Statistical Analysis Plan	
Study Code	D5980C00023
Edition Number	2.1
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A Randomized, Open-Label, Two Period Crossover, Chronic Dosing, 1-Week, Pilot Study to Assess the Efficacy and Safety of Budesonide and Formoterol Fumarate Inhalation Aerosol Administered with a Spacer Compared with Symbicort® Turbuhaler® in Subjects with Severe to Very Severe Chronic Obstructive Pulmonary Disease and Low Peak Inspiratory Flow

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
AE	Adverse Event
ANCOVA	Analysis of Covariance
ATC	Anatomic Therapeutic Class
ATS	American Thoracic Society
AUC0-4	Area Under the concentration-time Curve from time 0 to 4-hours post-dose
BDRM	Blinded Data Review Meeting
BFF	Budesonide/Formoterol Fumarate
BDR	Blind Data Review
BID	Bis In Die, twice daily
BLOQ	Below the Limit of Quantification
Cmax	Maximum Observed Plasma Concentration
Ctrough	The Concentration at the End of the Dosing Interval
COPD	Chronic Obstructive Pulmonary Disease
CPS	Clinical Pharmacology Scientist
CSR	Clinical Study Report
DAE	Discontinuation of Investigational Product due to Adverse Event
DPI	Dry Powder Inhalers
eCRF	electronic Case Report Form

Abbreviation or special term	Explanation
ERS	European Respiratory Society
FEV_1	Forced Expiratory Volume in 1 Second
FEV_1 AUC0-4	Area Under the Curve for change from baseline in FEV_1 from 0 to 4 hours
FVC	Forced Vital Capacity
gCV	Geometric Coefficient of Variation
gmean	Geometric Mean
HFA	Hydrofluoroalkane
IC	Inspiratory Capacity
ICS	Inhaled Corticosteroid
IMP	Investigational Medicinal Product
IP	Investigational Product
IPD	Important Protocol Deviation
ITT	Intent-To-Treat
MDI	Metered Dose Inhaler
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-To-Treat
NCA	Non-Compartmental Analysis
NC	Not Calculable
NQ	Non-Quantifiable
NR	Not Reportable
NS	No Sample

Abbreviation or special term	Explanation
PFT	Pulmonary Function Test
PIF	Peak Inspiratory Flow
PK	Pharmacokinetics
QID	Quater In Die, four times each day
SAE	Serious Adverse Event
TEAE	Treatment Emergent Adverse Event
tmax	Time to Maximum Observed Plasma Concentration
TP	Treatment Period
TRCAUC	Treatment Ratio of AUC
TRCmax	Treatment Ratio of Cmax
TRCtrough	Treatment Ratio of Ctrough
WHO-DD	World Health Organization Drug Dictionary

AMENDMENT HISTORY

Category*: Change refers to	Date	Description of change	In line with the CSP?	Rationale
Other	CCI	Population definition changed from "moderate to very severe" to "severe to very severe" to align with changed inclusion and randomization criteria.	Yes	Per CSP version 3.0 dated on CCI
Other	CCI	InCheck device setting changed from "Turbuhaler resistance" to "Turbuhaler S resistance" (which stands for "Turbuhaler Symbicort" as per InCheck device manual) throughout the protocol for clarification, because there are two different Turbuhaler resistance settings on the InCheck device.	Yes	Per CSP version 3.0 dated on CCI
Other	CCI	Approximate number of prospective subjects to be screened has been changed from "45" to "150" to accommodate high screen failure rate anticipated for the study.	Yes	Per CSP version 3.0 dated on CCI
Other	CCI	Revised wording to clarify that study will be conducted in "approximately 4 sites"	Yes	Per CSP version 3.0 dated on CCI
Other	CCI	Randomization stratification revised from setting "no resistance" to "Turbuhaler S resistance" and changed limit for PIF from "<45 L/min versus ≥45 to <60 L/min" to "<40 L/min versus ≥40".	Yes	Per CSP version 3.0 dated on CCI
Other	CCI	Revised Figure 1. Removed footnote stating possibility to combine Visit 1 and Visit 2, as this statement was not correct. Corrected week for Visit 2 from "-2" to "-1"	Yes	Per CSP version 3.0 dated on CCI
Other	CCI	Revised "Study Design Chart" in section 1.2. Removed footnote stating possibility to combine Visit 1 and Visit 2, as this statement was not correct. Corrected week for Visit 2 from "-2" to "-1"	Yes	Per CSP version 3.0 dated on CCI
Primary or secondary endpoints	CCI	In section 2.1.6 changed "primary endpoints" to "primary endpoint"	Yes	There is only 1 primary endpoint that is "Peak change from baseline in FEV_1 within 4 hours post-dose following 1 week of

