Clinical Study Protocol	
Study Intervention	Budesonide and Formoterol Fumarate
Study Code	D5982C00006
Version	4.0
Date	07 Nov 2024

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

Sponsor Name:

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Regulatory Agency Identifier Number(s)

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

Protocol Number: D5982C00006

Amendment Number: 3

Study Intervention: Budesonide and Formoterol Fumarate; Budesonide; Symbicort

Study Phase: III

Short Title: A 24-Week Efficacy and Safety Study to Assess Budesonide and Formoterol Fumarate Metered Dose Inhaler in Adult and Adolescent Participants with Inadequately Controlled Asthma (VATHOS)

Study Physician Name and Contact Information will be provided separately

International Co-ordinating Investigator:

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SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
CSP version 4.0	07-Nov-2024
CSP version 3.0	05-Dec-2023
CSP version 2.0	12-Oct-2021
CSP version 1.0	21-May-2021

CSP Version 4.0: 07-Nov-2024

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

Overall Rationale for the Amendment:

An amendment was required to update statistical methodological approaches to handling intercurrent events and the Type I error control procedure for [redacted].

Summary of Changes:

List of Substantial Modifications

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis, 3 Objectives and Endpoints, 9 Statistical Considerations	The strategies for handling intercurrent events were updated to reflect a composite strategy (treatment failure) if new asthma therapy or administration of prohibitive medication thought to impact efficacy occurs in conjunction with premature IP discontinuation. Otherwise, treatment policy will be used. To simplify reporting to health authorities, the same approach to handling intercurrent events will be used for every Health Authority, instead of having different approaches for different Health Authorities. An approach using “While On Treatment” strategy for intercurrent events will be used as supportive.	[redacted]

Section # and Name	Description of Change	Brief Rationale
	The supportive Hybrid strategy for intercurrent events was removed.	
9.2.1.3 CCI Approach	The text for the Type I error control procedure for CCI has been updated to reflect that Onset of Action is tested separately (as for CCI outside the Hochberg test procedure.	Correction to align Statistical Analysis Plan and CSP

List of Non-Substantial Modifications

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis 3 Objectives and Endpoints	ICEs of new asthma therapy and prohibited medications consolidated to be ICE of: Initiation of new asthma therapy or administration of prohibited asthma medications thought to impact efficacy.	Simplification as key medications identified as including biological therapy/monoclonal antibodies, LABA, LAMA, or LTRA.
8.3.7 Composite Exacerbation endpoint	Nighttime awakening removed from description and new reference added.	To be aligned with company standard and most recent reference.
9.3 Sample Size Determination	For sample size determination, added the references for the studies that the treatment effect and variability assumptions were based on.	Clarification in response to questions raised from the State Institute for Drug Control, CCI on LITHOS CSP amendment v3.0.
9.5.2.3 Tertiary/Exploratory Endpoint(s)	Analysis for the percentages of rescue-free days and symptom-free days updated to repeated measures analysis of covariance.	Correction.
9.5.2.2 Secondary Endpoints(s) 9.5.2.3 Tertiary/Exploratory Endpoint(s)	Clarification of models used for the pooled analysis. Furthermore, it has been clarified that all available data from studies D5982C00005 and C5982C00006 will be used in the pooled analysis.	Clarification in response to questions raised from the State Institute for Drug Control, CCI on LITHOS CSP amendment v3.0.
9.5.3.2 Vital signs	The baseline definition for vital signs was updated to last non-missing value prior to the first dose of randomized IP.	Consistency of baseline definition across endpoints
Throughout	Minor editorial and document formatting revisions.	Minor; therefore, have not been summarized.

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
ACQ	Asthma Control Questionnaire
AE	adverse event
AIRQ	Asthma Impairment and Risk Questionnaire
ANCOVA	analysis of covariance
AQLQ(s)+12	Asthma Quality of Life Questionnaire
ATS	American Thoracic Society
AUC_{0-3}	area under the curve 0 to 3 hours
BD	budesonide
BFF	budesonide and formoterol fumarate
BGF	budesonide, glycopyrronium, and formoterol fumarate
BID	twice daily
CFR	Code of Federal Regulation
CI	confidence interval
CCI	CCI
CCI	CCI
COPD	chronic obstructive pulmonary disease
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CTIS	Clinical Trial Information System
DES	Data Entry Site
DPI	Dry Powder Inhaler
ECG	electrocardiogram
eCRF	electronic case report form
eDiary	electronic diary
EQ-5D	European Quality-of-Life-5 Dimensions
ER	emergency room
ERS	European Respiratory Society
EU	Europe
FEF_{25-75}	forced expiratory flow at 25-75%
FEV_1	forced expiratory volume in 1 second
FVC	forced vital capacity
GCP	Good Clinical Practice
GINA	Global Initiative for Asthma
HCRU	healthcare resource utilization

Abbreviation or special term	Explanation
HFA	hydrofluoroalkane
ICE	intercurrent event
ICF	informed consent form
ICH	International Conference of Harmonisation
ICS	inhaled corticosteroid
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IPD	important protocol deviation
IRB	Institutional Review Board
IV	intravenous
IRT	Interactive Response Technology
LABA	long-acting $beta_2$-agonist
LAMA	long-acting muscarinic antagonist
MDI	metered dose inhaler
MedDRA	Medical Dictionary for Regulatory Activities
NI	non-inferiority
NIMP	Non-Investigational Medicinal Product
PEF	peak expiratory flow
pMDI	Pressurized Metered Dose Inhaler
PP	Per Protocol
PRO	patient reported outcome
QTcF	Fridericia-corrected QT interval
RoW	Rest of World
RR	rate ratio
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SoA	Schedule of Activities
TBH	Turbuhaler
US	United States
VAS	visual analogue scale

1 PROTOCOL SUMMARY

1.1 Synopsis

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

Short Title: A 24-Week Efficacy and Safety Study to Assess Budesonide and Formoterol Fumarate Metered Dose Inhaler in Adult and Adolescent Participants with Inadequately Controlled Asthma (VATHOS)

Rationale: This study will evaluate the efficacy and safety of Budesonide and Formoterol Fumarate Metered Dose Inhaler (BFF MDI) 320/9.6 µg BID compared with Budesonide MDI 320 µg, hereinafter referred to as BD MDI, and open-label Symbicort TBH 320/9 µg over 24 weeks. BFF MDI 160/9.6 µg BID is included to evaluate dose response by comparing to BFF MDI 320/9.6 µg BID. The study population will consist of adult and adolescent participants with asthma who remain inadequately controlled, as demonstrated by an ACQ-7 total score ≥ 1.5, despite treatment with medium dose ICS or ICS/LABA. This study is to assess the benefits and safety of BFF MDI on lung function and asthma health-related quality of life.

Objectives and Endpoints

<table>
<tr><th>Objective</th><th colspan="2">Estimand</th></tr>
<tr><td>Primary Endpoint</td><td>CCI [redacted] Approach [a]</td><td>CCI [redacted] Approach [a]</td></tr>
<tr><td rowspan="3">To assess the effect of BFF MDI 320/9.6 µg relative to BD MDI (superiority) on lung function.</td><td colspan="2">• Treatment: Randomized treatment of BFF MDI 320/9.6 µg or BD MDI 320 µg
• Population summary measure: Difference in mean change from baseline</td></tr>
<tr><td>• Endpoint:
– Change from baseline in FEV_1 AUC_{0-3} at Week 24</td><td>• Endpoint:
– CCI [redacted]: Change from baseline in morning pre-dose trough FEV_1 over 24 Weeks
– CCI [redacted]: Change from baseline in morning pre-dose trough FEV_1 over 12 to 24 Weeks</td></tr>
<tr><td colspan="2">• Primary method for handling ICEs:
– Premature discontinuation from study intervention: Treatment policy
– Prolonged exposure to systemic corticosteroids, increased ICS dose for more than 14 days, or depot corticosteroid injection: Treatment policy
– Initiation of new asthma therapy or administration of prohibited medications thought to impact efficacy: Composite (treatment failure) if in conjunction with premature IP discontinuation, else Treatment Policy
• Supportive approach for handling of ICEs uses While on Treatment (ie, data after ICE will not be used) for all ICEs
– Premature discontinuation from study intervention: While on Treatment
– Prolonged exposure to systemic corticosteroids, increased ICS dose for more than 14 days, or depot corticosteroid injection: While on Treatment
– Initiation of new asthma therapy or administration of prohibited medications thought to impact efficacy: While on Treatment</td></tr>
</table>

Objective	Estimand	
CCI only: To assess the effect of BFF MDI 320/9.6 µg relative to Symbicort TBH (non-inferiority) and BFF MDI 320/9.6 µg relative to BD MDI (assay sensitivity for non-inferiority) on lung function.	**N/A**	• **Endpoint:** Change from baseline in morning pre-dose trough FEV1 over 12 to 24 weeks • **Handling ICEs (non-inferiority): Principal Stratum (ie, data after ICE or any IPD that impacts efficacy will not be used)** – Premature discontinuation from study intervention – Prolonged exposure to systemic corticosteroids, increased ICS dose for more than 14 days, or depot corticosteroid injection – Initiation of any new asthma therapy or any additional prohibited medications thought to impact efficacy – Any IPD that impacts efficacy • **Handling ICEs (assay sensitivity):** Same as for primary method for primary endpoint
Secondary Endpoints		
To assess the effect of BFF MDI 320/9.6 µg relative to BD MDI (superiority) and Symbicort TBH (non-inferiority; CCI only) on lung function.	• **Endpoint:** Change from baseline in morning pre-dose trough FEV_1 at Week 24 • **Population summary measure**: Difference in mean change from baseline • **Handling of ICEs:** Same as for primary endpoint	• **Endpoint:** – CCI: Change from baseline in FEV_1 AUC_{0-3} over 24 weeks – CCI: Change from baseline in FEV_1 AUC_{0-3} over 12 to 24 weeks • **Population summary measure**: Difference in mean change from baseline • **Handling of ICEs (superiority):** Same as for primary endpoint • **Handling of ICEs (non-inferiority):** Same as for primary endpoint non-inferiority analysis (ie, Principal Stratum, using only data prior to ICE or IPD that impacts efficacy)

<table>
<tr><th>Objective</th><th colspan="2">Estimand</th></tr>
<tr><td>To assess the effect of BFF MDI 320/9.6 µg relative to BD MDI on asthma exacerbations</td><td>• Endpoint: Severe asthma exacerbation
• Population summary measure: Rate Ratio
• Handling of ICEs: Same as for primary method for the primary endpoint</td><td>N/A</td></tr>
<tr><td>To assess the effect of BFF MDI 320/9.6 µg or BFF 160/9.6 µg relative to BD MDI on asthma exacerbations (combined data from Studies D5982C00005 and D5982C00006).</td><td>• Endpoint: Severe asthma exacerbation
• Population summary measure: Rate Ratio
• Handling of ICEs: Same as for primary endpoint.
• Supportive approach for handling of ICEs uses While on Treatment (ie, data after ICE will not be used) for all ICEs</td><td>N/A</td></tr>
<tr><td rowspan="4">To assess the effect of BFF MDI 320/9.6 µg relative to BD MDI on lung function, symptoms, and PROs.</td><td>• Endpoint: Change from baseline in the mean number of puffs of rescue medication use (puffs/day) over 24 Weeks</td><td>• Endpoint:
– CCI : Change from baseline in the mean number of puffs of rescue medication use (puffs/day) over 24 Weeks
– CCI : Change from baseline in the mean number of puffs of rescue medication use (puffs/day) over 12 to 24 Weeks</td></tr>
<tr><td colspan="2">• Population summary measure: Difference in mean change from baseline
• Handling of ICEs: Same as primary method for primary endpoint</td></tr>
<tr><td>• Endpoint: Percentage of responders in ACQ-7 (≥ 0.5 decrease equals response) at Week 24</td><td>• Endpoint:
– 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</td></tr>
<tr><td colspan="2">• Population Summary Measure: Odds Ratio
• Primary method for handling ICEs:
– Premature discontinuation from study intervention: Treatment policy</td></tr>
</table>

<table>
<tr><th>Objective</th><th colspan="2">Estimand</th></tr>
<tr><td rowspan="3"></td><td colspan="2">
– Prolonged exposure to systemic corticosteroids, increased ICS dose for more than 14 days, or depot corticosteroid injection: Treatment policy
– Initiation of new asthma therapy or administration of prohibited medications thought to impact efficacy: Composite (treatment failure) if in conjunction with premature IP discontinuation, else Treatment Policy
• Supportive Composite
• Premature discontinuation from study intervention:
– For reasons related to global/country situation, data following such ICE will be considered missing and will not be imputed
– For other reasons, non-responder status will be assumed for participants following such ICE (Composite strategy)
• Prolonged exposure to systemic corticosteroids, increased ICS dose for more than 14 days, or depot corticosteroid injection: non-responder status will be assumed for participants following such ICE (Composite strategy)
• Initiation of new asthma therapy or additional prohibited medications thought to impact efficacy: non-responder status will be assumed for participants from (and including) day of first ICE (Composite strategy)
</td></tr>
<tr><td>
• Endpoint: Percentage of responders in ACQ-5 (≥ 0.5 decrease equals response) at Week 24
• Population Summary Measure: Odds Ratio
• Handling of ICEs: As for ACQ-7
</td><td>
• Endpoint:
– 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: As for ACQ-7
</td></tr>
<tr><td>
• Endpoint: Percentage of responders in AQLQ(s)+12 (≥ 0.5 increase equals response) at Week 24
• Population Summary Measure: Odds Ratio
• Handling of ICEs: As for ACQ-7
</td><td>
• Endpoint:
– CCI : Percentage of responders in AQLQ(s)+12 (≥ 0.5 increase equals response) over 24 weeks
</td></tr>
</table>

Objective	Estimand	
		– CCI : Percentage of responders in AQLQ(s)+12 (≥ 0.5 increase equals response) over 12 to 24 weeks • **Population Summary Measure:** Odds Ratio • **Primary approach for handling of ICEs:** As for ACQ-7
	• **Endpoint:** Onset of action on Day 1: Absolute change in FEV_1 at 5 minutes post-dose on Day 1 • **Population Summary Measure:** Difference in mean change from baseline • **Primary handling of ICEs:** Same as primary method for primary endpoint	

[a] Refers to submission strategy with respect to Health Authority responsible for reviewing marketing authorization, not the recruitment location/nationality of the participants.
[b] As defined in the SAP.

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

Overall Design

This is a Phase III randomized, double-blind, active comparison, parallel group, multicenter study comparing BFF MDI 320/9.6 µg to BD MDI 320 µg and open-label Symbicort TBH 320/9 µg in adult and adolescent participants who have asthma which remains inadequately controlled (ACQ-7 total score ≥ 1.5) despite treatment with medium dose ICS or ICS/LABA. Budesonide and Formoterol Fumarate MDI 160/9.6 µg is included in this study to evaluate dose response by comparing to BFF MDI 320/9.6 µg. All doses represent the sum of 2 actuations. All study interventions will be administered BID for 24 weeks.

This study will be conducted at approximately 125 sites worldwide and will randomize approximately 630 adult and adolescent participants.

The study consists of a 3-week screening period, a 24-week treatment period, and a follow-up phone visit 2 weeks after the last study visit. At Visit 4, participants eligible for the study will discontinue run-in BD MDI and be randomized in a CCI scheme to BD, BFF 160 µg or 320 µg, or open-label Symbicort. Randomization will be stratified by baseline asthma treatment (ICS versus ICS/LABA) and age (12 to < 18 years of age versus ≥ 18 years of age).

Disclosure Statement: This is a parallel group study with 4 treatment arms (including an open-label Symbicort arm) that is participant and Investigator blinded.

Number of Participants:

A total of 630 participants will be randomized to one of 4 arms. CCI participants will be randomized to the BFF MDI 160/9.6 µg arm and CCI participants in the BFF MDI 320/9.6 µg, BD MDI 320 µg and Symbicort TBH arms, respectively. The BFF MDI 160/9.6 µg arm will be included to demonstrate a dose response.

Intervention Groups and Duration:

The treatment period is 24 weeks in duration with up to 8 in-clinic visits and 2 telemedicine visits (telephone or video) during screening and treatment. The end of study is defined as the last expected visit/contact of the last participant undergoing the study. Participants who discontinue study intervention will be encouraged to continue in the study and complete all remaining study visits and procedures.

Data Monitoring Committee: No

Statistical Methods

Primary and Key Secondary Efficacy Analysis: Change from baseline in FEV_1 AUC_{0-3} (CCI key secondary endpoint for CCI and CCI and change from baseline in morning pre-dose trough FEV_1 (CCI and CCI key secondary endpoint for CCI will be analyzed using a repeated measures ANCOVA model. The model will include treatment, visit, prior maintenance medication (ICS versus ICS/LABA), and treatment-by-visit interaction as

categorical covariates and baseline trough FEV_1 and percent reversibility as continuous covariates. An unstructured variance-covariance matrix will be used to model the variance-covariance structure. Contrasts will be used to obtain estimates of the treatment differences at Week 24. Two-sided p-values and point estimates with two-sided 95% confidence intervals will be produced for each treatment difference. The model-based statistics for other visits, over 24 Weeks or over 12 to 24 Weeks will also be reported.

