions and Derivations

Participant's exposure to a study treatment 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)".

4.7.1.2 Presentation

The number of days of exposure to study treatment will be summarized for each treatment. Summary statistics will also be provided for the cumulative duration of exposure, where the number and percentage of participants treated for 0-24 Weeks and for 0-52 Weeks and corresponding patient years for those periods will be provided. 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, the PFT sub-study set, and the Holter Monitoring Set (for KALOS study only).

4.7.2 Adverse Events

4.7.2.1 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 SAEs 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 day, date of withdrawal, 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 9.1; 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 study medication after randomization to the date of first AE if an AE occurs, or to the minimum of (date of last dose + 1 day, date of death, or date of withdrawal of consent) if no AE occurs.

AEs will be coded using the latest version of the MedDRA available at the time of the clinical data lock of the study considered to be completing earlier (of the two replicate studies). 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 queries (SMQs) proposed to be used in the assessment of AEs associated with ICS, LAMAs, and LABAs are listed below. SMQs will be utilized when possible and a selection of HLGTs, HLTs, and PTs in other situations (as per supplementary document Standard MedDRA Queries for KALOS and LOGOS). When using the PTs of SMQs, 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

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

Other Systemic LAMA Effects

- Urinary retention
  - Urinary retention (10046555) PT
  - Urinary incontinence (10046543) PT
  - Pollakiuria (10036018) PT
  - Dysuria (10013990) PT
- Anticholinergic syndrome (20000048) Narrow SMQ
- Gastrointestinal obstruction (20000105) Narrow SMQ

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

Adjudication committees were established for these studies. The committees will review the following events:

1. Cases of ER or UC visits and hospitalizations related to respiratory conditions to evaluate whether any such events are related to a worsening of asthma and hence, diagnostic of a severe asthma exacerbation[1]

2. Cause of deaths for cardiovascular and respiratory related events (determine if the fatal cardiovascular events meet MACE criteria)[2]

3. Non-fatal Cardio and Cerebro-Vascular (CCV) events and classification of MACE[2]

4. Serious events of Cardiac Arrhythmias within the Cardiovascular SOC[2]

[1] Events will be adjudicated post randomization only

[2] Events will be adjudicated during the run-in period on BFF and post randomization

4.7.2.2 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. These will also be summarized during the on-treatment period for the following time period: 0 to <= 24 Weeks.

- 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 Safety Set during on-treatment period by treatment group:

- Number of participants with AEs and AEs per subject years by SOC and PT
- Number of participants and exposure adjusted incidence rate with AEs in >=2% participants in either BGF treatment groups by PT, sorted by decreasing frequency in BGF 320/28.8/9.6 µg treatment group
- Number of participants and exposure adjusted incidence rate with SAEs in >=2 participants in total (pooled treatment groups) by PT, sorted by decreasing frequency in BGF 320/28.8/9.6 µg treatment group
- Number of participants with non-serious AEs occurring in more than 5% of participants, by SOC and PT
- Number of participants with AEs 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 possibly related SAEs, by SOC and PT
- Number of participants with SAEs with outcome death, by SOC and PT
- Number of participants and exposure adjusted incidence rate with SAEs, by SOC and PT
- Number of participants with SAEs, by SOC and PT
- Number of participants and exposure adjusted incidence rate with AEs leading to discontinuation of IP, by SOC and PT
- Number of participants with AEs associated with use of ICS, LAMAs, and LABAs by medical concept and PT
- Number of participants with Adjudicated ER visit/UC visit/Hospitalization events by category (including Not Asthma related, Asthma related and Undetermined Event.)
- Number of Participants with Adjudicated Death Events by category (including Cardiovascular Death, Non-cardiovascular, Pulmonary-Asthma Related and Undetermined Event. For Cardiovascular Death, it will further be broken down

into Acute Myocardial Infarction, Sudden Cardiac Death, Heart Failure, Stroke, Cardiovascular Procedures, Cardiovascular Hemorrhage, or Other Cardiovascular Causes.)

- Number of participants with Adjudicated MACE by category (including Myocardial Infarction, Stroke and Cardiovascular Death. For Myocardial Infarction, it will further be broken down into Myocardial Infarction, Hospitalization for Unstable Angina, or Undetermined event. For Stroke, it will further be broken down into Ischemic Stroke, Hemorrhagic Stroke, Undetermined Stroke, or Undetermined Event.)
- Number of participants with Adjudicated Serious Cardiac Arrhythmia Event by category (including Cardiac Conduction Disorder, Rate and/or Rhythm Disorder, Supraventricular Arrhythmia, Ventricular Arrhythmia and Cardiac Arrest, and Undetermined event.)