				treatment"
Other	CCI	Revised Section 2.2, violations and deviations section to use the terminology "important protocol deviations" rather than major protocol deviations	Yes	In line with company standard operating procedures
Other	CCI	In section 2.2 in the paragraph of "Randomization Errors" changed "MPDs" to "IPD that lead to exclusion from mITT."	Yes	In line with company standard operating procedures
Other	CCI	In section 3.1.2 changed "no resistance" to "Turbuhaler S resistance".	Yes	Per CSP version 3.0 updated on CCI
Other	CCI	Section 3.4 revised to clarify reporting timeframes for non-serious and serious adverse events.	Yes	Per CSP version 3.0 dated on CCI
Primary or secondary endpoints	CCI	In section 4.2.1, after the sentence of "Demographics and baseline characteristics at screening will be summarized descriptively, including COPD disease duration, disease severity, and COPD assessment test (CAT) score", added ", as well as eosinophil count and whether receiving ICS at screening.:	Yes	Summarising further important aspects of the study population.
Statistical analysis method for the primary or secondary endpoints	CCI	In section 4.2.4.1 changed "PIF at screening (InCheck set at no resistance)" to "PIF at screening (InCheck set at Turbuhaler S resistance)"	Yes	Per CSP version 3.0: Randomization stratification revised from setting "no resistance" to "Turbuhaler S resistance"
Data presentations	CCI	In section 4.2.4.2 changed subgroup definitions to "(<40 L/min and ≥40 L/min)" in line with updated randomization strata	Yes	Per CSP version 3.0 dated on CCI
Primary or secondary endpoints	CCI	In section 4.2.4.2 in the paragraph for "Change from baseline in pre-dose PIF following 1 week of treatment", at the end added ", and without adjusting for PIF at screening (InCheck set at Turbuhaler S resistance."	Yes	Avoiding PIF at screening and PIF at baseline both being in the statistical model given they will be highly correlated. Resistance level as per CSP version 3.0 dated on CCI
Primary or secondary endpoints	CCI	In section 4.2.4.2 Supportive Analysis 2nd paragraph, added "with the Turbuhaler S resistance level" after "Subgroup analyses based upon PIF at screening"	Yes	Per CSP version 3.0 dated on CCI

Primary or secondary endpoints	CCI	Revised "Ctrough is not part of the protocol and added in the SAP." To "No changes of analysis from protocol are made." in section 6 as the two documents are now consistent.	Yes	Per CSP version 3.0 dated on CCI Version History for Section 9.4.2, "PK parameter Ctrough was added in Section 9.4.2 and to abbreviation list in order to align with the Statistical Analysis Plan."
Other	CCI	Signature pages were removed .	N/A	To comply with the requirements in the AZ ANGEL system. Signatures are added electronically
Other	CCI	In section 1.2 "Study Design" added paragraph discussing potential need to put study on hold or re-enrol subjects due to impact of COVID-19 pandemic.	Yes	Per CSP version 4.0 dated on CCI
Other	CCI	In sections 2.1.2, 2.1.3 and 2.1.4, updates made to analysis set definitions to include description of how data will be handled for patients affected by COVID-19 related study hold.	Yes	Per CSP version 4.0 dated on CCI
Other	CCI	Added section 3.7 "Handling of Re-Enrolments".	Yes	Per CSP version 4.0 dated on CCI
Data presentations	CCI	In section 4.2.1 "Disposition, Demographics and Baseline Characteristics", added descriptions on the subject disposition summaries due to COVID-19 related hold.	Yes	Per CSP version 4.0 dated on CCI
Other	CCI	In section 4.2.2 "Prior and Concomitant Medications", added descriptions for handling of "re-enrolling subjects".	Yes	Per CSP version 4.0 dated on CCI
Other	CCI	In section 4.2.3 "Exposure and Compliance", added descriptions for handling of "re-enrolling subjects".	Yes	Per CSP version 4.0 dated on CCI
Data presentations	CCI	In section 4.2.4.1 "Primary Efficacy Analysis", added "Individual data points will be included in the boxplots. In	Yes	To provide more detailed visualisation of efficacy findings.