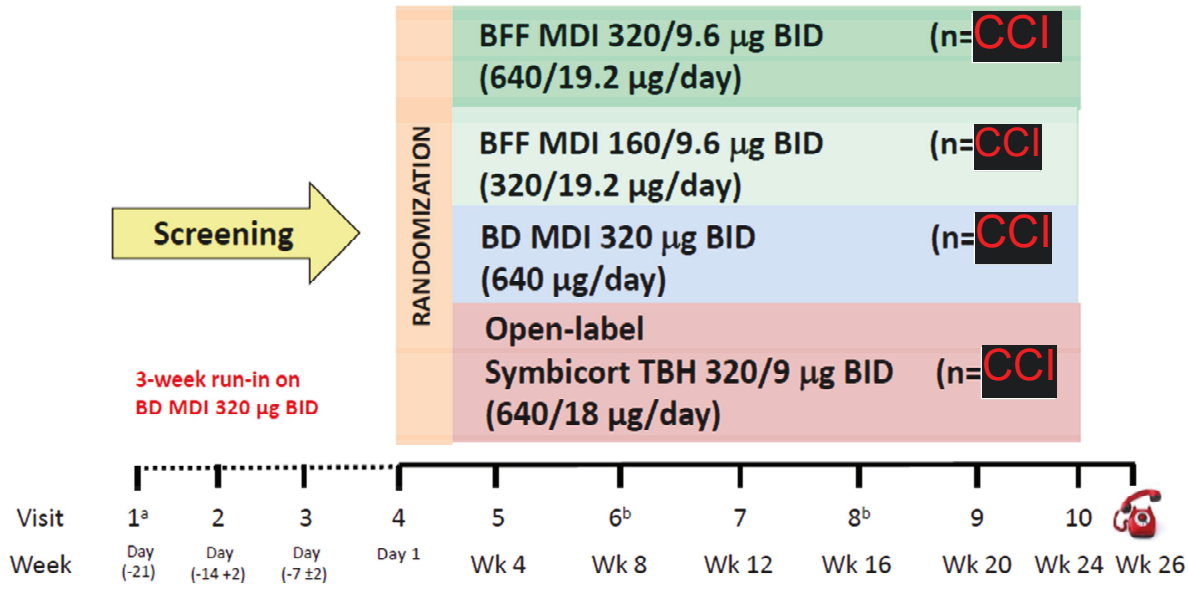
Sample Size: Sample size calculations either assume a While on Treatment or Treatment Policy strategy for ICEs. Using the While on Treatment estimand strategy for ICEs, a sample size of CCI participants per treatment arm will provide probabilities of over 90% to detect a CCI mL difference in the analysis of change from baseline in trough FEV_1 over 24 Weeks between BFF MDI 320/9.6 µg versus BD MDI 320 µg and over 99% power to detect a CCI mL difference in the analysis of change from baseline in FEV_1 AUC_{0-3}. Comparisons are based on a two-sided alpha=CCI test and standard deviation of CCI mL for trough FEV_1 and CCI mL for FEV_1 AUC_{0-3} at each visit with effective SD of CCI mL and CCI mL, respectively, for over 24 weeks. The effective SD for each endpoint over 24 Weeks assumes 2 post-dose visits assessing FEV_1 AUC_{0-3} and 3 post-dose visits assessing trough FEV_1 over the interval and that the correlation among visits is CCI. This sample size assumes that approximately CCI% of randomized participants will have discontinued study intervention prior to Week 12, and CCI% at Week 24.

Using the Treatment Policy estimand strategy for ICEs, a treatment difference of CCI mL for trough FEV_1 is assumed, providing a power at 24 weeks in trough FEV_1 of 84%. Assuming a treatment effect of CCI mL for FEV_1 AUC_{0-3}, the power would be at least 99%.

Populations for Analyses: The following populations for analyses are defined for this study. The Screened set is defined as all participants who sign the ICF. The Randomized set is defined as all participants who are randomized to study intervention. The Efficacy set is defined as all participants who are randomized to study intervention and receive any amount of study intervention and will be analyzed according to the study intervention assigned at randomization, regardless of the actual study intervention received. The Safety set is defined as all participants who are randomized to study intervention and receive any amount of the study intervention and will be analyzed according to the actual study intervention received rather than the randomized study intervention. The PP analysis set is defined as all participants in the Efficacy set without an IPD at the date of randomization.

1.2 Schema

Figure 1 Study Design



[a] Stop daily ICS/LABA or ICS regimen and start run-in BD MDI 320 µg BID.
[b] Telemedicine visit (telephone or video).
BD=Budesonide; BFF=Budesonide and Formoterol Fumarate; BID=twice daily; MDI=metered dose inhaler; TBH= Turbuhaler; Wk=week

1.3 Schedule of Activities

Table 1 Schedule of Activities

	Screening			Treatment Period							Study Intervention Discontinuation or Study Withdrawal	F/U TC	Details in CSP Section or Appendix
Visit[a,b]	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**			
Week	**-3**	**-2**	**-1**	**Rand**	**4**	**8**	**12**	**16**	**20**	**24**			
Study Day[c]	**-21**	**-14 (+ 2)**	**-7 (± 2)**	**1**	**29 (± 2)**	**57 (± 5)**	**85 (± 5)**	**113 (±5)**	**141 (±5)**	**169 (±5)**		**2 weeks (± 2 days) after last dose**	
Telemedicine Visit (telephone or video)						**X**		**X**					
Informed consent/assent[d]	X												Section 4.1, Section 5.1, Appendix A 3
Inclusion/exclusion criteria	X	X	X	X									Section 5.1, Section 5.2
Verify continuing eligibility					X	X	X	X	X	X			Section 7.1
Calculate FEV_1 stability limit	X												Section 5.1
Calculate PEF stability limit				X									Section 8.1.2.5
Routine clinical procedures													
Demography and medical/surgical history	X												Section 8.2.1
Prior/concomitant medication review	X	X	X	X	X	X	X	X	X	X	X	X	Section 6.5
Dispense and collect eDiary	X[e]									X	X		Section 8.1.2
eDiary/peak flow meter training and review	X[e]	X	X	X	X	X	X	X	X	X	X		Section 8.1.2, Section 8.1.2.5
Peak flow meter dispensed/collected	X[e]									X	X		Section 8.1.2.5
Dispense/collect albuterol (as needed)	X[e]	X	X	X	X		X		X	X	X		Section 4.1, Section 6, Section 6.5.1

Table 1 Schedule of Activities

	Screening			Treatment Period							Study Intervention Discontinuation or Study Withdrawal	F/U TC	Details in CSP Section or Appendix
Visit[a,b]	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**			
Week	**-3**	**-2**	**-1**	**Rand**	**4**	**8**	**12**	**16**	**20**	**24**			
Study Day[c]	**-21**	**-14 (+ 2)**	**-7 (± 2)**	**1**	**29 (± 2)**	**57 (± 5)**	**85 (± 5)**	**113 (±5)**	**141 (±5)**	**169 (±5)**		**2 weeks (± 2 days) after last dose**	
Telemedicine Visit (telephone or video)						**X**		**X**					
Reversibility to albuterol		X[f]	X[f]										Table 2, Section 8.1.1.3
Discontinue ICS or ICS/LABA	X[e]												Section 4.1, Section 6
Dispense/collect Run-in BD MDI	X[e]			X									Section 4.1, Section 6
Dispense/collect blinded/open-label study intervention				X	X		X		X	X	X		Section 4.1, Section 6
Routine safety measurements (pre-dose)													
Adverse event assessments[g]	X	X	X	X	X	X	X	X	X	X	X	X	Section 8.3, Appendix B
Asthma exacerbations assessment	X	X	X	X	X	X	X	X	X	X	X	X	Section 8.2.1, Section 8.2.7
Pregnancy testing[g]	X	X	X	X	X		X		X	X	X		Section 5.1, Section 8.3.10
Safety laboratory assessments (blood)	X									X	X		Section 8.2.6
Physical examination	X			X						X	X		Section 8.2.2
Height and weight	X									X	X		Section 8.2.3
Vital signs (blood pressure and pulse)	X			X						X	X		Section 8.2.4
12-lead ECG	X												Section 8.2.5
Genomics Initiative, optional exploratory genetic sample				X									Section 8.7, Appendix C

Table 1 Schedule of Activities

	Screening			Treatment Period							Study Intervention Discontinuation or Study Withdrawal	F/U TC	Details in CSP Section or Appendix
Visit[a,b]	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**			
Week	**-3**	**-2**	**-1**	**Rand**	**4**	**8**	**12**	**16**	**20**	**24**			
Study Day[c]	**-21**	**-14 (+ 2)**	**-7 (± 2)**	**1**	**29 (± 2)**	**57 (± 5)**	**85 (± 5)**	**113 (±5)**	**141 (±5)**	**169 (±5)**		**2 weeks (± 2 days) after last dose**	
Telemedicine Visit (telephone or video)						**X**		**X**					
Efficacy measurements[h]													
Serial spirometry[i]				X			X			X	X		Table 2, Section 8.1.1
Pre-dose spirometry[i]	X[j]	X	X	X	X		X		X	X	X		Table 2, Section 8.1.1
ACQ (pre-dose)	X			X	X		X		X	X	X		Section 8.1.2.7
AQLQ(s)+12 (pre-dose)				X	X		X		X	X	X		Section 8.1.2.7
EQ-5D (pre-dose)				X	X		X		X	X	X		Section 8.1.2.7
AIRQ (pre-dose)	X			X			X			X	X		Section 8.1.2.7
Healthcare resource utilization			X		X		X		X	X	X		Section 8.8
Study intervention administration													
Check of inhalation device technique and training	X[e]	X	X	X	X		X		X				Section 6
Administer Run-in BD MDI in clinic[j]	X	X	X										Section 4.1, Section 6
Administer blinded/open-label study intervention in clinic[k]				X	X[l]		X[l]		X	X			Section 4.1, Section 6

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

[b] Sites should call participants one to 2 days before each scheduled visit to remind the participant of the visit and the required medication washouts (6 hours for short-acting bronchodilators and 12 hours for run-in BD MDI and blinded/open-label study intervention). Participants will be required to return to the clinic at approximately the same time ± 1 hour as Visit 1 throughout the study for all in-clinic visits. For all visits after Visit 1, if albuterol and study intervention have not been withheld for the specified timeframes, the visit should be rescheduled and conducted within the specified visit window.

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

[d] Informed consent form may be signed at or prior to Visit 1.
[e] At Visit 1, issue/train participants on eDiary/peak flow meter use, discontinue ICS or ICS/LABA, and dispense albuterol and run-in BD MDI **only** after the participant has been found eligible to proceed to Visit 2. Should there be any concern that the ICS or ICS/LABA was taken prior to Visit 1, this visit can be rescheduled within 2 days.
[f] If reversibility criterion is not met at Visit 2, participants may continue to Visit 3. Reversibility criterion must be met either in the 12 months prior to Visit 1 or at Visit 2 or Visit 3, otherwise the participant will be screen failed.
[g] For all screen failures, an assessment of AEs and highly sensitive urine pregnancy testing (for women of childbearing potential) must be performed within 7 days of the screen failure date.
[h] The suggested order of assessments is vital signs, AE/SAE assessments, -60-minute spirometry, PRO questionnaires, -30-minute spirometry, ECG, blood draw, and then study intervention administration. **Spirometry MUST be performed in accordance with the specified timing.**
[i] All pre-dose (trough) spirometry will be required to be collected in the morning (0800 ± 2 hours).
[j] Participants who have not withheld asthma medications prior to Visit 1 and failed spirometry inclusion criteria at Visit 1 should return to the clinic to repeat spirometry testing (or have the spirometry postponed if it is known in advance that the participant has not washed out) within 2 days. If repeat spirometry fails to meet the inclusion criteria, then the participant must be screen failed.
[k] All dosing occurring during study visits must occur prior to 1000 (+ 1 hour allowance).
[l] Sufficient blinded/open-label study intervention should be provided to account for next physical visit.

Abbreviations: ACQ=Asthma Control Questionnaire; AEs=adverse events; AIRQ=Asthma Impairment and Risk Questionnaire; AQLQ(s)+12=Asthma Quality of Life Questionnaire for 12 years and older; BD=budesonide; CSP=Clinical Study Protocol; ECG=electrocardiogram; eDiary=electronic diary; EQ-5D=European Quality of Life-5 Dimensions; F/U=follow-up; ICS/LABA=inhaled corticosteroid/long-acting beta$_2$-agonist; MDI=metered dose inhaler; PEF=peak expiratory flow; PRO=Patient Reported Outcome; Rand=randomization; SAE=serious adverse event; TC=telephone call

Table 2 provides timing of specific assessments. Ensure pre-dose spirometry assessments are conducted as close to the specified timepoints as possible. All study procedures will be conducted prior to dosing, with the exception of post-dose spirometry.

Table 2 Timing of Spirometry Measurements

Visits	Pre-dose		Post-dose					
	Minutes		Minutes			Hours		
	-60 (±10)	-30 (±10)	5 (±2)	15 (±5)	30 (±5)	1 (±10 min)	2 (±10 min)	3 (±10 min)
1, 5, and 9	X	X						
2 (reversibility to albuterol) and 3 (reversibility to albuterol, if needed)	X	X			X	X[a]		
4	X	X	X	X	X	X	X	X
7 and 10, or Study Intervention Discontinuation/Withdrawal	X	X		X	X	X	X	X

[a] For reversibility, 1-hour post-dose spirometry may be assessed if not reversible at 30 minutes post-dose

2 INTRODUCTION

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

The test formulation to be evaluated in this study is an MDI with a CCI containing a fixed-dose combination of budesonide (an ICS) and formoterol fumarate (a LABA).

2.1 Study Rationale

Budesonide and Formoterol Fumarate MDI, hereinafter referred to as BFF MDI, is being developed for use in the treatment of asthma. Per GINA guidelines [GINA 2020] the recommended stepwise treatment approach for patients with asthma who have risk factors for asthma exacerbations or asthma symptoms at least several times a month, is to initiate treatment with low dose ICS (GINA Step 2). If a patient continues to be symptomatic, the preferred treatment escalation is to a low dose ICS/LABA (GINA Step 3), the alternate treatment option being a medium dose ICS controller. Subsequently, this treatment can be further increased to medium dose ICS/LABA (GINA Step 4). These guidelines provide the framework for the comparisons in this study between medium dose ICS/LABA and a medium dose ICS.

This study will evaluate the efficacy and safety of BFF MDI 320/9.6 µg BID compared with Budesonide MDI 320 µg, hereinafter referred to as BD MDI, and open-label Symbicort TBH 320/9 µg over 24 weeks. BFF MDI 160/9.6 µg BID is also included to evaluate dose response. The study population will consist of adult and adolescent participants with asthma who remain inadequately controlled, as demonstrated by an ACQ-7 total score ≥ 1.5, despite treatment with medium dose ICS or ICS/LABA. This study is to assess the benefits and safety of BFF MDI on lung function and asthma health-related quality of life.

2.2 Background

Asthma is a heterogeneous disease that is characterized by chronic airway inflammation and bronchial hyperreactivity. It is defined by a history of respiratory symptoms such as wheeze, shortness of breath, chest tightness, and cough that vary over time and in intensity, together with variable expiratory airflow obstruction. The variations in symptoms and airflow

obstruction are often triggered by factors such as exercise, allergen or irritant exposure, changes in weather, noxious fumes, or viral respiratory infections. These responses are more likely when asthma is uncontrolled and, in this scenario, deteriorations can be associated with significant risk [GINA 2020].

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

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

Dual combinations of ICS (low or medium dose) and a LABA can provide important treatment options in asthma, as described in Section 2.1.

A detailed description of the chemistry, pharmacology, efficacy, and safety of BD MDI and BFF MDI can be found in the Budesonide, Glycopyrronium, and Formoterol Fumarate (BGF) Investigator's Brochure and for Symbicort TBH can be found in the Symbicort TBH Investigator's Brochure. Note: Information pertaining to Glycopyrronium in the BGF Investigator's Brochure is not relevant for this study.

2.3 Benefit/Risk Assessment

Budesonide and formoterol fumarate are approved in many countries worldwide in multiple formulations for different indications, such as the treatment of COPD and asthma.

In order to evaluate the clinical benefit/risk balance, efficacy and safety data are available from Phase I, II, and III studies (AstraZeneca COPD/asthma programs) evaluating data with budesonide and formoterol fumarate as single agents or in dual combinations. Budesonide and formoterol have been well tolerated with favorable safety profiles identified in studies to date.

Potential risks with BFF MDI will be mitigated by the selected inclusion/exclusion criteria and continuous monitoring of safety data during the study. Benefits of BFF MDI over BD

MDI in this study are expected to include an improvement in lung function and asthma symptoms.

More detailed information about the known and expected benefits and potential risks of BFF MDI, BD MDI, and Symbicort TBH are provided in the Investigator's Brochures, as detailed above.

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

3 OBJECTIVES AND ENDPOINTS

For the following estimands, the estimand population is adults and adolescents with inadequately controlled asthma (symptomatic on medium dose ICS or ICS/LABA), with the exception of the estimand used for pooled analyses of severe asthma exacerbations which also includes the population from Study D5982C00005 on low dose ICS or ICS/LABA.