The following is a list of summary tabulations that will be prepared for Screened Set on-study period by treatment group:

- Serious AEs with outcome death - key participant information
- Serious AEs - key participant information
- AEs leading to discontinuation of IP – key participant information

In addition, the following summaries will be prepared for the Safety Set during the post-treatment and on-study periods by treatment group:

- Number of participants with AEs, by SOC and PT
- Number of participants with 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 the most common AEs by PT, AEs leading to discontinuation of IP by SOC and PT, and all SAEs 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).

All AEs (including during screening/run-in period) will be included in the listing for Screened Set. A listing of all reported overdoses will be provided.

4.7.3 Clinical Laboratory

4.7.3.1 Definitions and Derivations

Clinical chemistry, hematology and eGFR 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 17.

Table 17 Laboratory Variables

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

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

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

Absolute values will be compared to the relevant normal reference range used by central laboratory, 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 of all laboratory variables except for eGFR.

For eGFR, the classifications of chronic kidney disease grade are specified in Table 18. The grade definition from this table will be used for the eGFR shift tables. In addition, treatment emergent kidney function abnormalities are defined as ≥ 1 CTCAE grade change from baseline and ≥ 20% decrease from baseline.

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) whatever comes first.

Summary statistics will not be presented for laboratory parameters for which records are available for less than 20 patients in at least one treatment group per study.

Table 18CTCAE Grade for Chronic Kidney Disease

	Grade			
	1	2	3	4
Chronic kidney disease	eGFR >= 60 ml/min/1.73 m^2	30 <= eGFR <60 ml/min/1.73 m^2	15 <= eGFR <30 ml/min/1.73 m^2	eGFR < 15 ml/min/1.73 m^2

For the purposes of shift tables, baseline will be defined as the last available value prior to first dose of randomized IP. 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.

4.7.3.2 Presentations

Summary statistics (n, mean, SD, minimum, 1st quartile, median, 3rd quartile, maximum) of the absolute value and change from baseline for hematology, clinical chemistry laboratory and eGFR 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. Participants with a treatment emergent kidney abnormality will be summarized.

A shift table will display low, normal and high values at baseline and maximum and minimum on-treatment observation values for each variable. Shift table for kidney function (eGFR) will be provided based on shifts in grades.

4.7.4 Vital Signs

4.7.4.1 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 0.

Absolute values and changes from baseline (where applicable) will be compared to the relevant reference range specified in Table 19, 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.

Table 19 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	

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) whatever comes first.

4.7.4.2 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. 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.

A shift table will display low, normal and high values at baseline and maximum and minimum on-treatment observation values for each variable.

4.7.5 Electrocardiogram

4.7.5.1 Definitions and Derivations

The 12-lead ECG will be taken in supine position after 10 minutes of rest. ECGs will be measured according to the schedule and the variable specifications described in the CSP. The ECG parameters to be assessed include HR, PR interval, QRS interval, and QT/QTcF interval. Changes from Baseline will be evaluated, where baseline is defined as specified in Section 0.

Overall ECG evaluation will be recorded by site investigator in eCRF as “Normal”, “Abnormal”, and “Borderline”. Further, investigator will specify if the results are “not clinically significant” or “clinically significant”. These assessments will be applied for the shift table.

4.7.5.2 Presentations

Summary statistics (n, mean, SD, minimum, 1st quartile, median, 3rd quartile, maximum) of the absolute value and change from baseline for ECGs (Mean heart rate, RR interval, PR interval, QRS duration, QT interval, QTcB interval, QTcF interval) will be tabulated by treatment and visit. These summaries will be prepared for baseline, each scheduled post-baseline visit and end of treatment visit. For baseline definition, refer to Section 3.3.1.1. For post-baseline visit, the measurement closest to the scheduled visit date will be applied for the summary. End of treatment visit is defined as the last non-missing on treatment visit 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. No hypothesis tests will be performed.

A frequency table showing participants with QTcF values and increases from baseline at any time during the on-treatment period using pre-specified thresholds (Table 20) will be produced for the Safety Set.

Table 20 Summary Thresholds for QTcF

Parameter	Post-Baseline Criteria
QTcF Value	≥450 ms
	≥480 ms
	≥500 ms
QTcF Change From Baseline	≥30 ms
	≥60 ms
QTcF Value and or Change from Baseline	Value >500 ms or increase from baseline ≥60 ms

ms denotes milliseconds.

For the shift table, for each treatment, the participant’s baseline overall assessment will be cross tabulated by the participant’s overall assessment at end of treatment; also, the participant’s assessment at end of treatment will be tabulated for all baseline assessment combined. Percentages of participants in each assessment at end of treatment for a treatment will be calculated for each baseline assessment for the treatment.