		addition, a paired line plot will be produced for the primary endpoint only."		
Statistical analysis method for the primary or secondary endpoints	CCI	In section 4.2.4.2 "Analysis of Secondary Efficacy Variables" "Supportive analyses", added a subgroup analysis on primary endpoint using mITT accounting for COVID-19 study hold; revised with more details about using plots to investigate PIF thresholds with greatest separation of MDI vs. DPI effects.	Yes	Per CSP version 4.0 dated on CCI .
Other	CCI	In section 4.2.5 "Safety Data", added descriptions for handling of "re-enrolling subjects".	Yes	Per CSP version 4.0 dated on CCI
Other	CCI	In section 6 "CHANGES OF ANALYSIS FROM PROTOCOL", added clarification of mITT definition.	Yes	Clarified use of IPD terminology as per SAP update on CCI
Other	CCI	In section 2.2 "Violations and Deviations", excluded Budesonide from the list of medications requiring a minimal washout duration.	Yes	Acute short term effect of budesonide on lung function is small so would not be expected to have an important bearing on the efficacy findings.

* Pre-specified categories are
Primary or secondary endpoints; Statistical analysis method for the primary or secondary endpoints; Derivation of primary or secondary endpoints; Multiple Testing Procedure; Data presentations; Other

1 STUDY DETAILS

1.1 Study Objectives

Study objectives and endpoints are presented in Table 1. Detailed definitions of the endpoints are given in section 3.

Table 1 Study Objectives and Endpoints

Primary objective:	**Endpoint/variable:**
To assess the effects of BFF MDI administered with a spacer relative to Symbicort Turbuhaler on lung function, measured by peak forced expiratory volume in 1 second (FEV_1) within 4 hours post-dose at Week 1, in subjects with COPD and low PIF.	• Peak change from baseline in FEV_1 within 4 hours post-dose following 1 week of treatment
Secondary objective:	**Endpoint/variable:**
To assess the effects of BFF MDI administered with a spacer relative to Symbicort Turbuhaler on additional measures of lung function.	• Area under the curve for change from baseline in FEV_1 from 0 to 4 hours (FEV_1 AUC0-4) following 1 week of treatment • Change from baseline in pre-dose FEV_1 following 1 week of treatment • Change from baseline in 2-hour post-dose inspiratory capacity (IC) following 1 week of treatment • Change from baseline in pre-dose PIF (InCheck Device set to no resistance, resistance set equal to Turbuhaler S, and resistance set equal to ELLIPTA) following 1 week of treatment • Change from baseline in 2-hour post-dose FEV_1 following the first dose • Change from baseline in 2-hour post-dose IC following the first dose
Safety objective:	**Endpoint/variable:**

To assess the safety of BFF MDI administered with a spacer and Symbicort Turbuhaler	• AEs • Serious adverse events (SAEs) • Adverse events leading to treatment discontinuation (DAEs)
Pharmacokinetic Objective:	**Endpoint/variable:**
To characterize the steady state pharmacokinetics (PK) of budesonide and formoterol from drug administration of BFF MDI administered with a spacer and Symbicort Turbuhaler	The key endpoints following 1 week of treatment are: • Area under the concentration- time curve from time 0 to 4-hours post-dose (AUC0-4) • Time to maximum observed peak concentration (tmax) • Maximum observed plasma concentration (Cmax) • The concentration at the end of the dosing interval (Ctrough) Additional PK parameters may be calculated, as appropriate.

1.2 Study Design

This is a Phase IIIb randomized, open-label, 2 period (each 1-week treatment) crossover efficacy and safety pilot study comparing BFF MDI (Metered Dose Inhaler) 320/9.6 µg administered with a spacer twice daily (BID) with Symbicort Turbuhaler 320/9 µg BID in subjects with severe to very severe Chronic Obstructive Pulmonary Disease (COPD) and low peak inspiratory flow (PIF).