Table 3 Objectives and Endpoints

<table>
<tr><th>Objective</th><th colspan="2">Estimand</th></tr>
<tr><td>Primary</td><td>CCI Approach [a]</td><td>CCI Approach [a]</td></tr>
<tr><td rowspan="3">To assess the effect of BFF MDI 320/9.6 µg relative to BD MDI (superiority) on lung function.</td><td colspan="2">• Treatment: Randomized treatment of BFF MDI 320/9.6 µg or BD MDI 320 µg
• Population summary measure: Difference in mean change from baseline</td></tr>
<tr><td>• Endpoint: Change from baseline in FEV_1 AUC_{0-3} at Week 24</td><td>• Endpoint:
– CCI : Change from baseline in morning pre-dose trough FEV_1 over 24 weeks
– CCI : Change from baseline in morning pre-dose trough FEV_1 over 12 to 24 weeks</td></tr>
<tr><td colspan="2">• Primary method for handling ICEs:
– Premature discontinuation from study intervention: Treatment policy
– Prolonged exposure to systemic corticosteroids, increased ICS dose for more than 14 days, or depot corticosteroid injection: Treatment policy
– Initiation of new asthma therapy or administration of prohibited medications thought to impact efficacy: Composite (treatment failure) if in conjunction with premature IP discontinuation, else Treatment Policy
• Supportive approach for handling of ICEs uses While on Treatment (ie, data after ICE will not be used) for all ICEs
– Premature discontinuation from study intervention: While on Treatment
– Prolonged exposure to systemic corticosteroids, increased ICS dose for more than 14 days, or depot corticosteroid injection: While on Treatment
– Initiation of new asthma therapy or administration of prohibited medications thought to impact efficacy: While on Treatment</td></tr>
</table>

Table 3 Objectives and Endpoints

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

Table 3 Objectives and Endpoints

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

Table 3 Objectives and Endpoints

<table>
<tr><td></td><td colspan="2">

- **Population Summary Measure:** Odds Ratio
- **Primary method for handling ICEs:**
  - Premature discontinuation from study intervention: Treatment policy
  - Prolonged exposure to systemic corticosteroids, increased ICS dose for more than 14 days, or depot corticosteroid injection: Treatment policy
  - Initiation of new asthma therapy or administration of prohibited medications thought to impact efficacy: Composite (treatment failure) if in conjunction with premature IP discontinuation, else Treatment Policy
- **Supportive Composite**
- Premature discontinuation from study intervention:
  - For reasons related to global/country situation, data following such ICE will be considered missing and will not be imputed
  - For other reasons, non-responder status will be assumed for participants following such ICE (Composite strategy)
- Prolonged exposure to systemic corticosteroids, increased ICS dose for more than 14 days, or depot corticosteroid injection: non-responder status will be assumed for participants following such ICE (Composite strategy)
- Initiation of new asthma therapy or additional prohibited medications thought to impact efficacy: non-responder status will be assumed for participants from (and including) day of first ICE (Composite strategy)

</td></tr>
<tr><td></td><td>

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

</td><td>

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

</td></tr>
</table>

Table 3 Objectives and Endpoints

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

Table 3 Objectives and Endpoints

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

Table 3 Objectives and Endpoints

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

Table 3 Objectives and Endpoints

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

Table 3 Objectives and Endpoints

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

[a] Refers to submission strategy with respect to Health Authority responsible for reviewing marketing authorization, not the recruitment location/nationality of the participants.
[b] As defined in the SAP.

Intercurrent Events

- Discontinuation from randomized study intervention (may be further broken down for lack of efficacy or for tolerability/other as well as reasons related to global/country situation).
- Prolonged exposure to systemic corticosteroids or increased ICS for more than 14 days or having received depot corticosteroid injection. Furthermore, use of systemic corticosteroids or increased ICS for 14 days or less will also be considered as an ICE for lung function assessments during this temporary additional use.

- Initiation of any new asthma therapy or administration of prohibited medications thought to impact efficacy, including biological therapy/monoclonal antibodies, LABA, LAMA, or LTRA (further details provided in the SAP).
- For the Principal Stratum strategy, in addition to the above ICEs, any IPD that impacts efficacy.

4 STUDY DESIGN

4.1 Overall Design

This is a Phase III randomized, double-blind, active comparator, parallel group, multicenter study comparing BFF MDI 320/9.6 µg to BD MDI 320 µg and open-label Symbicort TBH 320/9 µg in adult and adolescent participants who have asthma which remains inadequately controlled (ACQ-7 total score ≥ 1.5) despite treatment with medium dose ICS or ICS/LABA. Budesonide and Formoterol Fumarate MDI 160/9.6 µg is included in this study to evaluate dose response by comparing to BFF MDI 320/9.6 µg. Symbicort TBH is included as a marketed comparator for regions that require this. All study interventions will be administered as 2 actuations BID for 24 weeks.

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

This study will be conducted at approximately 125 sites worldwide and will randomize approximately 630 adult and adolescent participants.

At Visit 1, participants (or the parents or legal guardians of participants 12 to < 18 years of age) will sign an ICF and participants 12 to < 18 years of age will sign an assent form. All participants must be taking a stable daily medium dose ICS or a combination of ICS/LABA (see Table 5) for at least 8 weeks prior to Visit 1. Participants who have not withheld asthma medications prior to Visit 1 and failed spirometry inclusion criteria at Visit 1 should return to the clinic to repeat spirometry testing within 2 days. If the repeat spirometry again fails to meet the inclusion criteria, the participant must be screen failed. After meeting all eligibility criteria, participants will discontinue their medium dose ICS or ICS/LABA at Visit 1 and initiate run-in BD MDI 320 µg taken BID until the evening prior to Visit 4 (randomization), when run-in BD MDI will be discontinued. All participants will receive albuterol sulfate inhalation aerosol or salbutamol sulfate inhalation aerosol, hereinafter referred to as albuterol, at Visit 1 for rescue use during the study (see Section 6.5.1).

Participants will return for Visit 2 after adequate washout of prohibited asthma medications. There will be a minimum of 7 days between Visit 1 and Visit 2. Participants must demonstrate a pre-bronchodilator FEV_1 of ≤ 90% of predicted normal value at Visits 1, 2, and 3, a pre-dose FEV_1 of 50% to 90% at Visit 4 (pre-randomization), and an ACQ-7 total score of ≥ 1.5 at Visit 1 and Visit 4 (pre-randomization). All participants must be assessed for reversibility to albuterol at Visit 2 (and Visit 3 if reversibility is not demonstrated at Visit 2; see Section 5.1 and Section 8.1.1.3) to provide reversibility baseline data for characterization. However, participants who have historically documented reversibility within 12 months of Visit 1 can still be randomized to the study even if they fail reversibility testing at Visits 2 and 3.

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

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

Participants will use an eDiary BID (morning and evening) to record albuterol use, asthma symptom scores, PEF, and confirmation of inhalations of run-in BD MDI during the Screening Period (see Section 8.1.2.2). Compliance of ≥ 70% during screening (defined as completing the daily eDiary and answering "Yes" to taking 2 puffs for run-in BD MDI for any 10 mornings and any 10 evenings in the last 14 days prior to randomization) must be demonstrated in order for a participant to be randomized to study intervention at Visit 4 (see Section 8.1.2.1).

At Visit 4, participants eligible for the study will discontinue run-in BD MDI and be randomized in a CCI scheme to BD, BFF 160 µg or 320 µg, or open-label Symbicort (see Figure 1 and Section 6.1).

Randomization will be stratified by baseline asthma treatment (ICS versus ICS/LABA) and age (12 to < 18 years of age versus ≥ 18 years of age).

Following randomization, participants will enter the Treatment Period and undergo 4 additional in-clinic treatment visits and 2 telemedicine visits (telephone or video) over a treatment period of 24 weeks. Participants will record daily asthma symptom scores, albuterol use, PEF, and study intervention use as well as PRO questionnaire responses as described in the SoA (Table 1) and Section 8.1.2.

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

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

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

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

Where allowable by local health authorities, ethics committees, healthcare provider guidelines (eg, hospital policies), or local government, if study participants cannot attend the visits at the study site due to significant regional disruption, evolving global pandemic or similar natural disaster, telemedicine sessions (video conference or telephone call) will be implemented for all participants currently randomized in the study and study intervention supply maintained for the participant given this comprises their asthma controller medications. These sessions should include all SoA (Table 1) assessments which can be performed virtually, to collect safety information as a minimum requirement. Assessments in the SoA (Table 1) which cannot be performed virtually should be captured at the next opportunity for an in-clinic visit, provided the Investigator assesses the participant to be safe to continue in the study. Alternatively, if the Investigator considers it appropriate for the participant to stop study intervention and have alternative asthma controller medications, arrangements for this will need to be made by the study staff, in accordance with local regulatory requirements and guidance. All participants who stop study intervention and are prescribed alternative asthma controller medications will require follow-up with a telephone call 2 weeks following the cessation of study intervention to assess safety.

If an emergent event results in centralized laboratory testing of samples not being available, AstraZeneca may decide to use local laboratories.

Visits 1 through 4 must be conducted at the study site. If mitigation practices are implemented at a site, until agreed otherwise with AstraZeneca, no further participants can be enrolled and all participants who are currently in Screening (Visits 1 through 4), must be screen failed (see Section 5.4).

4.2.1 Completing Participant Numbers to Maintain Study Integrity

In the event of a natural disaster or civil or public health crisis that prevents participants from attending on-site visits (as described in Section 4.2), participants will be followed remotely to collect symptomatic, PRO, and safety assessments for the event's duration; however, it will not be possible to collect spirometry assessments for the primary endpoint during this time. Additionally, owing to the likelihood of some participant drop-out during the event and to maintain study integrity which requires sufficient lung function data at Week 24 by completing participants, more participants may be required and subsequently enrolled. Additional analytic and operational approaches may be considered to address data limitations caused by the crisis. If this occurs, additional details may be included in the SAP.

4.3 Scientific Rationale for Study Design

The product being tested in this study, BFF MDI 320/9.6 µg BID, are being compared with BD MDI 320 µg BID and open-label Symbicort TBH 320/9 µg BID. BFF MDI 160/9.6 µg BID is included to evaluate dose response by comparing to BFF MDI 320/9.6 µg BID. Per GINA guidelines, the goal of the stepwise approach to treatment in asthma is to optimize lung function and improve control of asthma symptoms [GINA 2020]. Therapy with an ICS for asthma is well established in clinical practice and the inclusion of a LABA has demonstrated additional benefit in managing patients with poorly controlled asthma [GINA 2020]. The addition of a LABA is expected to improve lung function and health-related quality of life in this population. Inclusion of 2 doses of BFF MDI may demonstrate a dose ordering effect of BD when added to formoterol fumarate. The development of a dual combination product also provides the convenience of a single inhaler for patients, increasing the likelihood of adherence. The length of this study will allow safety to be captured and provide adequate time to observe lung function changes after 24 weeks of treatment.

4.3.1 Participant Input into Design

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

4.3.1.1 Coordinator Input

Four face-to-face coordinator meetings involving 25 coordinators from 17 countries were conducted. Coordinator perspectives and insights were collected around consenting, eligibility, requesting medical records, screening, randomization, safety/efficacy measures, study intervention, technology, retention, and data. The following changes to the protocol were made based on coordinator input:

- Reduced the number of serial spirometry assessments and added telemedicine visits to limit number of in-clinic visits required

- Broadened the window for performing morning assessments
- Added vaping to smoking history eligibility criteria
- Refined corticosteroid eligibility criteria to include oral and IV use

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

4.3.1.2 Participant Input

Two virtual meetings were conducted with 7 asthma patients from 4 countries. Insights were collected around exacerbations and the ability to collect medical records to support eligibility and/or an on-study event, eDiary burden, and virtual study visits. Patients indicated that ensuring direct lines of communication with site staff, allowing "in-clinic" assessments to be done at home, utilizing a personal device to collect data, and explaining why PROs are needed and how PRO data will be used, is important to them. These insights will be considered and when possible, incorporated into the protocol, Investigator, site and PRO eDiary training.

4.4 Justification for Dose

The budesonide doses of 320 µg and 160 µg administered as 2 puffs BID (total daily doses of 640 µg and 320 µg, respectively) being evaluated as part of BFF MDI are considered medium and low ICS doses within ICS/LABA combinations by GINA. The GINA treatment guidelines advocate the addition of a LABA to ICS, such as BFF MDI, as a step-up therapy to asthma patients who are inadequately controlled on a low or medium dose ICS alone [GINA 2020]. The efficacy and safety profile of BD, as part of BFF MDI 320/9.6 µg and BGF MDI 320/14.4/9.6 µg, has been established in the Phase III COPD program and is part of the approved BGF MDI dose submitted globally. The BD doses included in this study are the same doses, and the formoterol fumarate dose very similar, to those in Symbicort, a combination ICS/LABA containing the same molecules, that has been approved globally in asthma at an equivalent dose of 160/9 µg and 320/9 µg (both administered as 2 inhalations) BID. Subsequently, there is a wealth of safety and efficacy data to support the doses included in this study.

The formoterol fumarate dose of 9.6 µg administered as 2 puffs BID (total daily dose of 19.2 µg) is being evaluated as part of the current BGF MDI Phase III program in asthma. The efficacy and safety profile of formoterol fumarate, as part of Glycopyrronium and Formoterol Fumarate MDI 14.4/9.6 µg and BGF MDI 320/14.4/9.6 µg, has been established in the Phase III COPD programs and is part of the approved doses of Bevespi Aerosphere and Breztri/Trixeo Aerosphere. The formoterol fumarate dose of 9 µg in Symbicort TBH has a well-established safety and efficacy profile and is comparable to the formoterol fumarate dose

of 9.6 µg in the BGF MDI and BFF MDI treatment arms included in the BGF asthma Phase III program.

4.5 End of Study Definition

For the purpose of Clinical Trial Transparency, the definition of the end of the study differs under FDA and EU regulatory requirements:

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

Food and Drug Administration requirements define 2 completion dates:

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

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

A participant is considered to have completed the study when he/she has completed his/her last scheduled procedure shown in the SoA (Table 1).

Participants who discontinue study intervention will be encouraged to continue in the study and complete all remaining study visits and procedures.

5 STUDY POPULATION

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

5.1 Inclusion Criteria

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

Age

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

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

Type of Participant and Disease Characteristics

2. Participants who have a documented history of physician-diagnosed asthma ≥ 6 months prior to Visit 1, according to GINA guidelines [GINA 2020]. Healthcare records for one year prior to Visit 1 must be provided for adolescent participants (12 to < 18 years of age) to ensure consistent evaluation and follow-up of treatment in those participants.
3. Participants who have been regularly using a stable daily ICS or an ICS/LABA regimen (including a stable ICS dose), with the ICS doses allowed in Table 5, for at least 8 weeks prior to Visit 1.
4. ACQ-7 total score ≥ 1.5 at Visits 1 and 4.
5. Pre-bronchodilator/pre-dose FEV_1 < 90% predicted normal value at Visits 1, 2 and 3, and a pre-dose FEV_1 of 50% to 90% at Visit 4 (pre-randomization).

   Note: Participants who have not withheld asthma medications prior to Visit 1 and failed spirometry testing at Visit 1 should return to the clinic to repeat spirometry testing within 2 days. If repeat spirometry fails, then participants must be screen failed.
6. Reversibility to albuterol, defined as a post-albuterol increase in FEV_1 of ≥ 12% and ≥ 200 mL for participants ≥ 18 years of age OR a post-albuterol increase in FEV_1 of ≥ 12% for participants 12 to < 18 years of age, either in the 12 months prior to Visit 1 or at Visit 2 or Visit 3.

   Note: Even if there is documented history of reversibility, all participants must be assessed for reversibility at Visit 2 (and Visit 3, if reversibility is not demonstrated at Visit 2) to evaluate presence of reversibility during screening.
7. A pre-bronchodilator/pre-dose FEV_1 at Visits 2, 3, and 4 that has not changed 20% or more (increase or decrease) from the pre-bronchodilator/pre-dose FEV_1 recorded at the previous visit.
8. Asthma stability during run-in based on Investigator discretion using the symptom worsening assessment defined in Section 8.1.2.8 as a guideline.
9. Willing and, in the opinion of the Investigator, able to adjust current asthma therapy, as required by the protocol.

10. Demonstrate acceptable MDI administration technique.

    Note: Historical use of a spacer device within the 8 weeks prior to and/or during the Screening and Randomized Treatment Periods is not permitted.

11. eDiary compliance ≥ 70% during screening, defined as completing the daily eDiary and answering "Yes" to taking 2 puffs of run-in BD MDI for any 10 mornings and 10 evenings in the last 14 days prior to randomization.

Weight

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

Sex

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

- Female participants: Women not of childbearing potential are defined as women who are either permanently sterilized (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy), or who are postmenopausal. Women will be considered postmenopausal if they have been amenorrhoeic for 12 months prior to the planned date of randomization without an alternative medical cause. The following age-specific requirements apply:
  - Women < 50 years old would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatment and follicle stimulating hormone levels in the postmenopausal range.
  - Women ≥ 50 years old would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of all exogenous hormonal treatment.
- Female participants of childbearing potential must use a highly effective form of birth control. A highly effective method of contraception is defined as one that can achieve a failure rate of less than 1% per year when used consistently and correctly. Women of childbearing potential who are sexually active with a non-sterilized male partner must agree to use a highly effective method of birth control, as defined below, from enrollment throughout the study and until at least 16 weeks after last dose of study intervention. Cessation of contraception after this point should be discussed with a responsible physician. All women of childbearing potential must have a negative highly sensitive urine (at all clinic visits). Adolescent participants should be counselled appropriately by the Investigator.
- Highly effective birth control methods are listed below:
  - Sexual abstinence defined as complete abstinence from intercourse when it is the preferred and usual lifestyle of the participant (however, periodic abstinence eg,

calendar, ovulation, symptothermal, post-ovulation methods, declaration of abstinence for the duration of exposure to study intervention, and withdrawal are not acceptable methods of contraception)

- Contraceptive subdermal implant
- Intrauterine device or intrauterine system
- Oral contraceptive (combined or progesterone only)
- Injectable progestogen [Hatcher et al 2011]
- Contraceptive vaginal ring [Hatcher et al 2011]
- Percutaneous contraceptive patches [Hatcher et al 2011]
- Male partner sterilization with documentation of azoospermia prior to the female participant's entry into the study, and this male is the sole partner for that participant [Hatcher et al 2011]. The documentation on male sterility can come from the site personnel's review of participant's medical records, medical examination and/or semen analysis or medical history interview provided by her or her partner.
- Bilateral tubal ligation

Informed Consent

14. Capable of giving signed informed consent as described in Appendix A which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.
15. Provision of signed and dated written Optional Genomics Initiative Research Information consent form prior to collection of samples for Optional Genomics Initiative Research that supports Genomic Initiative.