4.7.6 24-Hour Holter Monitoring

This section only applies to KALOS study.

4.7.6.1 Definitions and Derivations

Continuous Holter monitoring will be conducted over 24 hours in a subset of approximately 440 randomized participants between Visit 4 and Visit 5 (Holter Monitor baseline) and at Visit 6 (Week 4) and Visit 11 (Week 24). If there is not at least 18 hours of acceptable quality monitoring for a given assessment, then the assessment is to be repeated. In these cases, the second assessment will be used whether for baseline and/or for the Visit 6 (Week 4) and Visit 11 (Week 24) value.

For participants in the Holter Monitor sub-study, at Visit 5 (randomization) 6 ECG readings will be taken pre-dose and triplicate ECG readings will be taken 30 minutes and 4 hours post-dose. Triplicate ECG readings will be taken pre-dose at all other visits as specified in the SoA as well as triplicate ECG readings at Visit 8 (Week 12) 15 minutes post-dose.

Note that ERT will provide mean 24-hour HR, which will be an average across hourly estimates collected during the specific Holter 24-hour monitoring period.

The mean daytime (0600 to 2200) HR and nighttime (2200 to 0600) HR will be calculated as the average across hourly estimates collected during the daytime and night-time monitoring periods, where observations within intervals containing the exact hours 0600 and 2200 will be excluded from the analysis and not counted in either the daytime or nighttime HR calculations.

Overall ECG evaluation based on pre-dose 6 ECGs or post-dose triplicate ECGs will be recorded by site investigator in eCRF as “Normal”, “Abnormal”, and “Borderline”. If at least one of the 6 or triplicate ECGs is abnormal, overall ECG evaluation will be considered as abnormal. Further, investigator will specify if the results are “not clinically significant” or “clinically significant”. These assessments will be applied for the shift table.

4.7.6.2 Presentations

Analysis for 24-hour Holter Monitoring will be performed with the While on Treatment strategy for all ICEs inr the Holter Monitoring Set.

Summary statistics (n, mean, SD, minimum, 1st quartile, median, 3rd quartile, maximum) of the absolute value and change from baseline for ECGs (Mean heart rate, RR interval, PR interval, QRS duration, QT interval, QTcB interval, QTcF interval) will be tabulated by treatment and visit. These summaries will be prepared for baseline, each scheduled post-baseline visit and end of treatment visit. For baseline definition, refer to Section 3.3.1.1. For post-baseline visit, the mean of the triplicate measurements from each visit will be applied for the summary. End of treatment visit is defined as the last non-missing on treatment visit

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. No hypothesis tests will be performed.

The change from baseline in mean 24-hour HR at Week 24 (Visit 11) will be analyzed using an ANCOVA model to evaluate treatment differences with baseline mean 24-hour HR (obtained during 24-hour Holter monitoring at Screening) as a covariate. LS means and estimated treatment differences with 95% CIs will be provided. The raw mean values and change from baseline values will also be summarized by treatment. A schematic box-plot will display the distribution of change from baseline in mean HR by treatment, with extreme values that are 1.5*IQR above/below the upper/lower quartiles identifiable, where IQR is the interquartile range.

The changes from baseline at Week 24 (Visit 11) for the mean daytime (0600 to 2200) HR, mean nighttime (2200 to 0600) HR, maximum 24-hour HR, and minimum 24-hour HR will be summarized and analyzed in a similar manner to the analysis of the change from baseline in mean 24-hour HR.

A frequency distribution of the following will be provided:

- Proportion of participants with maximum HR during treatment of >180, >160-≤180, >140-≤160, >120-≤140, >100-≤120, and 100 or less.
- Proportion of participants with minimum HR during treatment of >60, >50-≤60, >40-≤50, and ≤40.

The change from baseline in the number of Holter ventricular and supraventricular events will be summarized descriptively (mean, median, range, etc.) and analyzed with nonparametric methods. The Wilcoxon Rank Sum test will be used to produce p-values for the pairwise comparison of treatments. The median treatment differences will be presented with 95% confidence intervals based on the Hodges-Lehmann approach for the location shift (median treatment difference). This analysis will be performed for change from baseline for the following parameters (calculated per hour by dividing the number of events by the number of hours within the collection period): number of isolated ventricular events (PVCs), number of ventricular couplets (defined as 2 PVCs preceded or followed by regular beats), number of ventricular runs (defined as 3 or more PVCs preceded or followed by regular beats), number of isolated supraventricular events, number of supraventricular couplets, number of supraventricular runs, and number of supraventricular ectopic beats.