At Visit 1, subjects will discontinue their COPD maintenance therapies and will enter a 2- to 3-week run-in period on Berodual 20/50 µg QID and budesonide MDI 320 µg BID (budesonide to only be used for subjects receiving ICS therapy at screening). Albuterol/salbutamol sulfate (referred to as Ventolin HFA) will be provided to use as rescue medication throughout the study. Randomization will be stratified by the Visit 3 PIF set to Turbuhaler S resistance (<40 L/min versus ≥40 L/min).
Following randomization, subjects will undergo 2 treatment periods of 1 week each, with an

intervening two-week washout period where they will use Berodual and budesonide MDI 320 µg BID (budesonide to only be used for subjects receiving inhaled corticosteroid (ICS) therapy at screening).

This study will be conducted at up to approximately 4 sites.

Subjects that may have been in screening/run-in/randomized and considered either screen failures and/or discontinued when the study or site could be placed on hold on account of COVID-19 pandemic related events for e.g. local health advisory, travel restrictions, etc.; these subjects may be re-invited with a new subject identifier, starting with informed consent process and Visit 1 assessments as appropriate.

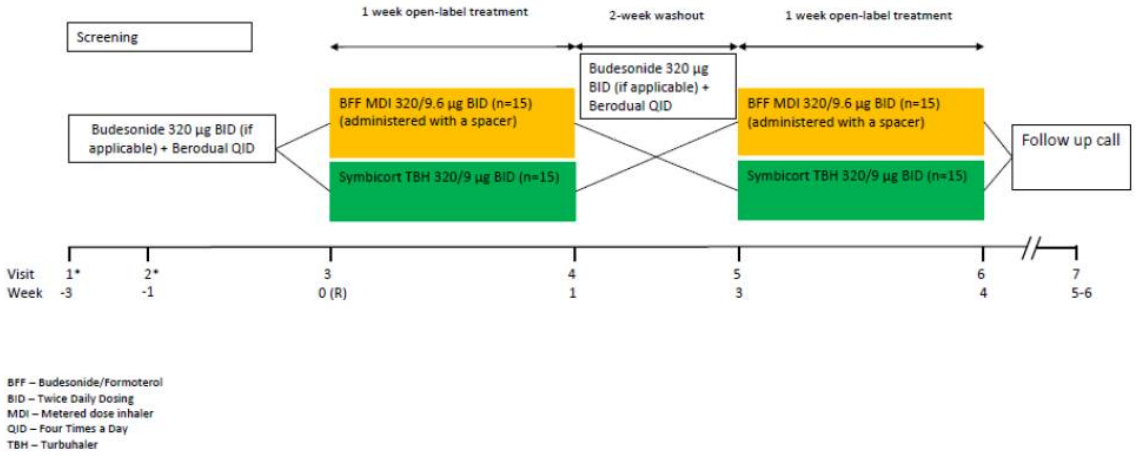
Study Periods:

There will be two treatment periods (TP) in this study. The first day on which a study treatment is received is Treatment Day 1 (Visit 3 for TP 1, Visit 5 for TP 2). Treatment day is numbered sequentially thereafter until the next scheduled visit (Visit 4 for TP 1, Visit 6 for TP 2), or until the subject withdraws from the study or is lost to follow-up. Each TP is intended to last until Day 8. Washout period between Visit 4 and Visits 5 is 14 days. If any visits are rescheduled, the latest visit will be used.
It is expected that IMP (Investigational Medicinal Product) dosing will not go beyond Visit 4 for TP 1, and beyond Visit 6 for TP 2. However, exposure to IMP will be calculated based on the day of actual last dose of each treatment.

Treatments and treatment duration:

The 2 cross-over treatments will be:
BFF: Budesonide/ Formoterol Fumarate, 320/9.6 µg (160/4.8 µg per actuation), MDI 2 oral inhalations in the morning and 2 oral inhalations in the evening.
Symbicort Turbuhaler: 320/9 µg (160/4.5 µg per inhalation), DPI (Dry Powder Inhaler) 2 oral inhalations in the morning and 2 oral inhalations in the evening.
During the washout period, treatment with Berodual and budesonide MDI (if applicable) will be administered.