5.2 Exclusion Criteria

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

Medical Conditions

1. Life-threatening asthma as defined as a history of significant asthma episode(s) requiring intubation associated with hypercapnia, respiratory arrest, hypoxic seizures, or asthma-related syncopal episode(s).
2. Any respiratory infection or asthma exacerbation treated with systemic corticosteroids and/or additional ICS treatment in the 8 weeks prior to Visit 1 and throughout the Screening Period.
3. Hospitalization for asthma within 8 weeks of Visit 1.
4. Historical or current evidence of a clinically significant disease including, but not limited to: cardiovascular, hepatic, renal, hematological, neurological, endocrine, gastrointestinal, or pulmonary (eg, active tuberculosis, bronchiectasis, pulmonary eosinophilic syndromes,

and COPD). Significant is defined as any disease that, in the opinion of the Investigator, would put the safety of the participant at risk through participation, or that could affect the efficacy or safety analysis.

5. Known history of drug or alcohol abuse within 12 months of Visit 1.
6. Unresectable cancer that has not been in complete remission for at least 5 years prior to Visit 1.

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

Prior/Concomitant Therapy

7. Participation in another clinical study with a study intervention administered in the last 30 days or 5 half-lives, whichever is longer. Any other study intervention that is not identified in this protocol is prohibited for use during study duration.
8. Previous or current randomization into studies within the AEROSPHERE program including KALOS, LOGOS, VATHOS, LITHOS, or any glycopyrronium studies (PT001).
9. Use of a nebulizer or a home nebulizer for receiving asthma medications.

   Note: Acute use of a nebulizer for an asthma exacerbation during hospitalization is allowed as long as there is no occurrence within 8 weeks of Visit 1.
10. Do not meet the stable dosing period prior to Visit 1 (see Table 6) or unable to abstain from protocol-defined prohibited medications during Screening and Treatment Periods (see Table 7 and Table 8).
11. Receipt of COVID-19 vaccine (regardless of vaccine delivery platform, eg, vector, lipid nanoparticle) < 7 days prior to Visit 1 (from last vaccination or booster dose).
12. Participants with known hypersensitivity to $beta_2$-agonists, corticosteroids, or any component of the MDI.

Diagnostic Assessments

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

    Note: Participants with ECG QTcF > 480 msec will be excluded. Participants with high degree atrioventricular block II or III, or with sinus node dysfunction with clinically significant pauses who do not have a pacemaker will also be excluded.

Other Exclusions

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

15. Planned hospitalization during the study.
16. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site).
17. Study Investigators, sub-Investigators, coordinators, and their employees or immediate family members.
18. Judgment by the Investigator that the participant is unlikely to comply with study procedures, restrictions, and requirements.
19. For women only – currently pregnant (confirmed with positive highly sensitive urine pregnancy test), breast-feeding, or planned pregnancy during the study or not using acceptable contraception measures, as judged by the Investigator.

5.3 Lifestyle Considerations

5.3.1 Caffeine, Tobacco, and Alcohol

Participants will abstain from ingesting caffeine- or xanthine-containing products (eg, coffee, tea, cola drinks, and chocolate) for 6 hours before and for the duration of each in-clinic study visit. Use of tobacco products or vaping will not be allowed from 6 months prior to Visit 1 until after the final follow-up visit. Participants will abstain from consuming any intoxicants within 24 hours before spirometry testing.

5.3.2 Illicit Drugs or Drugs of Abuse

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

5.4 Screen Failures

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

Rescreening is allowed for screen failure reason(s) that are transient (including, but not limited to, pre-defined time period requirements, respiratory tract infection not treated with systemic corticosteroids, equipment/procedure failure [eg, problems with the eDiary impacting availability of data], required study documentation, or unforeseen personal reasons).

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

Participants may not be rescreened due to failure to meet the study requirements of pre-bronchodilator FEV_1 (including stability) and ACQ score during the Screening Period.

Rescreened participants will be assigned the same participant number as for the initial screening. Rescreened participants will sign a new ICF. All procedures required for the screening/run-in periods, starting at Visit 1, should be repeated. Rescreening should be documented so that its effect on the study results, if any, can be assessed.

If a participant is rescreened and fails for any reason other than pre-bronchodilator FEV_1 and ACQ score, another rescreening is allowed after a 3-month period.

For all participants who are screen failures, an AE assessment and highly sensitive urine pregnancy test (for women of childbearing potential) must be performed within 7 days of the screen failure date.

6 STUDY INTERVENTION

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

Placebo MDI will be dispensed at Visit 1 and empty TBH devices will be dispensed at Visit 4 for in-clinic training purposes. Run-in BD MDI will be provided during the Screening Period.

Instructions for use of Investigational Products will be provided.

6.1 Study Intervention(s) Administered

6.1.1 Investigational Products

Table 4 Investigational/Non-Investigational Products

	BFF MDI 320/9.6 µg	BFF MDI 160/9.6 µg	Run-in BD/Blinded BD MDI 320 µg	Open-label Budesonide/ formoterol fumarate TBH 320/9 µg	Albuterol sulfate inhalation aerosol (CCI)/Salbutamol sulfate inhalation aerosol (CCI)
Intervention Name	Budesonide/formoterol fumarate pressurized inhalation suspension, CCI device	Budesonide/formoterol fumarate pressurized inhalation suspension, CCI device	Budesonide pressurized inhalation suspension, CCI device	Symbicort®	Albuterol/salbutamol
Type	Combination Product	Combination Product	Combination Product	Combination Product	Combination Product
Dose Formulation	Inhaler	Inhaler	Inhaler	Inhaler	Inhaler
Unit Dose Strength (Delivered Dose)	160/4.8 µg per actuation	80/4.8 µg per actuation	160 µg per actuation	160/4.5 µg per actuation	90 µg per actuation (CCI) 100 µg per actuation (CCI)
Dosage Level(s)	2 inhalations BID	2 inhalations BID	2 inhalations BID	2 inhalations BID	2 inhalations as needed; as directed for reversibility testing at Visits 2 or 3
Total Daily Dose	640/19.2 µg	320/19.2 µg	640 µg	640/18 µg	N/A
Route of Administration	Oral inhalation	Oral inhalation	Oral inhalation	Oral inhalation	Oral inhalation
Use	Experimental	Experimental	Experimental/ Comparator	Open-label Comparator	Rescue medication/ reversibility testing
IMP and NIMP	IMP	IMP	IMP	IMP	NIMP

Table 4 Investigational/Non-Investigational Products

	BFF MDI 320/9.6 µg	BFF MDI 160/9.6 µg	Run-in BD/Blinded BD MDI 320 µg	Open-label Budesonide/ formoterol fumarate TBH 320/9 µg	Albuterol sulfate inhalation aerosol (CCI)/Salbutamol sulfate inhalation aerosol (CCI)
Sourcing	Provided centrally by AstraZeneca	Provided centrally by AstraZeneca	Provided centrally by AstraZeneca	Provided centrally by AstraZeneca	Provided locally by the study site, subsidiary, or designee.
Packaging and Labelling	Study intervention will be provided in an MDI. Each MDI will be labeled as required per country requirement	Study intervention will be provided in an MDI. Each MDI will be labeled as required per country requirement	Study intervention will be provided in an MDI. Each MDI will be labeled as required per country requirement	Study intervention will be provided in an TBH. Each TBH will be labeled as required per country requirement	N/A

BID=twice daily; CCI, IMP=Investigational Medicinal Product; NIMP=Non-Investigational Medicinal Product; CCI CCI

6.1.2 Medical Devices Including Combination Products with Device Constituent

1. The AstraZeneca manufactured combination product with a device constituent provided for use in this study are the MDI (Approved) and pMDI (Approved).
2. Instructions for combination products with a device constituent use are provided in the Investigator Brochure and Combination Products section of the Summary of Medical Product Characteristics.
3. All device constituent deficiencies (including malfunction, use error and inadequate labeling) shall be documented and reported by the Investigator throughout the clinical investigation (see Section 8.3.12) and appropriately managed by AstraZeneca.

6.2 Preparation/Handling/Storage/Accountability

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

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

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

All handling instructions and further guidance and information for the final disposition of unused study interventions are provided separately outside of the protocol.

6.3 Measures to Minimize Bias: Randomization and Blinding

All participants will be centrally assigned to one of 4 randomized study interventions using an IRT system. Before the study is initiated, the log-in information and directions for the IRT system will be provided to each site.

The IRT system will provide to the Investigators or pharmacists the kit identification number to be allocated to the participant at the dispensing visit (as summarized in the SoA, Table 1).

Routines for this will be described in the IRT system user manual that will be provided to each center.

For blinded study intervention, the randomization code should not be broken except in medical emergencies when the appropriate management of the participant requires knowledge of the treatment randomization. The Investigator documents and reports the action to AstraZeneca, without revealing the blinded treatment that was given to the participant to the AstraZeneca staff.

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

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

6.4 Study Intervention Compliance

When participants are dosed during a study visit, they will take study intervention under medical supervision from the Investigator or designee. The date, and time if applicable, of dose administered during the study visit will be recorded in the source documents and recorded in the eCRF.

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

A record of the number of MDIs and TBHs dispensed to and used by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates will also be recorded in the eCRF.

6.5 Concomitant Therapy

Any medication or vaccine (including over the counter or prescription medicines, vitamins, and/or herbal supplements or other specific categories of interest) that the participant is

receiving from up to 3 months prior to Visit 1 or receives during the study must be recorded along with:

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

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

6.5.1 Rescue Medicine

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

Although the use of albuterol is allowable at any time during the study, the use of rescue medications should be withheld, if possible, for at least 6 hours prior to the start and during each clinic visit. If albuterol is used within 6 hours from the start of a clinic visit, then the visit will need to be rescheduled within the allowed visit window. The number of puffs of rescue medication will be recorded by the participant daily in the eDiary.

6.5.2 Prior Medications

Participants eligible for this study are required to be on a stable regimen, including fixed daily dosing, of an inhaled asthma maintenance therapy defined as an ICS or ICS/LABA for at least 8 weeks prior to Visit 1. The permitted total daily ICS dosage to qualify for the study is defined in Table 5. Any ICS not listed in the GINA 2020 guidelines or considerations outside this list should be discussed with the Medical Monitor prior to entry of the participant.

Table 5 Required ICS Dosages (Monotherapy or in Combination with LABA) Prior to Visit 1

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

[a] Daily doses in this table are shown as metered doses.
[b] The total daily dose of budesonide in Symbicort 160/4.5 µg pMDI, taken as 2 puffs BID equals a total delivered dose of 640 µg, which is equivalent to 800 µg metered dose.
DPI=Dry Powder Inhaler; HFA=hydrofluoroalkane; pMDI=Pressurized Metered Dose Inhaler

6.5.3 Concomitant Medications

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

Medications meeting the stable dosing period prior to Visit 1 are allowed during the study and listed in Table 6.

Table 6 Allowed Medications with Defined Stable Dosing Period Prior to Visit 1

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

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

6.5.3.1 Vaccinations

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

If a participant is being considered for enrollment into the study and also being considered for COVID-19 vaccination, the participant must not be randomized until at least 7 days after the last dose of vaccine or booster. If COVID-19 vaccination is in the best interest of the participant and the participant is vaccinated during the study, there should be at least 7 days between vaccination and subsequent spirometry assessments.

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

6.5.4 Prohibited Medications

Participants requiring medications presented in Table 7 are prohibited from participating in this study. Participants who recently discontinued use of these medications may be considered

for study enrollment provided they have met the minimum cessation period prior to Visit 1. These medications are prohibited throughout the course of the study. If participants require any of the prohibited medications listed in Table 7, the Investigator should discuss with the Medical Monitor the suitability of the participant continuing study intervention.

Table 7 Prohibited Medications Throughout the Study and Required Cessation Period Prior to Visit 1

Medication	Minimum Cessation Period Prior to Visit 1
Long-acting beta$_2$-agonist as reliever	8 weeks
Long-acting muscarinic antagonist	12 weeks
Leukotriene antagonists/modifiers (eg, Zileuton®)	3 months
Oral beta$_2$-agonist	3 months
Theophylline	7 days
Oral and IV corticosteroids[a]	8 weeks
Injectable systemic corticosteroids (eg, depot formulation, intra-articular, intradermal, intramuscular)	3 months
Any marketed (eg, omalizumab, mepolizumab, benralizumab, reslizumab) or investigational biological therapy for asthma or any other condition	6 months or 5 half-lives, whichever is longer
Prophylactic antibiotics	8 weeks
Roflumilast	30 days
Any immunomodulators or immunosuppressives[b]	3 months or 5 half-lives, whichever is longer
Medications not currently licensed for use in the treatment of asthma and not part of current standard of care	30 days
Any drug with potential to significantly prolong the QT interval[c]	14 days or 5 half-lives, whichever is longer
Other investigational drugs	30 days or 5 half-lives, whichever is longer
Live attenuated vaccines	30 days
Non-selective non-ocular β-blocking agents (except carvedilol)	7 days
Monoamine oxidase inhibitors	14 days
Systemic treatment with strong CYP3A4-inhibitors (eg, ketoconazole, itraconazole, and ritonavir)	30 days
Systemic anticholinergics[d]	7 days
Herbal remedies for the treatment of allergic, inflammatory, or respiratory diseases (eg, Chinese complementary and alternative bronchodilatory medicines)	10 days

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

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

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

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

Specific prohibited asthma and allergy medications and their required washout periods prior to Visit 2 are displayed in Table 8.

Table 8 Prohibited Asthma and Allergy Medications from Visit 1 Onwards

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

[a] Administration as fixed or loose combinations.

[b] Cromoglycate, nedocromil, and ketotifen eye drops are allowed for allergic conjunctivitis; no washout period.

6.6 Dose Modification

Not applicable for this study.

6.7 Intervention After the End of the Study

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

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Intervention

It may be necessary for a participant to permanently discontinue study intervention. If study intervention is permanently discontinued, the participant will be encouraged to remain in the study and complete the remainder of the study visits and procedures.

Note that discontinuation from study intervention is NOT the same thing as a withdrawal from the study.

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

- Development of exclusion criteria or other safety reasons as judged by the Investigator during the treatment period
- Pregnancy (see Section 8.3.10)
- An asthma exacerbation requiring in-patient hospitalization
- More than 2 severe asthma exacerbations requiring oral corticosteroid treatment

See the SoA (Table 1) for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed.

7.2 Participant Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.
- If a participant is unwilling/unable to attend the scheduled clinic visits, he/she will be informed by the Investigator about modified follow-up options (eg, telephone contact, a contact with a relative or treating physician, or information from medical records).
- At the time of withdrawal from the study, if possible, an Early Study Intervention Discontinuation visit should be conducted, as shown in the SoA (Table 1). See SoA for data to be collected at the time of study withdrawal and follow-up for any further evaluations that need to be completed.
  - The participant will discontinue the study intervention and be withdrawn from the study at that time.
- If the participant withdraws consent for disclosure of future information, AstraZeneca may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, it should be confirmed if he/she still agrees for existing samples to be used in line with the original consent. If he/she requests withdrawal of consent for use of samples, destruction of any samples taken and not tested should be carried out in line with what was stated in the informed consent and local regulation. The Investigator must document the decision on use of existing samples in the site study records and inform the Global Study Team.

7.3 Lost to Follow-up

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

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

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

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

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Table 1). Protocol waivers or exemptions are not allowed.
- The suggested order of assessments is vital signs, AE/SAE assessments, -60-minute spirometry, PRO questionnaires, -30-minute spirometry, ECG, blood draw, and then study intervention administration. **Spirometry MUST be performed in accordance with the specified timing.**
- Immediate safety concerns should be discussed with AstraZeneca immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA (Table 1), is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

8.1 Efficacy Assessments

8.1.1 Pulmonary Function Tests

8.1.1.1 Spirometry Standardization

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

The central spirometry vendor is responsible for assuring that the spirometer meets ATS/ERS recommendations [Miller et al 2005] and that the study site personnel who will be performing the testing are properly certified. Additional details will be provided in a Spirometry Procedures Manual.

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

8.1.1.2 Spirometry Schedule

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

Important requirements to support consistent spirometry assessments during study:

- Participants will be required to return to the clinic at approximately the same time of the day ± 1 hr as Visit 1 throughout study.
- All pre-dose (trough) spirometry will be required to be conducted in the morning (0800 ± 2 hours).
- During the Screening and Treatment Periods, sites should call 24 to 48 hours prior to each visit to remind participants that the evening dose of study intervention (run-in BD MDI or study intervention) should be 12 ± 1 hr prior to the expected dosing time at the next morning visit, having considered the time at which assessments prior to dosing will be completed.

  Note: If the site morning dose time is going to be > 13 hours from the prior evening dose time, then the visit should be rescheduled within the allowed visit window.
- All in-clinic dosing should occur prior to 1000 (+ 1 hour allowance) in the morning and visits must be planned accordingly. Participants will be dispensed and administered new study intervention at each clinic visit during the treatment period.

- The morning dose on the day of the clinic visit must be withheld until after all pre-dose assessments are completed at the clinic.

  Note: Albuterol must be withheld at least 6 hours prior to the start time of the morning visit. If these requirements are not met, then the visit will need to be rescheduled within visit windows.
- Participants will be required to remain at the clinic until completion of all protocol-defined assessments and procedures.

Screening Period (Visit 1 through Visit 4):

- The average of the 2 pre-bronchodilator FEV_1 values (-60 and -30 minutes) will be calculated to determine if the participant meets the inclusion criteria. If a participant does not meet this criterion at any one of the screening visits, the participant will be screen failed at that visit.
- Participants who have not withheld asthma medications prior to Visit 1 and failed spirometry testing per criterion at Visit 1 should return to the clinic to repeat spirometry testing within 2 days. Participants whose repeat spirometry testing fails to meet the criterion will be screen failed.

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

Visit 1:

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

Visit 2:

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

Visit 3:

- For participants who did meet the albuterol reversibility criterion at Visit 2, spirometry will be conducted 60 and 30 minutes prior to run-in BD MDI administration.

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

Visit 4 (Randomization):

- Serial spirometry will be conducted 60 minutes and 30 minutes prior to the first dose of study intervention and 5, 15, and 30 minutes, and 1-, 2-, and 3-hours post-dose.