The number of participants experiencing an isolated ventricular event, ventricular couplet, ventricular run, isolated supraventricular event, supraventricular couplet, supraventricular run and supraventricular ectopic beat at Week 24 will be analyzed with a logistic regression model comparing across the treatment groups with baseline value of the Holter variable as a

continuous covariate, and treatment and prior ICS dose (medium vs. high) as categorical covariates. P-values and odds ratios with 95% CIs will be produced for each treatment comparison.

Additionally, the following will be tabulated:

- The proportion of participants in each category of change from baseline in the number of isolated PVCs per hour (no change, increase of >0-<60, ≥60-<120, and ≥120, and decrease of >0-<60, ≥60-<120, and ≥120).
- The number of participants who had atrial fibrillation with a rapid ventricular response (>100 bpm) will be tabulated by treatment.

A frequency table showing participants with QTcF values and increases from baseline at any time during the on-treatment period using pre-specified thresholds (Table 20) will be produced in a similar manner as described in Section 4.7.5.2, except that the Holter Monitoring Set will be used.

For the shift table, for each treatment, the participant's baseline overall assessment will be cross tabulated by the participant's overall assessment at end of treatment; also, the participant's assessment at end of treatment will be tabulated for all baseline assessment combined. Percentages of participants in each assessment at end of treatment for a treatment will be calculated for each baseline assessment for the treatment.

4.7.7 Physical Examination

4.7.7.1 Definitions and Derivations

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

4.7.7.2 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.

4.7.8 Consistency Analyses for Safety

Subgroup analyses will be conducted to support local registration requirements including by-country and by-region assessments of consistency. Subgroups are defined as[CCI] [CCI]

5 ANALYSIS OF DATA FROM [CCI] AND [CCI]

[CCI] a CSR addendum or supplemental CSR will be written to present the study results in the[CCI] opulations with the objective of demonstrating

consistency with the overall LOGOS population for individual study endpoints and pooled KALOS/LOGOS study population for pooled study endpoints.

Similarly, study results in the CCI population will be conducted CCI CCI CCI

5.1 Definition of CCI Cohorts

CCI cohort will include all participants enrolled at the sites in CCI

CCI cohort will include all participants enrolled at the sites in CCI

Analysis Sets

Unless otherwise specified, the definition of the analysis sets will be the same as stated in Section 3.2 with only participants from CCI cohorts respectively.

Analysis sets for CCI and CCI cohorts analysis include the following:

- CCI Screened Set
- CCI Efficacy Set
- CCI Per-protocol Set (for CCI only)
- CCI Safety Set

The analysis set used for each endpoint will also be the same as defined in Section 4. More specifically, efficacy of BGF MDI will be summarized for the CCI Efficacy Set, and efficacy of BFF MDI will be summarized for the CCI Per-protocol Set. Selected analyses on study population (subject disposition, demographic and baseline characteristics, and exposure) will be conducted for the CCI corresponding populations as specified in Section 4.1. Safety and tolerability (AEs, laboratory parameters, vital signs, and ECGs) of BGF MDI and BFF MDI will be summarized for the CCI Safety Set. Similarly, AEs and treatment emergent abnormalities in laboratory parametrs and vital signs will be summarized for the CCI Safety Set.

5.2 Analysis Considerations for CCI and CCI Cohorts

All selected endpoints to be summarized or analyzed for the CCI and CCI cohorts will be derived in the same way as detailed in Section 4. The same analysis methods described in Section 4 will be applied to the CCI cohorts accordingly. However, the analyses for the efficacy endpoints for the CCI cohorts include the following differences:

- All statistical analyses will be considered exploratory in the CCI cohorts. No adjustment for multiplicity will be made and so the Type I error control procedure detailed in Section 3.3.8 will not be employed directly to the CCI cohorts results. The calculated p-values are considered nominal.

Where necessary (e.g., for analysis using as covariates such as country or region), the model factor country/region will be reduced.

- Unstratified/unadjusted analysis may be used as the primary analysis method if low number of events observed in a stratum.

- No sensitivity analysis or subgroup analysis will be performed in the CCI cohorts.

No separate listings of individual participants in the CCI cohorts will be produced.

6 INTERIM ANALYSIS

Not Applicable.

7 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).