Study design chart



1.3 Number of Subjects

It is planned that approximately 150 prospective subjects will be screened, with approximately 30 subjects randomized, 15 per sequence, in order to ensure at least 26 subjects completing the study. The sample size has been selected based on practical considerations to obtain reasonable estimates of treatment effects related to device, as well as variability, for the primary and secondary endpoints. These will be used to further inform on the design and sample size needed for future studies.

Randomization will be stratified by the Visit 3 PIF set to Turbuhaler S resistance (<40 L/min versus ≥40 L/min).

1.4 Blinding

All subjects will be centrally assigned to randomized study treatment sequence using an interactive web response system (IWRS). Potential bias will be reduced through central randomization. Although this is an open-label study to subjects and investigators, sponsor blind roles are being maintained to minimize bias. A sponsor blind model will be followed and described in the Trial Integrity Document, whereby it is expected that statistical and programming personnel will be blinded. Blind data reviews (BDRs) will be produced using dummy treatment sequences. PK data will not be used at the BDR. Versions of exposure data will be required that do not contain treatment revealing data.

2 ANALYSIS SETS

2.1 Definition of Analysis Sets

The following analysis populations are defined in this study:

2.1.1 Enrolled Analysis Set

Enrolled analysis set is defined as all subjects who sign the informed consent form (ICF).

2.1.2 Intent-to-Treat (ITT) Analysis Set

The Intent-to-Treat (ITT) analysis set is defined as all subjects who are randomized to treatment and receive at least one dose of study treatment. Subjects will be analyzed according to the treatment they were assigned to as randomized, regardless of the treatment actually received.

Subjects affected by the study being put on hold for the COVID-19 pandemic will be handled as follows:

- Subjects who were discontinued due to the study being put on hold and who restarted the study will only be included in the ITT analysis set for the instance of enrolment after they restarted.
- Discontinued subjects who do not restart will be included in the ITT analysis set.

This ensures that all randomized subjects are included in the ITT set once and once only.

2.1.3 Modified ITT (mITT) Analysis Set

The modified ITT (mITT) analysis set is defined as all subjects in the ITT Population with post-baseline spirometry data from both treatment periods at Visits 4 and 6. Subjects with data judged to be impacted by important protocol violations will be excluded. Subjects will be analyzed according to the treatment they were assigned to as randomized.

Subjects affected by the study being put on hold for the COVID-19 pandemic will be handled as follows:

- Subjects who were discontinued due to the study being put on hold and who restarted the study will only be included in the mITT analysis set for the instance of enrolment after they restarted, if they have post-baseline spirometry data for both treatment periods after restart and meet the definition described above.
- Discontinued subjects who do not restart will not be included in the mITT analysis set as they will not have post-baseline spirometry data from both treatment periods.

This ensures that all randomized subjects are included in the mITT set at most once, if they meet the relevant definition.

2.1.4 Safety Analysis Set

The Safety analysis set is defined as all subjects who are randomized to treatment and receive at least one dose of the study treatment. Subjects will be analyzed according to the treatment actually received.

Subjects affected by the study being put on hold for the COVID-19 pandemic will be handled as follows:

- Subjects who were discontinued due to the study being put on hold and who restarted the study will only be included in the Safety analysis set for the instance of enrolment after they restarted.
- Discontinued subjects who do not restart will be included in the Safety analysis set.

This ensures that all randomized subjects are included in the Safety set once and once only.

2.1.5 Pharmacokinetic (PK) Analysis Set

The PK Analysis Set is defined as all subjects in the mITT population with Cmax defined in both treatment periods and who do not have important protocol deviations which affect the PK analysis.

Important protocol deviations can result in exclusion of all data collected for a particular subject from the PK Analysis Set or require exclusion of data from a specific analyte, timepoint and/or subsequent time points for an endpoint. Protocol deviations for exclusion of subjects or data from the PK Analysis Set will be agreed upon by the study team and documented prior to database lock.

Steady state is expected to be achieved within 3 days for all analytes (budesonide, and formoterol). If a subject has missed any of the scheduled doses in the 3 days prior to Day 8 of each Treatment Period, the Day 8 concentration data for that subject will be excluded from the PK Analysis Set.

The PK analysis will be performed on data from all subjects in the PK Analysis Set. Analyses will be according to the treatment actually received.