Visits 5 and 9:

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

Visits 7 and 10 or the Treatment Discontinuation/Study Withdrawal Visit:

- Serial spirometry will be conducted 60 minutes and 30 minutes prior to study intervention administration and 15 and 30 minutes, and 1-, 2-, and 3-hours post-dose.

8.1.1.3 Reversibility to Albuterol

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

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

The procedures for testing reversibility to albuterol are as follows:

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

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

Please note, reversibility testing is still required at Visit 2 and/or Visit 3, even if the participant has documented historical reversibility reported in the 12 months prior to Visit 1.

8.1.2 Participant's eDiary Data Collection

Participants will be supplied with a hand-held eDiary device at Visit 1 to take home and enter data electronically at home in the morning and in the evening of each day. Participants will also be trained on the device at Visit 1. Prior to issuing the eDiary to the participant, site personnel will receive eDiary training. The site staff are responsible for setting up the eDiary for each participant's use and for ensuring each participant is trained to complete the questionnaires on the eDiary according to the SoA (Table 1).

Important reminders regarding eDiary use prior to study visits:

- On the evening prior to the visit, participants will complete their eDiary before dosing. Dosing should be 12 hours (± 1 hour) prior to the expected dosing time at the next morning visit.
- On the morning of a visit, participants **will not** complete their eDiary before the visit, but will instead wait to fill out the eDiary during the visit.

8.1.2.1 eDiary Compliance Requirement

Compliance with eDiary is required throughout the study. Participants must have an eDiary compliance of ≥ 70% during Screening to be eligible for randomization (defined as completing the daily eDiary and answering "Yes" to taking 2 puffs of run-in BD MDI for any 10 mornings and any 10 evenings in the last 14 days prior to Visit 4). During the treatment period, daily eDiary compliance is critical for capturing worsening symptoms and use of study interventions. The Investigator/authorized delegate will check the participant's adherence to the eDiary at each visit during the study. An alert will be generated when a participant is not consistently completing the eDiary and/or confirming on the eDiary that they have taken their study intervention. Sites will respond to the alert as per Section 8.1.2.8.

8.1.2.2 Daily eDiary Reporting

The eDiary will include the following daily recordings: morning and evening home PEF data (obtained from the home peak flow meter), asthma symptoms, inhalations of rescue medication use, nights with awakenings due to asthma symptoms, and background (maintenance) medication use.

The eDiary will alert the participant with an alarm when it is time to fill out the questions and will also prompt the participant to collect PEF. Reporting via the eDiary will occur before administration of run-in BD MDI during the Screening Period and study intervention or asthma maintenance medication during the Treatment Period.

Participants will record the following in their eDiary each day (pre-dose):

- Respond to eDiary alerts, as applicable (Section 8.1.2.1 and Section 8.1.2.8)
- Daily asthma symptoms, activity limitations, and night-time awakening questions (Section 8.1.2.3)
- Number of puffs of rescue medication (albuterol) (Section 8.1.2.4)
- Ensure collection of PEF (Section 8.1.2.5)
- Daily use of inhaled asthma maintenance treatment including run-in BD MDI and study interventions (Section 8.1.2.6)

8.1.2.3 Asthma Symptoms

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

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

function assessment. Night-time is defined as the time period between the evening peak flow/lung function assessment (at bedtime) and the morning peak flow/lung function assessment.

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

8.1.2.4 Rescue Medication Use

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

8.1.2.5 Peak Expiratory Flow

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

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

At Visit 4, a PEF baseline will be calculated to define a stability limit. The stability limit is defined as the average of the available morning PEF eDiary recordings during the last 7 days before Visit 4 (ie, the baseline PEF), multiplied by 0.8. The PEF stability limit will be used to define a threshold for an eDiary alert.

8.1.2.6 Inhaled Asthma Maintenance Use

Inhaled asthma maintenance use includes run-in BD MDI, study intervention or asthma maintenance medication (for participants who discontinue study intervention). The eDiary will ask participants about daily inhaled asthma maintenance use each morning and each evening. Participants will record the prior evening dose in the morning eDiary entry, and the morning dose will be recorded in the evening eDiary entry.

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

8.1.2.7 Study Visit eDiary Data Collection

Participants will also fill out PRO questionnaires electronically on the eDiary at study visits according to the SoA (Table 1). On the morning of a visit day, participants will wait until the visit before filling out the eDiary. Participants will complete all required eDiary questions prior to dosing during the visit; all PROs should be completed after the -60-minute spirometry assessment. Participants will bring their eDiary to every clinic visit after Visit 1.

Table 9 describes the number of items and an estimate of the time to complete the PROs administered at visits; however, not every questionnaire is administered at every visit and the completion time varies by participant. The eDiary device will be programmed to administer the appropriate questionnaires in the correct order in accordance with the SoA (Table 1). Site personnel must trigger a study visit for the PROs to appear on the eDiary device. Training on the eDiary device will be provided prior to study start up.

The estimated timeframe for completion of all the PROs during a visit is about 20 minutes.

Table 9 Patient Reported Outcomes Administered at the Clinic Visit

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

Asthma Control Questionnaire (ACQ), Asthma Impairment and Risk Questionnaire (AIRQ), Asthma Quality of Life Questionnaire 12 Years of Age and Older (AQLQ(s)+12), European Quality of Life-5 Dimensions (EQ-5D)

Asthma Control Questionnaire

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

There are 3 ways to score the ACQ that are being analyzed in this study to support the endpoints: ACQ-5, ACQ-6, and ACQ-7. The ACQ-5 and ACQ-6 scores are supported entirely by patient-reported symptom and reliver use data. The ACQ-7 scoring includes both the ACQ-

6 PRO items and a clinician reported pre-bronchodilator FEV_1 percent predicted normal value in the scoring algorithm.

The ACQ-6 will be administered to participants. Participants are asked 6 questions to recall how their asthma has been during the previous week by responding to one bronchodilator use question and 5 symptom questions. Questions are weighted equally and scored from 0 (totally controlled) to 6 (severely uncontrolled). The mean ACQ-6 score is the mean of the responses to items 1-6, and the mean ACQ-5 score is the mean of the responses to items 1-5.

The score for the ACQ-7 includes the ACQ-6 PRO items and FEV_1 reported by the clinician. The mean ACQ-7 score is the mean of responses to the ACQ-6 PRO items and the one clinician reported FEV_1 item.

Control categories based on the ACQ-5, ACQ-6, and ACQ-7 scores are the same. A mean score of ≤ 0.75 indicates 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 et al 2006]. Individual changes of at least 0.5 are considered clinically meaningful.

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

Asthma Quality of Life Questionnaire 12 Years of Age and Older

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

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

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

The questionnaire will be completed according to the SoA, starting at randomization.

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

European Quality of Life-5 Dimensions

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

EQ-5D-5L and EQ-5D-Y index score can be calculated based upon participants' responses to the 5 dimensions and using an appropriate value set [Corren et al 2007, EQ-5D User Guides: EQ-5D-5L 2019, EQ-5D-Y 2014]. A value set provides values (weights) for each health state description according to the preferences of the general population of a country/region.

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

The EQ-5D will be completed on the eDiary by the participant per the SoA (Table 1). The Investigator/authorized delegate will check participant's adherence to the EQ-5D at each visit.

Asthma Impairment and Risk Questionnaire

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

The AIRQ items have 2 different recall periods: The first 7 impairment items are evaluated over the past 2 weeks and the last 3 risk items over the past 3 months or the past year. This

study will use the past 3 months recall. The AIRQ will be administered and completed on the eDiary by the participant as per SoA (Table 1).

8.1.2.8 Symptom Worsening Assessment and eDiary Alert System

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

- PEF: a decrease in morning PEF of ≥ 20% as compared with baseline average (baseline is defined in Section 9.5.1.3), and/or
- Rescue albuterol use: an increase of ≥ 4 inhalations compared with baseline average use, and/or
- Nighttime awakening: an increase of 2 or more nights with awakenings due to asthma requiring rescue medication use over a 7-day period compared with the average baseline and/or ≥ 6 out of the 7 previous nights with awakenings due to asthma requiring rescue medication, and/or
- Asthma symptoms: an increase of total asthma symptom score (the sum of daytime plus nighttime) of at least 2 units above the average baseline or the highest possible score (daily score of 6)

An eDiary alert is not an asthma exacerbation per se. Although the eDiary alert should initiate contact between the participant and the investigational site within 48 hours of the alert, the Investigator or designee will always assess the participant's symptoms and determine whether to treat the participant for an asthma exacerbation.

8.2 Safety Assessments

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

8.2.1 Medical/Surgical History

Medical history will be collected at Visit 1 and updated during the Screening Period, if necessary. The number of asthma exacerbations requiring systemic corticosteroids, ER visits, and/or hospitalizations within the previous 12 months will be collected at Visit 1.

8.2.2 Physical Exam

A brief physical examination will be performed as specified in the SoA (Table 1). The brief physical examination will include the following:

General appearance, respiratory, cardiovascular, and abdomen

8.2.3 Height and Weight

Height and weight will be measured as specified in the SoA (Table 1). Body mass index will be automatically calculated in the eCRF.

8.2.4 Vital Signs

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

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

8.2.5 Electrocardiograms

An ECG will be performed using the study-provided device at visit as specified in the SoA (Table 1).

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

8.2.6 Clinical Safety Laboratory Assessments

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

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

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

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

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

The following laboratory variables will be measured (Table 10):

Table 10 Laboratory Variables

Hematology (whole blood)	Clinical Chemistry (serum or plasma)
Hemoglobin	Creatinine
Leukocyte count (including differential count)	Bilirubin, total
Eosinophil count	Alkaline phosphatase
Platelet count	Aspartate transaminase
	Alanine transaminase
Other Tests	Albumin
Highly sensitive urine pregnancy test for women of childbearing potential	Potassium
	Calcium, total
	Sodium
	Glucose

8.2.7 Asthma Exacerbations

An asthma exacerbation is defined as worsening of asthma that requires a medical intervention as described in Section8.2.7.4.

Worsening of asthma is defined as at least one of the following 3 elements of worsening listed below fulfilled for at least 2 consecutive days (see Section 8.1.2.8 for eDiary alerts):

- worsening of asthma signs/symptoms (see Section 8.2.7.1)
- increased use of 'as-needed' rescue/reliever medication (see Section 8.1.2.4)
- deterioration of PEF (see Section 8.1.2.5)

8.2.7.1 Definition of Worsening of Asthma Signs/Symptoms

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

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

8.2.7.2 Investigator Justified Asthma Exacerbations

The majority of asthma exacerbations should be associated with worsening of asthma signs/symptoms described in Section 8.2.7.1. However, clinical presentations may vary among participants and the associated asthma worsening signs/symptoms and/or duration may not meet the definition of a moderate or severe exacerbation. For moderate and severe exacerbations without an eDiary alert date recorded in the eCRF, the Investigator will record the worsening signs/symptoms with duration and provide the justification(s) for diagnosing the exacerbation (eg, rapid onset and/or severity of worsening asthma) in the eCRF. If an exacerbation is recorded in the setting of treatment with additional systemic corticosteroids for less than 3 days (Section 8.2.7.3), the Investigator will record whether it is considered severe or moderate and the justification(s) for diagnosis and treatment duration (eg, single administration of IV corticosteroid without follow-up oral corticosteroid prescribed) in the eCRF.

8.2.7.3 Severity of Asthma Exacerbation

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

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

- A course of systemic corticosteroids for at least 3 consecutive days to treat symptoms of asthma worsening.
- An ER or urgent care visit (defined as evaluation and treatment for < 24 hours in an emergency department or urgent care center) due to asthma that required treatment with systemic corticosteroids
- An in-patient hospitalization (defined as admission to an in-patient facility and/or evaluation and treatment in a healthcare facility for ≥ 24 hours) due to asthma
- Death related to asthma

A moderate asthma exacerbation is defined as a worsening of asthma symptoms (defined in Section 8.2.7.1) that results in an additional ICS for at least 3 days and did not meet any of the criteria for a severe asthma exacerbation.

8.2.7.4 Treatment for Asthma Exacerbations

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

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

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

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

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

8.2.7.5 Onset and Duration of Asthma Exacerbations

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

For **severe** asthma exacerbations:

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

  Note: The start date could be the start date of an additional ICS when treatment is switched to at least 3 days of systemic corticosteroids as described in Section 8.2.7.4.
- The stop date is defined as the last day of prescribed systemic corticosteroids, hospital/ER discharge date or the date of death (from the exacerbation), whichever is later.
- If multiple treatments are prescribed for the same exacerbation, the earliest start date and the latest stop date will be used.
- For a **severe** asthma exacerbation requiring hospitalization with no documented systemic corticosteroid treatment, hospitalization admission/discharge dates will be used as start/stop dates as described in Section 8.2.7.3.

For **moderate** asthma exacerbations:

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

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

8.2.7.6 Approach for Capturing Asthma Exacerbations

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

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

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

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

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

8.2.8 Other Safety Assessments

8.2.8.1 Paradoxical Bronchospasm

Monitoring for paradoxical bronchospasm will occur at each in-clinic visit in which there are post-dose spirometry assessment during the Treatment Period (Visits 4 and 7 or Treatment Discontinuation/Study Withdrawal Visit) at 15- and 30-minutes post-dose. In this study, paradoxical bronchospasm is defined as a reduction in FEV_1 of > 20% from baseline (ie, the mean FEV_1 values obtained 60 and 30 minutes prior to study intervention administration) that occurs within 30 minutes post-dosing with associated symptoms of wheezing, shortness of breath, or cough. If an event meets both the spirometry and the symptoms for a paradoxical bronchospasm, then it will be reported as an AE.

8.3 Adverse Events and Serious Adverse Events

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

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

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

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

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

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

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

If the Investigator becomes aware of an SAE with a suspected causal relationship to the IMP that occurs after the end of the clinical study in a participant treated by him or her, the Investigator shall, without undue delay, report the SAE to AstraZeneca.

8.3.2 Follow-up of AEs and SAEs

Any AEs that are unresolved at the participant's last AE assessment or other assessment/visit as appropriate in the study are followed up by the Investigator for as long as medically indicated, but without further recording in the eCRF. AstraZeneca retains the right to request additional information for any participant with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

Adverse event variables

The following variables will be collected for each AE:

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

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

- Date AE met criteria for SAE
- Date Investigator became aware of SAE
- AE is serious due to
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to study procedure(s)
- Causality assessment to other medication

8.3.3 Causality Collection

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

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

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

8.3.4 Adverse Events Based on Signs and Symptoms

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

8.3.5 Adverse Events Associated with Use of ICS and LABAs

Certain AEs have been identified as associated to the class of drugs being studied. Known effects of LABAs include cardiovascular and tremor effects. Local corticosteroid effects include oral candidiasis, oropharyngeal candidiasis, dysphonia, and throat irritation. These

AEs will be captured as described in Section 8.3.4 and presented in summary tabulation in the CSR.

8.3.6 Adverse Events Based on Examinations and Tests

The results from the CSP-mandated laboratory tests and vital signs will be summarized in the CSR.

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

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

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

8.3.7 CCI

CCI

8.3.8 Disease Under Study

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

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

8.3.9 Reporting of Serious Adverse Events

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

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

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

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

Once the Investigator or other site personnel indicate an AE is serious in the eCRF, an automated email alert is sent to the designated AstraZeneca representative.

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

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

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

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

8.3.10 Pregnancy

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

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

8.3.10.1 Maternal Exposure

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

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

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

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety DES **within one or 5 calendar days** for SAEs (see Section 8.3.9) and **within 30 days** for all other pregnancies.

The same timelines apply when outcome information is available.

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

8.3.11 Medication Error, Drug Abuse, and Drug Misuse

8.3.11.1 Timelines

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

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is completed within **1** (Initial Fatal/Life-Threatening or follow-up Fatal/Life-Threatening) **or 5** (other serious initial and follow-up) **calendar days** if there is an SAE associated with the medication error, drug abuse, or misuse (see Section 8.3.9) and **within 30 days** for all other events.

8.3.11.2 Medication Error

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

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

8.3.11.3 Drug Abuse

Drug abuse is the persistent or sporadic **intentional**, non-therapeutic excessive use of IMP or AstraZeneca NIMP for a perceived reward or desired non-therapeutic effect.

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

8.3.11.4 Drug Misuse

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

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

8.3.12 Device Constituent Deficiencies

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

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

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

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

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

8.3.12.1 Time Period for Detecting Device Constituent Deficiencies

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

If the Investigator learns of any device constituent deficiency at any time after a participant has been discharged from the study, and such incident is considered reasonably related to a device constituent provided for the study, the Investigator will promptly notify AstraZeneca.

8.3.12.2 Follow-up of Device Constituent Deficiencies

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

8.3.12.3 Prompt Reporting of Device Constituent Deficiencies to AstraZeneca

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

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

8.4 Overdose

For this study, any dosing of BFF MDI, BD MDI, or Symbicort TBH of more than 2 inhalations BID will be considered an overdose.

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

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

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety DES **within one or 5 calendar days** for overdoses associated with an SAE (see Section 8.3.9) and **within 30 days** for all other overdoses.

8.5 Human Biological Samples

8.5.1 Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.5.2 Immunogenicity Assessments

Immunogenicity assessments are not evaluated in this study.

8.5.3 Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.6 Human Biological Sample Biomarkers

Biomarkers are not evaluated in this study.

8.7 Optional Genomics Initiative Sample

Collection of optional samples for Genomics Initiative research is also part of this study as specified in the SoA and is subject to agreement in the Optional Genomics Initiative Research Information of the ICF.

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

See Appendix C for information regarding the Genomics Initiative genetic sample. Details on processes for collection, shipment, and destruction of these samples can be found either in the appendices or in the Laboratory Manual.

For storage and destruction of genetic samples see Appendix C.