8 REFERENCES

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9 APPENDIX

9.1 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	All data, regardless of 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 with RETREFID = 0 (best effort) will be mapped to ADAM. 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", "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

Category	Description	Data Handling Rule
		consent/assent date is on or prior to June).
	Missing day of "First appearance of asthma symptoms date", "Asthma first diagnosed date", "Most recent Severe exacerbation date".	The missing day of Diagnosis will be imputed for all participants as the 1st of the month.
	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

Category	Description	Data Handling Rule
		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 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 treatment	The date and time (24 hr. clock) of the first dose of study treatment will be taken from the Exposure eCRF. The date of the last dose of study treatment will be the later of the last date of dosing from the eDiary or the last date of dosing from the 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 dose of randomized IP (First Dose Day).
	Study Day Post-Treatment of	Study Day = 'P' concatenated with the number of days post-treatment that the

Category	Description	Data Handling Rule
	Assessment or event which occurs after study treatment	assessment or event occurred which is defined as Date of assessment/event – date of last dose of study treatment.
	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.
	Last Dose Day	**Last Dose Day** in the study is defined as the study day of the last dose of randomized IP in the study (defined as the later of the last date of dosing from the eDiary and the last date of dosing from the Exposure CRF pages).
	Last Study Day	**For participants who did not receive study treatment 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 treatment 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 or Disposition CRF) – date of first dose of randomized IP + 1.

Category	Description	Data Handling Rule
	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 treatment.
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.
11. Adverse event	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 study medication after 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

Category	Description	Data Handling Rule
		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.
		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.

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 of the AE. If start date is found to be after the end date then set start date to equal the 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 prior to enrolment date. If it cannot be identified, then it is considered prior medication. • 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. • Post-Treatment period: start date is on or after treatment end date.
	Concomitant medication's start or end date is partial/missing	If concomitant medication's start date is partial/missing, and the investigator has filled in that the medication is taken prior to study, then: o Missing day – Impute the 1st of the month.

Category	Description	Data Handling Rule
		o Missing day and month – impute 1st January. o 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 medication is taken prior to study, then: o Missing day – Impute the 1st of the month or participants visit 1 date whichever is later. o Missing day and month – impute 1st January. or participants visit 1 date whichever is later. o Completely missing – impute participants visit 1 date. If concomitant medication's end date is partial/missing, then: o Missing day – impute last day of the month or participant's end of study date whichever is earlier. o Missing day and month – impute 31st December or participant's end of study date whichever is earlier. o Completely missing – impute participant's end of study date. When imputing a start date ensure that the new imputed date is sensible i.e. is

Category	Description	Data Handling Rule
		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. 24-hr Holter Monitoring Multiple Measurements	Repeated 24-hr Holter monitoring	If 24-hr Holter monitoring is deemed unacceptable, then that data will not be included in any analyses and a repeat of the 24-hr Holter monitoring may be performed and that data will be used in all analyses.
16. AUC calculation for spirometry endpoints	AUC_{0-3}, AUC_{0-6}, AUC_{0-12}, and AUC_{6-12}	AUC_{0-3}, AUC_{0-6}, AUC_{0-12}, and AUC_{6-12} will be calculated using the trapezoidal rule and actual time of assessment when available and nominal time of assessment otherwise.
17. 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.

9.2 DETAILS OF STATISTICAL METHODS

9.2.1 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. prior ICS dose (medium vs. high), and by box plots of residuals for model variables with a potential effect on variance (treatment, visit, prior ICS dose).

Over-dispersion of SGRQ, 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.

The proportional hazards assumption of the Cox model will be checked for time to first asthma exacerbation, time to CID, time to first[CCI] and time to intercurrent event. 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.

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.

9.2.2 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, are valid under the MAR assumption. This assumption is made about the given endpoint during the time interval the participant is not considered to be exposed for the given estimand. 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 set to missing following 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.

Separate tipping point analyses will be performed for each treatment comparison of interest: BGF 320/28.8/9.6 vs. respective control group and BGF 320/14.4/9.6 vs. respective control group. Particularly, the effect of BGF will be gradually worsened and the effect of the respective 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 BGF and control group means by pre-specified constants δ_1 and δ_2, respectively. δ_1 will be ranging from 0 (no change) to -500 ml (worsening) and δ_2 will be ranging from 0 (no change) to 500 mL (improvement). 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.

9.2.2.1 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 participants 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 (baseline trough FEV_1, percent reversibility, prior ICS dose, and randomized treatment). At this stage, the imputed values will not yet be adjusted for any participants.
ii. After imputations are obtained in Step (i), for BGF participants missing data at time point 1, the imputed value at time point 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.

9.2.2.2 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 except that "between-within" method for computing the degrees of freedom will be used instead of Kenward-Roger approximation due to computational considerations. This is not expected to impact the analysis conclusions due to the large dataset for analysis.