2.1.6 Use of Analysis Sets

Analyses will be performed as follows:

Demographics and subject characteristics will be summarized for the ITT and mITT analysis set by randomized treatment group. Subjects who did not have any assessments in TP 2 will only be summarized for the randomized treatment group of TP 1.

Extent of exposure and safety data will be summarized for the safety analysis set by actual treatment group. Subjects who did not receive any dose of IMP in TP 2 will only be summarized for the actual treatment group of TP 1.

The mITT analysis set will be considered the primary analysis population for efficacy. The ITT analysis set will be used to conduct sensitivity analyses for the primary endpoint for each treatment group, see section 4.2.4.

Pharmacokinetic analysis will be performed using the PK Analysis Set.

2.2 Violations and Deviations

Important protocol deviations (IPDs) are a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being. Only important protocol deviations will be listed and tabulated in the CSR. These will be identified during the blinded data review meeting (BDRM) before database lock.

The following are examples that could be considered as important protocol deviations:

- Subjects who deviate from key entry and randomization criteria relating to clinical diagnosis and severity of COPD (Deviation 1) as defined in the CSP version 2. These are inclusion criteria 3, 4, 7, 8 and 9, exclusion criteria 1 and 6, and randomization criteria 1 and 2.
- Subjects unable to demonstrate proper usage of inhalers and InCheck device at entry and during the study (Deviation 2).
- Subjects who do not have required washout of prohibited COPD medications prior to baseline (Visit 3). Please refer to Table 5 in CSP Section 6.5.2.1 for minimum washout periods. In addition, late use of study provided medications Berodual or Ventolin (within 6 hours of spirometry assessments) at visit 3 or 5 is prohibited and will be considered important protocol deviations unless the visit or assessments are rescheduled. (Deviation 3).
- Subjects who use prohibited COPD medications during the study treatment periods (Deviation 4). Please refer to Table 5 in CSP Section 6.5.2.1 for relevant classes of COPD medication.
- Subjects with treatment compliance in either treatment period of <70% or >130% (Deviation 5).
- Subjects receiving the wrong or incorrect dose of randomized study treatment (Deviation 6).
- Subjects without informed consent provided (Deviation 7).

- Subjects requiring discontinuation from the study due to safety related reasons who were not withdrawn (Deviation 8).
- Additional important protocol deviations may be identified.

Subjects with IPDs that may significantly impact the accuracy and/or reliability of efficacy data (Deviations 1-6 above) will be excluded from the mITT analysis set. Deviations 7 and 8 will not lead to exclusions from the mITT analysis set. None of the deviations will lead to subjects being excluded from the ITT or Safety analysis sets.

The master list of important protocol deviations (along with descriptions) corresponds to section 4 of the study Non-Compliance Handling Plan.

All data supporting identification of important deviations will be blinded.

Randomization Errors

Randomization errors, such as a subject is given a treatment pack for a different subject or is randomized out of chronological order, will not necessarily be identified as IPD that lead to exclusion from mITT. Only if the error caused the subject to receive a treatment other than randomized, the affected subject will be excluded from mITT. Subjects receiving both treatments, but out of order, will be an allowable exception and the subject will still be used in ITT and analysed according to treatment actually received.

3 PRIMARY AND SECONDARY VARIABLES

3.1 Visits and Visit Windows

3.1.1 Pulmonary Function Tests (PFT)

All PFTs including FEV_1, FVC and FEV_1/FVC as defined in ATS/ERS guidelines will be performed in accordance with ATS criteria, following the schedule presented in Table 2. Pulmonary function tests will be limited to 3 attempts. Every effort should be made to get 3 reproducible and acceptable maneuvers; however, if this is not possible, the best of the 3 attempts will be recorded.

Forced expiratory spirometry maneuvers will be assessed to derive the following parameters:

- FEV_1 is the volume of air exhaled under forced conditions in the first second.
- FVC is the determination of the vital capacity from a maximally forced expiratory effort.
- FEV_1/FVC ratio.

Spirometry will be collected at the Early Discontinuation/Withdrawal Visit only if the subject is still taking IP (last dose of IP on day before or day of visit).

Inspiratory capacity (IC), the amount of air that can be inhaled after the end of a normal expiration, will be assessed.