8.8 Healthcare Resource Utilization Data

Healthcare resource utilization data associated with medical encounters, will be collected in the eCRF by the Investigator and study site personnel for all participants throughout the study. During screening at Visit 3, HCRU information will be collected with a ‘one year’ recall period. All the subsequent visits after Visit 4, will collect HCRU information with a recall period of ‘since the last scheduled visit’. Protocol-mandated procedures, tests, and encounters are excluded.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

For the efficacy comparisons for the primary objective, the null hypothesis will be that the mean treatment difference (BFF MDI 320/9.6 µg vs BD MDI 320 µg) is zero (mean treatment effects are equal). The alternative hypothesis is that the mean treatment difference is not zero (mean treatment effects are not equal). All p-values will be reported as two-sided.

For the pooled analysis of exacerbation rate, it is assumed that the rate ratio (RR) comparing BFF and BD will not depend on the dose of BD, that is $RR_{BFF\ 320/9.6\ vs\ BD\ 320} = RR_{BFF\ 160/9.6\ vs\ BD\ 160} = RR_{BFF\ vs\ BD}$. The null and alternative hypotheses are hence:

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

To support CCI of CCI MDI in CCI, an additional objective of this study is to assess the effect of BFF MDI 320/9.6 µg relative to Symbicort TBH on lung function. For these comparisons, the null hypothesis for each pair-wise comparison will be that the mean treatment difference is in excess of the NI margin (see Section 9.2 for the NI margins relevant to each endpoint). The alternative hypothesis is that the mean treatment difference is within the NI margin. All CIs will be two-sided with 95% confidence and p-values will reflect the test for NI.

9.2 Analysis Methods for Estimands

Due to variation in the registrational requirements across regions, the estimand strategy will be different depending on the region.

Analyses utilizing the primary estimand strategy for ICEs answer the clinical question of what the effect of randomized treatment at the end of the planned treatment period is regardless of the occurrence of any ICEs unless asthma medication is initiated in conjunction with premature discontinuation of therapy (which will be considered an unfavourable outcome).

Analyses utilizing the While on Treatment estimand strategy for ICEs answer the clinical question of what the effect of the randomized treatments is assuming continuation of randomized treatments for the duration of the planned treatment period regardless of actual compliance.

Analyses of lung function endpoints utilizing the primary strategy, where initiating new treatment for asthma in conjunction with prematurely discontinuing randomized treatment is considered an unfavourable outcome, will impute the worst FEV1 value of: CCI% decrease from participant's baseline value or participant's worst observed value post baseline during the study. For binary outcome variables, the occurrence of an ICE utilizing the composite strategy is taken to be a component of the variable resulting in a non-responder status, ie, the ICE is integrated with one or more other measures of clinical outcome as the variable of interest.

More details on the imputation approaches will be provided in the SAP.

Analyses utilizing the Principal Stratum estimand strategy for ICEs as described in Lou et al 2019 will be conducted in the PP set for efficacy endpoints. Non-inferiority comparisons of BFF MDI 320/9.6 µg versus open-label Symbicort TBH will be conducted in order to support CCI of CCI in CCI. The Principal Stratum estimand strategy for ICEs will be the focus for the NI comparison. The NI assessment for FEV_1 AUC_{0-3} will apply a NI margin of CCI mL and the NI assessment for morning pre-dose trough FEV_1 will use a NI margin of CCI mL. These margins are consistent with CCI

CCI

CCI

The following efficacy comparisons will be made:

- Superiority of BFF MDI 320/9.6 µg versus BD MDI 320 µg (also used for assay sensitivity)
- NI of BFF MDI 320/9.6 µg versus Symbicort TBH 320/9 µg
- Numerical trend of BFF MDI 320/9.6 µg versus BFF MDI 160/9.6 µg

9.2.1 Type I Error Control

Due to variation in the registrational requirements across regions, the multiple testing procedure will be different depending on the region. The change from baseline in FEV_1 AUC_{0-3} will be the primary endpoint for CCI and key secondary endpoint for CCI and CCI The change from baseline in morning pre-dose trough FEV_1 will be the primary endpoint for CCI and CCI and key secondary endpoint for CCI

9.2.1.1 CCI Approach

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

Figure 2 CCI Type I Error Control Procedure

CCI

[redacted]

[a] CCI
CCI

The procedure is applied to both this study, D5982C00006, as well as Study D5982C00005 in order to allow data from both studies to be combined for analyses of severe exacerbation, thus utilizing data from higher numbers of participants to support that endpoint. The analyses in Study D5982C00005 will be comparing BFF MDI 160/9.6 µg BID to BD 160 µg MDI BID at Week 12 (except for testing onset of action, where at the timepoint of interest is at the 5-minute post-dose timepoint on Day 1, as well as the analyses on change from baseline in puffs of rescue medication and severe exacerbation rate, where the evaluation is made over the duration of the study), whereas the analyses in this study, D5982C00006, will be comparing BFF MDI 320/9.6 µg BID to BD 320 µg MDI BID at Week 24 (except for testing onset of action, where the timepoint of interest is at the 5-minute post-dose timepoint on Day 1).

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

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

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

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

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

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

9.2.1.2 CCI Approach

Strong control of the Type I error rate will be maintained at the two-sided 0.05 level for the primary endpoint, change from baseline in trough FEV_1 over 12 to 24 Weeks, across

comparisons using a sequential approach as detailed below. The Type I error control will be strongly controlled to test the primary and secondary endpoints within each comparison.

The superiority comparisons of BFF MDI 320/9.6 µg versus BD MDI 320 µg for the primary endpoint, change from baseline in trough FEV_1, will be conducted first in order to demonstrate assay sensitivity. If this comparison is statistically significant (alpha = 0.05, two-sided), the NI comparison of BFF MDI 320/9.6 µg versus Symbicort TBH for change from baseline in trough FEV_1 will be conducted, using the Principal Stratum estimand strategy for ICEs. If this comparison statistically excludes (alpha = 0.025, one-sided) the NI margin of -CCI mL, then the procedure will proceed to testing of the secondary endpoints.

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

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

9.2.1.3 CCI Approach

The Type I error for other regions, including the CCI will be strongly controlled across the primary and secondary endpoints of BFF MDI 320/9.6 µg versus BD MDI 320 µg (alpha = 0.05, two-sided). The procedure will test the primary, change from baseline in trough FEV_1, and key secondary, FEV_1 AUC_{0-3}, endpoints over 24 Weeks in sequential order. If the result is statistically significant (alpha = 0.05, two-sided) for the primary and key secondary endpoint, the onset of action on Day 1 will be tested by comparing BFF MDI 320/9.6 µg vs BD MDI 320 µg (alpha = 0.05, two-sided). If the result is statistically significant (alpha = 0.05, two-sided), the remaining secondary endpoints will be simultaneously tested (alpha=0.05, two-sided) with a Hochberg procedure [Gou 2014].

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

9.3 Sample Size Determination

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

A total of 630 participants will be recruited with CCI participants in the BFF MDI 160/9.6 µg arm and CCI participants in the BFF MDI 320/9.6 µg, BD MDI 320 µg and Symbicort TBH arms. The BFF MDI 160/9.6 µg arm will be included to demonstrate a dose response. Under the While on Treatment estimand strategy for ICEs, a sample size of CCI participants per treatment arm will provide more than 90% power to detect a CCI mL difference in the analysis of change from baseline in trough FEV_1 over 24 Weeks between BFF MDI 320/9.6 µg versus BD MDI 320 µg and over 99% power to detect a CCI mL difference in the analysis of change from baseline in FEV_1 AUC_{0-3}. Each comparison is based on a two-sided alpha=CCI test and SD of CCI mL for trough FEV_1 and CCI mL for FEV_1 AUC_{0-3} at each visit with effective SD of CCI mL and CCI mL, respectively. The effective SD for each endpoint over 24 Weeks assumes 2 post-dose visits assessing FEV_1 AUC_{0-3} and 3 post-dose visits assessing trough FEV_1 over the interval and that the correlation among visits is CCI This sample size assumes that approximately CCI% of randomized participants will have discontinued study intervention prior to Week 12, and CCI% at Week 24.

Using the Treatment Policy estimand strategy for ICEs, a smaller treatment difference of CCI mL for trough FEV_1 is assumed, providing a power at 24 weeks in trough FEV_1 of 84%. Assuming a smaller treatment effect of CCI mL for FEV_1 AUC_{0-3}, the power would be at least 99%.

The treatment effect and variability for the power calculation was based on 4 Symbicort studies (as Symbicort is a similar strength of BFF in a pMDI) (Corren et al 2007, Noonan et al 2006, Peters et al 2008, and Zangrilli et al 2011).

9.4 Populations for Analyses

The following populations are defined:

Table 11 Populations for Analyses

Analysis set	Description
Screened set	All participants who sign the ICF.
Randomized set	All participants who are randomized to study intervention.
Efficacy set	All participants who are randomized to study intervention and receive any amount of study intervention. Participants will be analyzed according to the study intervention they were assigned at randomization, regardless of the actual study intervention received.
PP set	All participants in the Efficacy set without an IPD impacting efficacy at the date of randomization. Furthermore, data obtained after any IPD impacting efficacy or ICE will be excluded. Since receiving the wrong treatment will be an IPD, participants in the PP analysis set will be analyzed as randomized (which for this analysis set is identical to analysis by the actual treatment received).

Table 11 Populations for Analyses

Analysis set	Description
Safety set	All participants who are randomized to study intervention and receive any amount of the study intervention. Participants will be analyzed according to the actual study intervention received rather than randomized.

9.5 Statistical Analyses

The SAP will be finalized before the earliest of the following milestones: 90 days after first participant in, first Data Monitoring Committee or first Dry Run and will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and secondary endpoints. Additional analyses assessing the impact of SARS-CoV-2 pandemic, or any other natural event may be included in the SAP.

9.5.1 General Considerations

9.5.1.1 Demographic and Baseline Characteristics

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

9.5.1.2 Visit Windows

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

9.5.1.3 Baseline

For FEV_1 and onset of action on Day 1, baseline is defined as the mean of the pre-dose FEV_1 assessments on Visit 4 (Day 1). For the asthma PROs, baseline is defined as the last non-missing value before first dose of randomized IP. For daily eDiary metrics (rescue medication, awakenings, PEF, and asthma symptoms scores), baseline is defined as the average of eDiary metrics measured during last 7 days before randomization. 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 eCRF page.

9.5.2 Efficacy

9.5.2.1 Primary Endpoint(s)

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 ANCOVA model. The model will include treatment, visit, prior maintenance medication (ICS versus ICS/LABA), and treatment-by-visit interaction as categorical covariates and baseline trough FEV_1 and percent reversibility as continuous covariates. An unstructured variance-covariance matrix will be used to model the variance-covariance structure. If this model fails to converge, an alternative structure will be employed as pre-specified in the SAP. Contrasts will be used to obtain estimates of the treatment differences at Week 24. Two-sided p-values and point estimates with two-sided 95% CIs will be produced for each treatment difference. The model-based statistics for other visits, over 24 Weeks or over 12 to 24 Weeks will also be reported.

Derivation of FEV_1 AUC_{0-3}

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

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

Change from baseline in morning pre-dose trough FEV_1 will be analyzed using a repeated measures ANCOVA 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 12 to 24 Weeks for CCI and over 24 Weeks will be used for regions such as the CCI Two-sided p-values and point estimates with two-sided 95% CIs will be produced for each treatment difference. The model-based statistics for the change at Week 24 and other visits will also be reported.

Intermittent missing data for the primary endpoint (all regions) will not be imputed and will be handled through the analysis model.

Sensitivity analyses will be conducted for the primary endpoint (all regions) to evaluate the robustness of the primary analysis findings to missing data. Robustness of results to missing data will be explored using tipping point analyses. More details will be provided in the SAP.

9.5.2.2 Secondary Endpoints

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

Rate of Severe Asthma Exacerbations

The rates of severe asthma exacerbations will be analyzed using negative binomial regression in the D5982C00005 and D5982C00006 studies separately. The negative binomial model for each study will include treatment, baseline trough FEV1, percent albuterol reversibility, baseline severe asthma exacerbation history (0, ≥ 1), prior maintenance medication (ICS versus ICS/LABA), and region as covariates. Furthermore, the rates of severe asthma exacerbations will be analyzed for the pooled individual participant data from both studies (D5982C00006: BFF 320/9.6 μg, BFF 160/9.6 μg, BD 320 μg and D5982C00005: BFF 160/9.6 μg, BD 160 μg treatment arms. The Symbicort treatment arm in Study D5982C00006 will not be included in the pooled analysis.). The pooled analysis will use all available data (over the planned 12-week treatment period in D5982C00005 and over the 24-week treatment period for study D5982C00006) to maximize the amount of data included. For the pooled analysis, a negative binomial additive model will be used with the same covariates, except it will also include study, budesonide (1 if the budesonide dose is 320 μg, and 0 if the budesonide dose is 160 μg), and formoterol (1 if the formoterol dose is 9.6 μg, and 0 if no formoterol dose) instead of treatment as covariates. The comparison of interest is the formoterol effect. For the pooled analysis, one dispersion parameter will be estimated. Further details will be specified in the SAP.

Under the primary strategy for handling ICEs, all available data will be utilized irrespectively of any ICE, except new medication in conjunction with premature IP discontinuation which will be considered an unfavourable outcome. In addition, a supportive analysis utilizing While on Treatment strategy will be performed.

Asthma exacerbations will be considered separate events if more than 7 days are between the recorded stop date of the earlier event and start date of the later event. Time at risk of experiencing a severe exacerbation will be used as an offset variable in the model. Time during a severe exacerbation or in the 7 days following a severe exacerbation will not be included in the calculation of exposure.

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

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

The mean daily number of puffs of rescue medication use will be calculated overall and for each of the 4-week intervals during the Treatment Period. For every period of time for which the mean number of puffs of rescue medication will be calculated, missing values will be ignored in both the numerator and denominator. As such, the denominator will be adjusted based on the number of days (including half days) with non-missing values. Under the primary strategy for handling ICEs, all available data will be utilized irrespectively of any ICE except new medication in conjunction with premature IP discontinuation which will be

considered an unfavourable outcome. A repeated measures ANCOVA model will be used to analyze change from baseline in average daily rescue albuterol use. The model will include treatment, the number of the relevant 4-week interval (interval 1 to 6), prior maintenance medication (ICS versus ICS/LABA), severe asthma exacerbation history (0, ≥ 1), and the treatment-by-4-week interval interaction as categorical covariates and baseline daily rescue albuterol use, baseline trough FEV_1, and percent reversibility as continuous covariates. An unstructured variance-covariance matrix will be fit. If this model fails to converge, an alternative structure will be employed as pre-specified in the SAP. Contrasts will be used to obtain estimates of the treatment differences over 24 Weeks or over 12 to 24 Weeks. Two-sided p-values and point estimates with two-sided 95% CIs will be produced for each treatment difference.

Percentage of Responders in ACQ-7 and ACQ-5 (≥ 0.5 Decrease Equals Response)

Responder analyses will be performed for ACQ-7 and ACQ-5 at Week 24, over 24 Weeks or over 12 to 24 Weeks. Responders are defined as participants with a decrease in total score of ≥ 0.5 points from baseline. Under the primary strategy for handling ICE, all available data will be utilized to determine response irrespectively of any ICE except new medication in conjunction with premature IP discontinuation where a participant will be considered non-responder. For supportive analyses, participants who experience an ICE (except for discontinuation of study intervention for reasons related to global/country situation) will be classified as non-responders at visits subsequent to the ICE under the Composite estimand strategy approach to ICEs. Data following study intervention discontinuation for reasons related to global/country situation will be considered missing and will not be imputed. Those datapoints are considered to be missing completely at random and will be excluded from the analysis. Intermittently missing data will be classified as non-response. Logistic regression will be used to compare the treatment groups with treatment and prior maintenance medication (ICS versus ICS/LABA) as categorical covariates and baseline instrument score, baseline trough FEV_1, and percent reversibility as continuous covariates. P-values and Odds Ratios with 95% CIs will be produced for each treatment comparison.

Percentage of Responders in AQLQ(s)+12 (≥ 0.5 Increase Equals Response)

Responder analyses will be performed for AQLQ(s)+12 at Week 24, over 24 Weeks or over 12 to 24 Weeks for participants 12 years and older. Responders are defined as participants with an improvement of ≥ 0.5 points increase over baseline. The strategies for handling ICEs and missing data are similar to the ones used for percentage of responders in ACQ-5. Logistic regression will be used to compare the treatment groups, similar to the one used for percentage of responders in ACQ-5. P-values and Odds Ratios with 95% CIs will be produced for each treatment comparison.

Onset of Action on Day 1

All spirometry attempts at Visit 4 (Day 1) that meet ATS/ERS acceptability criteria will be recorded along with the actual time. The onset of action for BFF MDI 320/9.6 µg will be evaluated on Day 1 by comparing BFF MDI 320/9.6 µg vs BD MDI in the mean change from baseline in FEV_1 at the 5-minute post-dose timepoint. Comparisons will also be made at additional timepoints but will not be controlled for multiplicity. A repeated measures ANCOVA will be fit to the Day 1 post-baseline data. This model will include treatment, timepoint, prior maintenance medication (ICS versus ICS/LABA), and treatment-by-timepoint interaction as categorical covariates and baseline trough FEV_1 and percent reversibility as continuous covariates. An unstructured variance-covariance matrix will be used to model the variance-covariance structure. If this model fails to converge, an alternative structure will be employed as pre-specified in the SAP. Contrasts will be used to obtain estimates of the treatment differences on Day 1 at the 5-minute post-dose timepoints. Two-sided p-values and point estimates with two-sided 95% CIs will be produced for each treatment difference of BFF MDI 320/9.6 µg vs BD MDI, and BFF MDI 320/9.6 µg vs BFF MDI 160/9.6 µg. Furthermore, descriptive statistics will be presented by treatment group. A supportive within-group T-test to demonstrate that the mean change from baseline in FEV_1 at 5 minutes post-dose is statistically greater than 100 mL will also be provided with corresponding p-value and 95% CI.