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

9.2.2.3 The Choices of δ in the Tipping Point Analysis

The tipping point analysis is to be conducted for BGF MDI vs. BFF MDI and BGF MDI vs. Symbicort pMDI comparisons depending on the regional approach . 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 and estimand. 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 ranging from 0 to -500ml (a worsening) and δ_2 ranging from 0 to 500 mL (improvement), 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 more precise estimation may be done with change of 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 covering the square region $[0, -500] \times [0,500]$ of the (δ_1, δ_2) space.

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^*) can be estimated as the crossing point of p_0 by the smoother.

9.2.3 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} , Z_{2i}, and Z_{3i}: having $Z_{1i} = 1$ and $Z_{2i} = 0$ and $Z_{3i} = 0$ denotes treatment group 1; having $Z_{1i} = 0$ and $Z_{2i} = 1$ and $Z_{3i} = 0$ denotes treatment group 2; having $Z_{1i} = 0$ and $Z_{2i} = 0$ and $Z_{3i} = 1$ denotes control group 1 (or pooled control groups, for the analyses is performed on pooled control groups); having $Z_{1i} = 0$ and $Z_{2i} = 0$ and $Z_{3i} = 0$ denotes comparator group 2.

- X_i - baseline covariate(s)

- τ_i - planned duration of follow-up

- Y_{i1} - number of events during the relevant follow-up period (e.g. up to the occurrence of an ICE+1 day or participant's last dose date + 1 day, if no ICE for the While-on-Treatment strategy, up to time of last recorded date of (any asthma status assessment in planned treatment period, last visit in planned treatment period) in case of no ICE of interest for the Primary strategy for handling ICEs, or planned last visit date during treatment period in case of an ICE of interest)

- T_{i1} - time to end of relevant follow-up*

- Y_{i2} - number of events between time T_{i1} and τ_i, which is to be imputed

* occurrence of an ICE for the while on treatment estimand; withdrawal from study for the Treatment Policy estimand.

Standard Efficacy Analysis

Fit a negative binomial model where Y_i is the dependent variable, X_i and Z_i are covariates, and $\log(T_{i1})$ 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 $1/k$.

9.2.4 Sensitivity Analyses Using a Tipping Point Analysis Under a MNAR Assumption for Severe Asthma Exacerbations

The following description of the tipping point analysis is for the endpoint of rate of severe asthma exacerbations (count data).

The estimation and inference performed for the Primary strategy for handling ICEs, are valid under the MAR assumption. This assumption is made about the event count following withdrawal from study or loss to follow up. The tipping point analysis will address the question of robustness of the treatment effect estimates and statistical significance with respect to the MAR, by considering alternative distributions for the missing count data, i.e. under a MNAR condition. Imputations for the sensitivity analysis will not be performed for participants who have had an ICE of new asthma therapy or use of prohibited medications thought to impact efficacy with severe exacerbation imputation under the Primary strategy for handling ICEs.

There are 2 comparisons for which the tipping point analysis will be conducted: BGF 320/28.8/9.6 vs. respective control group and BGF 320/14.4/9.6 vs. respective control group. Separate sets of imputations (and separate tipping point analyses) will be created for the comparisons involving BGF 320/28.8/9.6 and the comparisons involving BGF 320/14.4/9.6. Particularly, the effect of BGF 320/28.8/9.6 (or BGF 320/14.4/9.6) will be gradually worsened, to the point where the comparison becomes not statistically significant, or the amount of worsening reaches a level that is not believed to be realistic. This will be achieved by considering a class of distributions defined by multiplication of the negative binomial mean in the BGF group by a pre-specified constant δ_1:

$$\varphi_{i2,\delta} = \varphi_{i2} * \delta_1 \quad (12)$$

with the penalty δ_1 ranging from 1 (no worsening) to 1.5 (50% increase in exacerbation rate). At the same time, the distribution for the comparator treatment will be modified to improve its negative binomial mean by multiplying by another constant δ_2 ranging from 1 (no worsening) to 0.67 (33% decrease in exacerbation rate):

$$\Phi_{i2,\delta} = \varphi_{i2} * \delta_2 \quad (13)$$

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

9.2.4.1 Imputation for the Tipping Point Analysis for Severe Asthma Exacerbations: the Primary Strategy for Handling ICEs

For the Primary strategy for handling ICEs, the imputations will utilize the Markov Chain Monte-Carlo algorithm available in PROC GENMOD. We assume that M imputed datasets are to be generated, where M is initially 100. If the amount of Monte Carlo error is large, M could be increased up to a maximum of 1000. Following the arguments made by White *et al.* (2011), the imputation process may be re-run, using the same seed but with a larger value of M, according to scheme. For each log rate ratio contrast of interest, the fraction of missing information (FMI) will be calculated based on the 100 initial imputations as FMI=B/(W+B) where B denotes the between imputation variance (of the log rate ratio estimate) and W denotes the average within imputation variance (of the log rate ratio estimate) for the contrast. The Monte-Carlo standard error of the test statistic is approximately $1/(1+M/FMI)^{1/2}$. In order for the Monte-Carlo error of the corresponding test statistic to be 0.01, we require $M=FMI*100^2$. Thus with FMI=0.01, M=100. The value of M required to give a Monte-Carlo standard error for each test statistic of interest will be calculated. If the largest of these values across the contrasts of interest (which we denote M2), is larger than 100, and the imputation process will be repeated using M2 imputations.