9.5.2.3 Tertiary/Exploratory Endpoint(s)

The following tertiary/exploratory endpoint efficacy analyses will be conducted for the While on Treatment estimand strategy for ICEs except for ACQ and AQLQ(s)+12 endpoints which will use the primary strategy for handling of ICEs. Results from tertiary/exploratory analyses may be reported outside of the CSR.

Percentage of Rescue-Free and Symptom-Free Days

The percentages of rescue-free days and symptom-free days will each be analyzed over 24 Weeks and over 12 to 24 Weeks. Additionally, analyses will be conducted over each 4-week interval in the study. A repeated measures analysis of covariance model will be used with treatment, the number of the relevant 4-week interval (interval 1 to 6), prior maintenance medication (ICS versus ICS/LABA), severe asthma exacerbation history (0, ≥ 1), and the treatment-by-4-week interval interaction as categorical covariates. Baseline percentage of endpoint days (where endpoint is rescue-free or symptom-free), baseline trough FEV_1, and percent reversibility will be continuous covariates.

Peak Change from Baseline in FEV_1

Peak change from baseline in FEV_1 will be analyzed using a repeated measures ANCOVA model. The model will be similar as the one used for the primary analyses. Contrasts for treatment comparisons over 24 Weeks and for each visit will be derived from the model.

Time to Peak FEV_1 on Day 1

Time to peak FEV_1 on Day 1 will be analyzed with ANCOVA model to compare the treatment groups, adjusted for prior maintenance medication (ICS versus ICS/LABA), baseline trough FEV_1, and percent reversibility. The time to peak will be based on the actual rather than nominal assessment time. If necessary, non-parametric or semi-parametric methods may be used. Details will be provided in the SAP.

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

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

Supportive analyses of the proportion of participants meeting improvement thresholds on Day 1 will also be conducted to compare the speed of onset between treatments. The percentage of participants with ≥ 12% improvement over baseline in FEV_1 at 5 minutes post-dose and at other timepoints on Day 1 will be compared between treatment groups using logistic regression adjusted for prior maintenance medication (ICS versus ICS/LABA), percent reversibility, and baseline trough FEV_1. Details will be given in the SAP, where alternative thresholds and timepoints may be defined.

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

Change from baseline in FVC, PEF, and FEF_{25-75} evaluated using AUC_{0-3} will be analyzed using a repeated measures ANCOVA model. The model will be similar as the one used for the primary analyses. Contrasts for treatment comparisons over 12 Weeks and for each visit will be derived from the model.

Change from Baseline in Morning Pre-Dose Trough PEF

Change from baseline in morning pre-dose trough PEF will be analyzed using a repeated measures ANCOVA model. The model will include treatment, 4-week interval (interval 1 to 6), prior maintenance medication (ICS versus ICS/LABA), and treatment-by 4-week interval interaction as categorical covariates and baseline morning pre-dose trough PEF, baseline trough FEV_1, and percent reversibility as continuous covariates. An unstructured variance-covariance matrix will be used to model the variance-covariance structure. If this model fails to converge, an alternative structure will be employed as pre-specified in the SAP. Contrasts will be used to obtain estimates of the treatment differences over 24 weeks, over 12 to 24 Weeks, and for each 4-week interval. Two-sided p-values and point estimates with two-sided 95% CIs will be produced for each treatment difference.

Change from Baseline in Evening Pre-Dose PEF

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

Percentage or Responders in ACQ-6 (≥ 0.5 Decrease Equals Response)

Responder analyses will be performed for ACQ-6 at Week 24, over 24 Weeks or over 12 to 24 Weeks. Responders are defined as participants with an improvement (decrease of ≥ 0.5 points) over baseline. The strategies for handling ICEs and missing data are similar to the ones used for percentage of responders in ACQ-5. Logistic regression will be used to compare the treatment groups, similar to the one used for percentage of responders in ACQ-5. P-values and Odds Ratios with 95% CIs will be produced for each treatment comparison.

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

Change from baseline in ACQ-5, ACQ-6, ACQ-7 and AQLQ(s)+12 will each be analyzed using a repeated measures ANCOVA model. The model will include treatment, visit, prior maintenance medication (ICS versus ICS/LABA), and treatment-by-visit interaction as categorical covariates and baseline trough FEV_1, 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 12 to 24 Weeks. Two-sided p-values and point estimates with two-sided 95% CIs will be produced for each treatment difference. The strategies for handling ICEs and missing data are similar to those ones used for percentage of responders in ACQ-5.

Asthma Exacerbations

Moderate/severe asthma exacerbation and severe asthma exacerbation will each be analyzed in a similar manner as described for the secondary endpoint of rate of severe asthma exacerbations utilizing the While on Treatment strategy for handling ICEs based on data from Study D5982C00006 only.

Time to first severe asthma exacerbation will be analyzed with a Cox regression model in Studies D5982C00005 and D5982C00006 separately and with the pooled individual participant data from both studied (D5982C00006: BFF 320/9.6 µg, BFF 160/9.6 µg, BD 320 µg and D5982C00005: BFF 160/9.6 µg, BD 160 µg treatment arms. The Symbicort treatment arm in Study D5982C00006 will not be included in the pooled analysis.), utilizing the While on Treatment strategy for ICEs. The Cox regression model for each study will be adjusted for asthma exacerbation history (0, ≥ 1), prior maintenance medication (ICS versus ICS/LABA), region, baseline trough FEV_1, and percent reversibility. For the pooled analysis, a Cox regression additive model will be used which will also include study, and budesonide (1 if the budesonide dose is 320 µg, and 0 if the budesonide dose is 160 µg) and formoterol (1 if the formoterol dose is 9.6 µg, and 0 if no formoterol dose) instead of treatment as covariates. The comparison of interest is the formoterol effect. Time to first severe asthma exacerbation is the time from the first dose of study intervention to the time of onset of the first severe asthma exacerbation.

Participants not having any severe asthma exacerbations will be censored at the date of their last asthma status assessment + 1, last study visit in the planned treatment phase, or death.

CCI

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

CCI

CCI will be analyzed up to the Week 24 visit with a Cox regression model to compare the treatment groups, adjusting for severe asthma exacerbation history (0, ≥ 1), prior maintenance medication (ICS versus ICS/LABA), region, baseline trough FEV_1, and percent reversibility. A reduced model or only descriptive statistics will be presented if insufficient events occur. Descriptive statistics will include the number and percentage of participants with an event, number of events, annualized rate, and person years at risk. Participants not having any events will be censored at the date of their latest follow-up or end of study visit. Additionally, under the While on Treatment estimand, participants experiencing one or more ICEs will be censored on the day of their first ICE.

CCI

There will be 2 analyses for time to first event. First analysis will include only data up to and including Visit 7 (Week 12). Participants who did not have an event by then would be censored at their Week 12 visit. The second analysis will include all observed data with censoring at the last visit. Both analyses will be analyzed in a manner similar to the analysis of CCI.

EQ-5D

The EQ-5D data will be scored to calculate an index score based upon participants' responses to the 5 dimensions. The VAS will be scored from 0 (worst imaginable health state) through 100 (best imaginable health state) to represent the participant's self-report concerning how bad or how good their health was during that day. The percentage of participant's categorical responses to each of the 5-dimensions will be summarized for the EQ-5D-Y and EQ-5D-5L

questionnaires. Descriptive statistics (number, mean, mean changes from baseline, SD, minimum, maximum) for the index score and VAS will be presented by treatment group and type of questionnaire. The index and VAS scores at each post-randomization visit and end of study visit will be analyzed using repeated measures ANCOVA model with age and baseline score as continuous covariates and region, gender, treatment, prior maintenance treatment (ICS vs ICS/LABA), visit, and treatment-by-visit as categorical covariates.

AIRQ

The AIRQ is a 10-item questionnaire with equally weighted yes/no responses. Greater values indicate a participant has less control. Percentage of control Well (0 to 1), Not Well (2 to 4) and Very Poorly (5 to 10) will be presented by treatment group.

Furthermore, dose response will be evaluated by comparing BFF MDI 320/9.6 µg to BFF MDI 160/9.6 µg on lung function, symptoms, exacerbations, and PROs using the same estimands as for the comparison of BFF MDI 320/9.6 µg vs BD MDI.

9.5.2.4 Healthcare Resource Utilization

All HCRU endpoints will be summarized for mean annualized rate or percentage by treatment group. Both overall and asthma specific HCRU will be reported.

9.5.3 Safety

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

9.5.3.1 Adverse Events

Adverse events during the Treatment Period will be summarized by the number of participants experiencing an event. Adverse events will be tabulated at the level of the MedDRA system organ class and preferred term. The version of MedDRA current at the time of database lock will be used in the tabulations and listings. Tabulations will be broken down by intensity, seriousness, AEs leading to discontinuation, and by relationship to study intervention. No hypothesis testing will be performed. However, treatment groups will be compared as detailed in the SAP. Adverse events associated with use of ICS and LABAs will be presented in summary tabulations in the CSR. The selection of MedDRA terms proposed to be used in the assessment of these AEs will be described in the SAP.

9.5.3.2 Vital Signs

Summary statistics (mean, median, SD, and range) of change from baseline will be tabulated by vital sign parameter and treatment for each scheduled assessment time. For vital signs, baseline will be defined as the last non-missing value prior to the first dose of randomized IP. In addition, potentially clinically significant values will be identified and summarized.

9.5.3.3 Clinical Laboratory Values

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

9.5.4 Subgroup Analyses

Analyses of the primary, secondary, and tertiary endpoints may be performed by various subgroups. Any potential subgroup analyses will be described fully in the SAP.

9.6 Interim Analyses

Not applicable

9.7 Data Monitoring Committee

A Data Monitoring Committee will not be used in this study.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A Regulatory, Ethical, and Study Oversight Considerations

A 1 Regulatory and Ethical Considerations

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

Regulatory Reporting Requirements for SAEs

- Prompt notification by the Investigator to AstraZeneca of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- AstraZeneca has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. AstraZeneca will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and Investigators.
- For all studies except those utilizing medical devices, Investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.
- An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from AstraZeneca will

review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

Regulatory Reporting Requirements for Serious Breaches of Protocol or GCP

- Prompt notification by the Investigator to AstraZeneca of any (potential) serious breach of the protocol or regulations is essential so that legal obligations and ethical obligations are met.
- A "serious breach" means a breach likely to affect to a significant degree the safety and rights of a participant or the reliability and robustness of the data generated in the clinical trial.

AstraZeneca will comply with country-specific regulatory requirements relating to serious breach reporting to the regulatory authority, IRB/IEC, and Investigators.

- Where the EU Clinical Trials Regulation 536/2014 applies, AstraZeneca has in place processes to enter details of serious breaches into the European Medicines Agency CTIS. It is important to note that redacted versions of serious breach reports will be available to the public via CTIS.
- If any (potential) serious breach occurs in the course of the study, Investigators or other site personnel will inform the appropriate AstraZeneca representatives immediately.

In certain regions/countries, AstraZeneca has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about such breaches.

The Investigator should have a process in place to ensure that:

- The site staff or service providers delegated by the Investigator/Institution are able to identify the occurrence of a (potential) serious breach.
- A (potential) serious breach is promptly reported to AstraZeneca or delegated party, through the contacts (email address or telephone number) provided by AstraZeneca.

A 2 Financial Disclosure

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

A 3 Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary, and they are free to refuse to participate and may withdraw their consent at any time and for any reason during the study. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

A 4 Data Protection

- Participants will be assigned a unique identifier by AstraZeneca. Any participant records or datasets that are transferred to AstraZeneca will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by AstraZeneca in accordance with local data protection law. The level of disclosure and use of their data must also be explained to the participant in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by AstraZeneca, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The participant must be informed that data will be collected only for the business needs. We will only collect and use the minimum amount of personal data to support our business activities and will not make personal data available to anyone (including internal staff) who is not authorized or does not have a business need to know the information.
- The participant must be informed that in some cases their data may be pseudonymized. The General Data Protection Regulation defines pseudonymization as the processing of personal data in such a way that the personal data can no longer be attributed to a specific

individual without the use of additional information, provided that such additional information is kept separately and protected by technical and organizational measures to ensure that the personal data are not attributed to an identified or identifiable natural person.

Personal Data Breaches

A 'personal data breach' means a breach of security leading to the accidental or unlawful destruction, loss, alteration, unauthorized disclosure of, or access to, personal data transmitted, stored or otherwise processed.

- In compliance with applicable laws, the Data Controller[1] for the processing activity where the personal data breach occurred (AstraZeneca or respectively the site), will notify the data protection authorities without undue delay within the legal terms provided for such notification and within the prescribed form and content.
- While AstraZeneca has processes in place to deal with personal data breaches it is important that Investigators that work with AstraZeneca have controls in place to protect patient data privacy.

The Investigator should have a process in place to ensure that:

- allow site staff or service providers delegated by the Investigator/institution to identify the occurrence of a (potential) personal data breaches.
- Any (potential) personal data breach is promptly reported to AstraZeneca or delegated party, through the contacts (email address or telephone number) provided by AstraZeneca.

AstraZeneca and the site must demonstrate that they:

- have taken all necessary steps to avoid personal data breaches and

[1] The **data controller** determines the **purposes** for which and the **means** by which personal data are processed, as defined by the European Commission

- have undertaken measures to prevent such breaches from occurring in the first place and to mitigate the impact of occurred data breaches (eg, applying encryption, maintaining and keeping systems and IT security measures up-to-date, regular reviews and testing, regular training of employees, and developed security policies and standards).
- where possible, have developed an internal data breach reporting and investigation process and internal protocols with guidance on how to respond swiftly and diligently to the occurrence of a personal data breach.
- where it has not been possible to develop an internal data breach reporting and investigation process, the site follows AstraZeneca's instructions.

Notification of personal data breach to participants:

- notification to participants is done by the site for the data breaches that occurred within the processing activities for which the site is the Data Controller and for data breaches occurred within the processing activities of AstraZeneca as the Data Controller, the notification is done in collaboration with the site and is performed by the site and/or Principal Investigator, acting on behalf of AstraZeneca, so that AstraZeneca has no access to the identifying personal information of the participants. The site and/or Principal Investigator shall conduct the notification by contacting the participants using the information that they gave for communication purposes in clinical research.
- If a personal data breach occurs in a processor's systems, engaged by AstraZeneca, the processor under contractual obligations with AstraZeneca promptly and in due course after discovering the breach notifies AstraZeneca and provides full cooperation with the investigation. In these cases, to the extent AstraZeneca is the Data Controller for the processing activity where the breach occurred, it will be responsible for the notification to data protection authorities and, if applicable, to participants. If the personal data breach needs to be notified to the participants, the notification to participants is done in collaboration with the site and is performed by the site and/or Principal Investigator, acting on behalf of the Sponsor, so that AstraZeneca has no access to the identifying personal information of the participants.
- If a personal data breach involving an AstraZeneca's representative device (ie, Study Monitor laptop), AstraZeneca representative will provide AstraZeneca with all of the information needed for notification of the breach, without disclosing data that allows AstraZeneca directly or indirectly to identify the participants. The notification will be done by AstraZeneca solely with the information provided by the Study Monitor and in no event with access to information that could entail a risk of re-identification of the participants. If the data breach must be notified to the data participants, the notification will be done directly by the Study Monitor in collaboration with the site and/or Principal Investigator, acting on behalf of the Sponsor, so that AstraZeneca has no access to the

identifying personal information of the participants. The contract between AstraZeneca and the Study Monitor shall expressly specify these conditions.

- The contract between the site and AstraZeneca for performing the clinical research includes the provisions and rules regarding who is responsible for co-ordinating and directing the actions in relation to the breaches and performing the mandatory notifications to authorities and participants, where applicable.

A 5 Dissemination of Clinical Study Data

Any results, both technical and lay summaries for this trial, will be submitted to EU CTIS within a year from global End of Trial Date in all participating countries, due to scientific reasons, as other statistical analysis is not relevant.

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

A 6 Data Quality Assurance

- All participant data relating to the study will be recorded on eCRF unless transmitted to AstraZeneca or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy, including definition of study-critical data items and processes (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- AstraZeneca or designee is responsible for medical oversight throughout the conduct of the study which includes clinical reviews of study data in accordance with the currently approved protocol. Monitoring details describing clinical reviews of study data from a medical perspective are included in more detail in the Monitoring Plan.

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

A 7 Source Documents

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

A 8 Study and Site Start and Closure

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

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

AstraZeneca designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of AstraZeneca. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

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

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

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

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

A 9 Publication Policy

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

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

B 1 Definition of Adverse Events

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

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

B 2 Definition of Serious Adverse Events

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

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

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

Life-threatening

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

Hospitalization

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

Important Medical Event or Medical Treatment

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

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgment must be used.

Examples include:

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

Intensity Rating Scale:

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

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

B 3 A Guide to Interpreting the Causality Question

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

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

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

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

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

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

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

B 4 Medication Error, Drug Abuse, and Drug Misuse

Medication Error

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

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

Medication error includes situations where an error.

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

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

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

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

- Errors related to or resulting from IRT/RTSM – including those which lead to one of the above listed events that would otherwise have been a medication error
- Participant accidentally missed drug dose(s), eg, forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Participant failed to return unused medication or empty packaging

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

Drug Abuse

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

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

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

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

Drug Misuse

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

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

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

- The drug is used with the intention to cause an effect in another person
- The drug is sold to other people for recreational purposes
- The drug is used to facilitate assault in another person
- The drug is deliberately administered by the wrong route
- The drug is split in half because it is easier to swallow, when it is stated in the protocol that it must be swallowed whole
- Only half the dose is taken because the study participant feels that he/she is feeling better when not taking the whole dose
- Someone who is not enrolled in the study intentionally takes the drug

Appendix C Optional Genomics Initiative Research

C 1 Use/Analysis of DNA and Blood Derivatives

- AstraZeneca intends to collect and store DNA for genetic research to explore how genetic variations may affect clinical parameters, risk and prognosis of diseases, and the response to medications. This genetic research may lead to better understanding of diseases, better diagnosis of diseases or other improvements in health care and to the discovery of new diagnostics, treatments, or medications. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting participants.
- This optional genetic research may consist of the analysis of the structure of the participant´s DNA, ie, the entire genome.
- The results of genetic analyses may be reported in a separate study summary.
- AstraZeneca will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

C 2 Multi-omics Research Plan and Procedures

Selection of Multi-omics Research Population

- All participants will be asked to participate in this genetic research. Participation is voluntary and if a participant declines to participate there will be no penalty or loss of benefit. The participant will not be excluded from any aspect of the main study.

Inclusion Criteria

For inclusion in this genetic research, participants must fulfill all of the inclusion criteria described in the main body of the CSP and provide informed consent for the Genomics Initiative sampling and analyses.

Exclusion Criteria

- Exclusion from this genetic research may be for any of the exclusion criteria specified in the main study or any of the following:
  - Previous allogeneic bone marrow transplant
  - Non-leukocyte depleted whole blood transfusion in 120 days of genetic sample collection
  - Adolescent participant (12 to < 18 years of age) samples will not be collected for Genomics Initiative.

Withdrawal of Consent for Multi-omics Research

- Participants may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary withdrawal will not prejudice further treatment. Procedures for withdrawal are outlined in Section 7.2.

Collection of Samples for Multi-omics Research

- The blood sample for this genetic research will be obtained from the participants at Visit 4 after randomization. Although DNA is stable, early sample collection is preferred to avoid introducing bias through excluding participants who may withdraw due to an AE. If for any reason the sample is not drawn at Visit 4, it may be taken at any visit until the last study visit. Only one sample should be collected per participant for genetics during the study.

Coding and Storage of DNA and Multi-omics Samples

- The processes adopted for the coding and storage of samples for genetic analysis are important to maintain participant confidentiality. Samples will be stored for a maximum of 15 years, from the date of last participant last visit, after which they will be destroyed. DNA is a finite resource that is used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.
- An additional second code will be assigned to the sample either before or at the time of DNA extraction replacing the information on the sample tube. Thereafter, the sample will be identifiable only by the second, unique number. This number is used to identify the sample and corresponding data at the AstraZeneca analysis laboratories, or at the designated organization. No personal details identifying the individual will be available to any person (AstraZeneca employee or designated organizations working with the DNA).
- The link between the participant enrollment/randomization code and the second number will be maintained and stored in a secure environment, with restricted access at AstraZeneca or designated organizations. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit, and permit tracing of samples for destruction in the case of withdrawal of consent.

Ethical and Regulatory Requirements

- The principles for ethical and regulatory requirements for the study, including this genetics research component, are outlined in Appendix A.

Informed Consent

- The genomic and multi-omics component of this study is optional, and the participant may participate in other components of the main study without participating in this multi-omics component. To participate in the genetic component of the study the participant must sign and date both the consent form for the main study and the Optional Genomics Initiative Research Information consent form. Copies of both signed and dated consent forms must be given to the participant and the original filed at the study center. The Principal Investigator(s) is responsible for ensuring that consent is given freely, and that the participant understands that they may freely withdrawal from the genetic aspect of the study at any time.

Participant Data Protection

- AstraZeneca will not provide individual genotype results to participants, any insurance company, any employer, their family members, general physician unless required to do so by law.
- Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the participant. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a participant. For example, in the case of a medical emergency, an AstraZeneca Physician or an Investigator might know a participant's identity and also have access to his or her genetic data. Regulatory authorities may require access to the relevant files, though the participant's medical information and the genetic files would remain physically separate.

Data management

- Any genetic data generated in this study will be stored at a secure system at AstraZeneca and/or designated organizations to analyze the samples.
- AstraZeneca and its designated organizations may share summary results (such as genetic differences from groups of individuals with a disease) from this genomics research with other researchers, such as hospitals, academic organizations, or health insurance companies. This can be done by placing the results in scientific databases, where they can be combined with the results of similar studies to learn even more about health and disease. The researchers can only use this information for health-related research purposes. Researchers may see summary results, but they will not be able to see individual participant data or any personal identifiers.
- Some or all of the clinical datasets from the main study may be merged with the multi-omics data in a suitable secure environment separate from the clinical database.

Appendix D Protocol Amendment History

The Summary of Change Table for the current amendment is located directly before the Table of Contents.

D 1 Amendment 2 (05 Dec 2023)

CSP Version 3.0: 05-Dec-2023

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

Overall Rationale for the Amendment:

An amendment was required to update statistical methodology, including changes to estimands, the Type I error control procedure, covariates in the analysis models, and analysis sets and to add updated wording from the new AstraZeneca protocol standard template.

Summary of Changes:

List of Substantial Modifications

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis, 3 Objectives and Endpoints, 9.1 Statistical Hypotheses, 9.2 Analysis Methods for Estimands, 9.2.1.1 CCI Approach, 9.5.2.1 Primary Endpoints, 9.5.2.2 Secondary Endpoint(s)	The Type I error control procedure for the CCI has been updated to: • Reflect the use of Treatment Policy as the primary ICE strategy across registrational endpoints for the CCI The While on Treatment approach and Composite approach are no longer planned to be conducted on registrational endpoints for the CCI submission. • Include the analysis of severe asthma exacerbation rate in the pooled D5982C00006 and D5982C00005 data as well as in the individual studies as secondary analyses. Information on power estimates based on analyses under the While on Treatment strategy for handling ICEs at Week 24 has been removed.	CCI [redacted]
1.1 Synopsis, 3 Objectives and	The CCI Type I error control procedure was updated to remove the	

Section # and Name	Description of Change	Brief Rationale
Endpoints, 9.1 Statistical Hypothesis, 9.2.1.2 CCI Approach, 9.5.2.1 Primary Endpoint	NI tests for secondary endpoints. The NI test of FEV_1 AUC_{0-3} for the BFF MDI 320/9.6 µg versus Symbicort TBH comparison was added but was kept outside of the procedure for multiplicity control and therefore, not subject to Type I error control. Assay sensitivity of Symbicort TBH vs BD MDI 320 µg was removed as it was deemed not necessary.	CCI
1.1 Synopsis, 3 Objectives and Endpoints, 9.5.2.2 Secondary Endpoint(s)	The population summary measure for the test of onset of action on Day 1 has been changed to "difference in mean change from baseline" and will no longer be performed as a within-group test but will compare the BFF MDI 320/9.6 µg relative to BD MDI 320 µg in the multiple testing procedure. The within-group test was kept as a supportive/exploratory analysis.	To allow assessment of the relative performance of BFF MDI 320/9.6 µg compared with BD MDI 320 µg arm.

List of Non-Substantial Modifications

Section # and Name	Description of Change	Brief Rationale
List of Abbreviations	The List of Abbreviations has been moved from Appendix D to the beginning of the protocol and definitions have been removed from the body of the document.	To match updated Protocol Standard template.
1.1 Synopsis	Details of PP analysis set from the main body of the protocol have been included in the Synopsis.	To provide clarity.
1.1 Synopsis	Details of sample size from the main body of the protocol have been included in the Synopsis.	To provide clarity.
1.1 Synopsis	Details of power calculations for trough FEV_1 and FEV_1 AUC_{0-3} at Week 24 and using the Treatment Policy have been added.	To add clarity to power calculations for the primary and secondary endpoints.
1.1 Synopsis, 3 Objectives and Endpoints	Expanded definitions of ICE to improve clarity. Additional details added on the handling of each ICE with each	Providing clarity on estimand strategy.

Section # and Name	Description of Change	Brief Rationale
	estimand within the Objectives and Endpoints Table.	
1.1 Synopsis, 3 Objectives and Endpoints, 9.2 Analysis Methods for Estimands, 9.5.2.1 Primary Endpoints, 9.5.2.2 Secondary Endpoint(s)	Hybrid estimand strategy for ICEs was added as a supplemental estimand for primary and secondary endpoints for all regions, and the Attributable estimand approach was removed.	The Hybrid estimand approach is deemed to answer an important clinical question of interest, where outcomes following a non-attributable ICE will use a Treatment Policy strategy and outcomes following an attributable ICE will be considered an unfavorable outcome. Attributable estimand removed to simplify the number of estimands used as supportive that would be reported in the CSR.
1.1 Synopsis, 9.4 Populations for Analysis	Intent-to-Treat Population was replaced with Efficacy set; modified Intent-to-Treat Population was removed	The terms “Intent-to-Treat analysis set” and modified Intent-to-Treat analysis set” were replaced with “Efficacy set”.
1.1 Synopsis, 9.5.2 Efficacy	Clarified that the model for analysis of repeatedly measured continuous variables is “repeated measures ANCOVA”.	Model includes both continuous and categorical predictor variables.
1.1 Synopsis, 9.5.2. Efficacy	Details of covariates updated.	Consistency of covariates across analyses. Covariates deemed clinically relevant to the respective endpoints of interest and have been updated accordingly.
1.3 Schedule of Activities	Footnote “d” added stating ICF could be signed at or before Visit 1.	To provide clarity.
1.3 Schedule of Activities	Tick mark added to Visit 1 for administration of Run-in BD MDI in clinic.	To provide clarity that this activity should occur.
1.3 Schedule of Activities	Note added to footnote “e” allowing for rescheduling of Visit 1 if there are concerns that ICS/LABA was not withheld.	To provide clarity.
1.3 Schedule of Activities	Note added to footnote “j” that spirometry should be postponed if participant has not washed-out asthma medications.	To provide clarity.
3 Objectives and Endpoints	It was clarified that the safety objective is for comparing BFF MDI 320/9.6 µg relative to BD MDI and Symbicort TBH. A comparison of	To provide clarity on safety comparisons.

Section # and Name	Description of Change	Brief Rationale
	BFF MDI 320/9.6 µg relative to BFF MDI 160/9.6 µg was included to provide supportive safety information.	
3 Objectives and Endpoints	While on Treatment estimand deleted for Safety	For Safety, the only ICE of interest is discontinuation of study intervention. Moreover, data following this ICE is also of interest for some analyses. Those analyses are therefore defined outside of the estimand framework specified for the Efficacy analysis.
3 Objectives and Endpoints, 9.2.1.3 CCI Approach, 9.5.2.2 Secondary Endpoints	An exploratory objective was added to compare BFF MDI 320/9.6 µg to BFF MDI 160/9.6 µg on lung function, exacerbations symptoms, and PROs.	To evaluate dose response.
3 Objectives and Endpoints, 9.5.2.3 Tertiary/Exploratory Endpoint(s)	An analysis on the rate of moderate/severe asthma exacerbations utilizing the Treatment Policy estimand was added as an exploratory analysis. An analysis of time to first severe asthma exacerbation in the combined D5982C00006 and D5982C00005 data utilizing the Treatment Policy strategy for ICEs has been added as an exploratory analysis.	To support analysis on severe exacerbation rate, included in the multiplicity strategy for CCI
4.1 Overall Design, 5.1 Inclusion Criteria, 8.1.1.2 Spirometry Schedule, 8.1.1.3 Reversibility to Albuterol	Reversibility testing wording modified. Resolved inconsistences across the sections to reflect Inclusion Criterion relating to historical reversibility in the last 12 months.	Wording throughout protocol modified to match the inclusion criterion.
4.5 End of Study Definition, 5.1 Inclusion Criteria, 6.1.2 Medical Devices Including Combination Products with Device Constituents, 8.3.11 Medication Error, Drug Abuse, and Drug Misuse, 8.3.12 Device Constituent Deficiencies, 8.7 Optional Genomics	Updated AstraZeneca standard protocol template wording added.	Protocol standard template was recently updated and required wording has been added to this protocol.

Section # and Name	Description of Change	Brief Rationale
Initiative Sample, A1 Regulatory and Ethical Considerations, A4 Data Protection, A5 Dissemination of Clinical Study Data, A6 Data Quality Assurance, B4 Medication Error, Drug Abuse, and Drug Misuse, Appendix C Optional Genomics Initiative Research		
5.2 Exclusion Criteria	Wording added to Exclusion Criterion #8 to identify exact studies where previous or current inclusion is prohibited.	To provide clarity.
6.5.2 Prior Medications, Table 5	For mometasone furoate, the specific dose was removed, and a statement added to discuss with study physician. Footnote added to clarify doses of Symbicort pMDI.	To align with GINA 2022 and complexities around different doses across formulations.
6.5.4 Prohibited Medication, Table 7	Removed reference to intraocular corticosteroids and decreased cessation period for LAMAs to 12 weeks and injectable systemic corticosteroids to 3 months.	Amended to alleviate constraints on study recruitment.
8.2.8.1 Paradoxical Bronchospasm	Removal of Visit 6 as this is a telemedicine visit where this activity cannot occur.	Correction of error.
9.4 Populations for Analysis	Randomized set was added.	Randomized set defined for clarity.
9.5.1.2 Visit Windows	Visit windows for analysis have been defined.	To map data to closest scheduled visit.
9.5.1.3 Baseline	Severe asthma exacerbation baseline definition added.	To provide clarity.
9.5.2.1 Primary Endpoint, 9.5.2.2 Secondary Endpoint(s)	It was clarified that data will not be imputed for the analyses of the primary endpoint and that sensitivity analyses exploring the robustness of results due to missing data will be conducted.	To provide clarity. Additional details will be provided in the SAP.
9.5.2.2 Secondary Endpoint(s),	It was clarified that the endpoints of onset of action and percentage of	To provide clarity.

Section # and Name	Description of Change	Brief Rationale
9.5.2.3 Tertiary/Exploratory Endpoints	peak FEV_1 improvement achieved are based on data 5 minutes post-dose on Day 1.	
9.5.2.3 Tertiary/Exploratory Endpoints	Change from baseline in evening pre-dose peak expiratory flow will not be analyzed by visit.	Evening peak expiratory flow is not assessed at clinic visits.
9.5.2.3 Tertiary/Exploratory Endpoints	EQ-5D presentation will be split by questionnaire populations (12-15 years, ≥ 16 years). It was clarified that the EQ-5D index score will be analyzed using repeated measures ANCOVA model similarly to the VAS score.	EQ-D5 presentation will be split by questionnaire population due to practical considerations in mapping questions from the 2 questionnaires (adults and adolescents). The analysis on index score was included for clarity.
Throughout	Minor editorial and document formatting revisions.	Minor; therefore, have not been summarized.

D 2 Amendment 1 (12 Oct 2021)

CSP Version 2.0: 12-Oct-2021

This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/ED of the European Parliament and the Council of the European Union because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific values of the study.

Overall Rationale for the Amendment:

Clarity added for telemedicine visit conduct, order of assessments, and birth control methods. Additional details added for Treatment Policy estimand and sample size calculations.

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
1.2. Schema; 1.3. Schedule of Activities; 4.1. Overall Design	Telemedicine visits can be conducted either by telephone or video.	To add clarity that telemedicine visits can be conducted by either telephone or video.	Non-substantial
1.3. Schedule of Activities	Review of inhalation technique and administration of study intervention requirements removed from Visits 6 and 8.	Visits 6 and 8 have been modified to be performed as telemedicine (telephone or video) visits, therefore observing inhalation technique and administration of study intervention are no longer	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
		possible at these visits when conducted by telephone.	
1.3. Schedule of Activities; 8. Study Assessments and Procedures; 8.1.2.7. Study Visit eDiary Data Collection	Details added describing the order of assessments.	To add clarity to the order in which assessments should be performed during a visit.	Non-substantial
2.3. Benefit/Risk Assessment	Reference to patient reported outcomes and health-related quality of life measures removed from benefit statement.	The patient reported outcomes and health-related quality of life measures are not powered for this study and therefore cannot conclusively determine benefit.	Non-substantial
3. Objectives and Endpoints	Strategy for ICEs was updated for the primary and key secondary endpoints, moving Treatment Policy from Supplemental to Secondary for the CCI testing approach.	To reflect CCI considerations of the existing Treatment Policy estimand analyses that were already included in the CSP by controlling type I error across these.	Non-substantial
5.1. Inclusion Criteria	Inclusion criterion 6: reversibility to albuterol in 12 months prior to Visit 1 added.	To allow inclusion of participants with documented historical reversibility in the past 12 months.	Non-substantial
	Inclusion criterion 13: definition of abstinence added; clarity provided for acceptable oral contraceptives; bilateral tubal ligation added.	To add clarity to birth control requirements.	
5.2. Exclusion criteria	Exclusion criterion 13: QTcF exclusion criterion changed to > 480 msec.	Updated for consistency across asthma program.	Non-substantial
8.2.1.7. Study Visit eDiary Data Collection	Estimated PRO completion time updated to 20 minutes.	To provide a more accurate estimate of PRO completion time.	Non-substantial
9.2. Analysis Methods for estimands; 9.2.1. Type I Error Control; 9.2.1.1. US Approach; 9.5.2.1. Primary Endpoints;	For the primary and key secondary endpoints moving to Treatment Policy analysis from Supplemental to Secondary for the US testing approach.	To reflect CCI considerations around the Treatment Policy estimand analyses that were already included in the CSP by controlling type I error across these.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
9.5.2.2. Secondary Endpoints			
9.3. Sample Size Determination	Details of power calculation for FEV_1 AUC_{0-3}, at Week 24, and using the Treatment Policy estimand have been added.	To add clarity to power calculations for the primary and key secondary endpoints.	Non-substantial
9.5. Statistical Analyses	Details added for when SAP will be finalized.	To add clarity to timelines for finalization of SAP in line with company operating procedures	Non-substantial
9.5.2.3. Tertiary/Exploratory Endpoints	Details of supportive analyses provided. Time to Peak FEV_1 on Day 1 and Percentage of Peak FEV_1 Improvement Achieved at 5 Minutes on Day of Randomization.	To add clarity of supportive analyses that may be conducted and that details will be included in SAP.	Non-substantial
Throughout	Minor editorial and document formatting revisions	Minor, therefore have not been summarized	Non-substantial

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