Fit the efficacy observed data model with BAYES statement

First, we fit the observed data model again, but adding a BAYES statement. This should include OUTPOST to specify a dataset that SAS will generate with the saved draws from the model posterior. The number of burn-in (NBI) and main iterations (NMC) needs to be specified. The choice of number of main iterations will depend on how large *M*, the number of imputations is, and also how quickly the auto-correlation plots indicate the auto-correlation goes to zero. The THIN argument should be specified so that the OUTPOST dataset contains *M* sets of values. For example, suppose that auto-correlation plots indicate the auto-correlation goes to (close to) zero within 100 iterations, and that we want to generate $M = 100$ imputations. Then we will need to use NMC = 10000 iterations, and THIN = 100. NMC would be scaled up appropriately if M is increased.

Generating the m^{th} dataset

From the OUTPOST dataset, obtain the m^{th} set of parameter values. This will give a value for $1/k$ and the regression coefficients. To generate $k^{(m)}$, take the reciprocal of the corresponding dispersion parameter value. Let $\beta_0^{(m)}, \beta_1^{(m)}, \beta_2^{(m)}, \beta_3^{(m)}, \beta_4^{(m)}$ denote the regression coefficient values.

We now describe how to impute the missing data for participant *i*. For participant *i*, conditional on $\beta^{(m)}$ and $k^{(m)}$, the mean/expected number of events up to time T_{i1} is given by

$$\varphi_{i1} = T_{i1}\exp\left(\beta_0^{(m)} + \beta_1^{(m)}X_i + \beta_2^{(m)}Z_{1i} + \beta_3^{(m)}Z_{2i} + \beta_4^{(m)}Z_{3i}\right)$$

Under the MAR assumption, the corresponding mean from time T_{i1} to the planned end of follow-up, τ_i, is

$$\varphi_{i2} = (\tau - T_{i1})\exp\left(\beta_0^{(m)} + \beta_1^{(m)}X_i + \beta_2^{(m)}Z_{1i} + \beta_3^{(m)}Z_{2i} + \beta_4^{(m)}Z_{3i}\right)$$

For the BGF treatment, φ_{i2} will be replaced by the penalized version, $\varphi_{i2,\delta}$. The number of events between T_{i1} and τ_i, Y_{i2}, is then negative binomial distributed. SAS's RAND function parametrizes the negative binomial with a parameter it calls 'k' ('number of successes') and a parameter called 'p' for the probability of success. These should be set to:

$$\text{Probability of success} = \frac{k^{(m)}+\varphi_{1i}}{k^{(m)}+\varphi_{1i}+\varphi_{2i}}$$

$$\text{Number of successes} = \boldsymbol{k^{(m)} + Y_{i1}}$$

9.2.4.2 Estimation for the Tipping Point Analysis for Severe Asthma Exacerbations

For all estimands, 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 BGF 320/28.8/9.6 vs. respective control group and BGF 320/14.4/9.6 vs. respective control group contrasts reported as functions of (δ_1, δ_2).

9.2.4.3 The Choices of δ in the Tipping Point Analysis

The tipping point analysis is to be conducted for BGF vs. respective control group comparisons in each estimand. 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 and estimand. It will thus be assumed that $p < p_0$ in the main analysis, and the tipping point is defined as any 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 ranging from 1 up to (a worsening by multiple of) 1.5 and δ_2 ranging from 1 down to (an improvement by multiple of) $\frac{1}{1.5}$ = 0.67. The result at $\delta_1 = \delta_2 = 1$ should agree with the main analysis, because it corresponds to the MAR imputations, up to the Monte-Carlo error. If $p(1.5,0.67) < p_0$, 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 covering the square region $[1,1.5] \times [1,0.67]$ of the (δ_1, δ_2) space.

The following grid shows the plausible range of worsening and improvement in the BGF 320/28.8/9.6 (or BGF 320/14.4/9.6) and comparator treatment arms respectively. Those pairs of δ are considered unlikely due to resulting in more extreme and opposing event rates in the treatment and comparator arms.

			Comparator arm (BFF MDI/Symbicort pMDI)					
			Improvement of exacerbation rate by up to 33% ($\varphi_\delta = \varphi^*\delta_2$) →					
			$\delta_2 = 1$	$\delta_2 = \frac{1}{1.1}$	$\delta_2 = \frac{1}{1.2}$	$\delta_2 = \frac{1}{1.3}$	$\delta_2 = \frac{1}{1.4}$	$\delta_2 = \frac{1}{1.5} = 0.67$
Treatment arm (BGF MDI)	**Worsening** of exacerbation rate by up to 50% ($\varphi_\delta = \varphi^*\delta_1$) ↓	$\delta_1 = 1$						
		$\delta_1 = 1.1$						
		$\delta_1 = 1.2$						
		$\delta_1 = 1.3$						
		$\delta_1 = 1.4$						
		$\delta_1 = 1.5$						

φ_δ is the negative binomial mean of the event rate in the respective treatment arm modified by δ (worsening and improving in the treatment and comparator arms respectively)

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^*) can be estimated as the crossing point of p_0 by the smoother.

9.3 ASTRAZENECA SCORING GUIDELINE FOR LOGIC ITEMS OF THE SGRQ

This appendix describes how the SGRQ should be programmed for ePRO, and how skipped SGRQ questions should be scored. The guidance described is supported via developer notes and correspondence with the developer.

ePRO programming of the SGRQ

- All logically skipped items and patterns should be programmed accordingly

- Section 1 (employment/job): add response option for 'not applicable'. When 'not applicable' is selected, it is scored as zero, and is retained in the denominator
- Section 5 (medication questions): do not include a gateway Y/N question, do not include any additional response options that differ from paper version

Scoring: Question 5 (severe or very bad unpleasant attacks of chest trouble) and 6 (length of worst attack of chest trouble)

- If a patient reports 'no attacks' to Q5 and Q6 is logically skipped, then:
  - Q6 should be scored as zero
  - The weight for Q6 remains in the denominator
  - Score Q5 according to the manual
- In paper administration, if a patient reports 'no attacks' to Q5 and Q6 is answered, then:
  - Q6 should be scored as zero. Question 6 should not be considered missing, a value of 0 will be added to numerator
  - A value of "0" will be added to the numerator and the weight value of 41.9 for Q6 remains in the denominator
  - Score Q5 according to the manual
- In paper administration, if the patient reports any other response besides 'no attacks' to Q5 and Q6 is missing, then:
  - Q6 response should be scored as missing
- In paper administration, if Q5 is missing and Q6 has a response, then:
  - Score Q6 according to patient reported response
  - Score Q5 as missing

		Item 6 response	
		Any response	**Missing**
Item 5 response	**No attacks**	Score Q6 as zero, impute to 'less than a day'. Score Q5 according to the manual.	Score Q6 as missing. Score Q5 according to the manual.
	1 to more than 3	Score both	Score Q6 as missing. Score Q5 according to patient reported response, retain weight in denominator.
	Missing	Score Q6 as not missing according to the patient reported response, retain weight in denominator. Score Q5 as missing.	Score both as missing

Scoring: Question 4 (frequency of wheezing attacks) and 8 (wheeze worse in the morning): No skip patterns for these items

- There are no skip patterns for questions 4 & 8
- Each item should be scored according to patient reported response

Scoring: Question 14 (section 5, part 1-4, medication does not help very much, embarrassed using medication in public, having side effects from medication, medication interferes with life a lot)

- If a patient is not taking any relevant medication, Q14 will be logically skipped. Therefore, if all 4 responses are missing, all will be imputed as zero and the denominator for the domain / total score(s) will not be changed.
- In paper administration, if at least 1 of the 4 are answered, any of the remaining questions not answered will be treated as missing.

Q14 (section 5)	**All answered**	Score both
	Some missing	Q14 missing scored as missing, deduct from denominator. Q14 items answered score according to patient response
	All missing	Q14 missing scored as missing, deduct from denominator

9.4 ADDITIONAL REPORTING TO ASSESS THE IMPACT OF STUDY DISRUPTIONS DUE TO CASES OF CIVIL CRISIS, NATURAL DISASTER, OR PUBLIC HEALTH CRISIS

In order to assess the impact of study disruptions due to cases of civil crisis, natural disaster, or public health crisis, 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 SAP in which they relate to.

9.4.1 Protocol Deviations

All IPDs related to global/country situation (i.e. epidemic/pandemic, healthcare crisis, natural disaster etc.) will be grouped and summarized together with all other related IPDs. A listing of all IPDs will be provided.

9.4.2 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.

9.4.3 Summary of global/country situation study disruptions

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

9.4.4 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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