All available data up to 270 minutes with the actual timepoints (versus nominal timepoints) will be used for AUC and Peak calculations, unless an actual time is not available; when an actual time is not available, nominal windows will apply. Individual time points will use the closest observation to the window's nominal time point. Assessments will be allocated to derived nominal collection time windows using the time intervals specified for each below. 0 to 20 minutes window will not be summarized as such observations are not expected.

For FEV_1 the largest acceptable result from each set of repeat efforts at a protocol-scheduled time-point will be used in analyses. For IC, after the removal of unacceptable efforts, if all remaining efforts are acceptable and repeatable (according to criteria set out in study overread guidelines), then the average of these will be used in analyses. If repeatability cannot be achieved then the highest acceptable value will be taken.

Table 2 Schedule of Pulmonary Function Tests (PFT) and Inspiratory Capacity (IC)

Visit	Calculated Study Time Window	Time Interval for the Study Time Window	PFT	IC
Visit 2	45 minutes pre-bronchodilator		X	
	30 to 60 minutes post-bronchodilator		X	
Visit 3	45 minutes pre-dose	<0 min Post-dose	X	X
	<20 minutes post-dose	0 to 20 min Post-dose	X	
	2 hours post-dose	90 to 180 min Post-dose	X	X
Visit 4	45 minutes pre-dose	<0 min Post-dose	X	
	<20 minutes post-dose	0 to <20 min Post-dose	X	
	30 minutes post-dose	20 to <45 min Post-dose	X	
	1 hour post-dose	45 to <90 min Post-dose	X	
	2 hours post-dose	90 to <180 min Post-dose	X	X
	4 hours post-dose	180 to 270 min Post-dose	X	
Visit 5	45 minutes pre-dose	<0 min Post-dose	X	X
	<20 minutes post-dose	0 to <20 min Post-dose	X	
	2 hours post-dose	90 to 180 min Post-dose	X	X
Visit 6	45 minutes pre-dose	<0 min Post-dose	X	
	<20 minutes post-dose	0 to <20 min Post-dose	X	
	30 minutes post-dose	20 to <45 min Post-dose	X	
	1 hour post-dose	45 to <90 min Post-dose	X	
	2 hours post-dose	90 to <180 min Post-dose	X	X
	4 hours post-dose	180 to 270 min Post-dose	X	

Note: The time of the study drug dose will be available to the minute. The time of the spirometry assessment will be available to the second, and will be truncated downward to whole minutes prior to calculation of the study time window. Any assessments for which the time interval is 0 due to truncation but are marked as post-dose nominally, will be assigned to the <20 post-dose time window.

3.1.2 Peak Inspiratory Flow (PIF)

At Visits 2, 3, 4, 5, and 6 (Screening and Days 1, 8, 22, and 29), 3 PIF endpoints will be measured. PIF will be measured at 3 different levels of resistance (i.e., InCheck Device set to no resistance, resistance set equal to Turbuhaler S, and resistance set equal to ELLIPTA). For each resistance level, triplicate measurements of pre-dose PIF assessment will be conducted and all 3 measurements will be captured in the eCRF. The PIF endpoints will be based upon the average of these triplicate measurements. The average of the 3 measurements with the device set to Turbuhaler S resistance will be used to determine eligibility at Visit 2 and Visit 3.

3.1.3 Inspiratory Capacity (IC)

On Day 1 of each Treatment Period (Visits 3 and 5), IC assessments will be conducted approximately 45 minutes pre-dose and prior to any other spirometry assessments and 2 hours post-dose. On Day 8 of each Treatment Period (Visits 4 and 6), IC assessments will be conducted 2 hours post-dose (Table 2).

3.2 Definition of Baselines

The focus of this study is on estimation of the individual effects of treatment with BFF MDI 320/9.6 µg and Symbicort Turbuhaler 320/9 µg. For this purpose, a subject level baseline averaging across pre-dose values at Visit 3 and Visit 5 will be used. For spirometry, the average of the last pre-dose assessments at Visits 3 and 5 will be used as the subject level baseline. If Visit 5 value is missing, the Visit 3 value will be used, and vice versa. If both are missing, the last pre-dose assessment during screening visits will be used. When missingness occurs, baseline will be handled as described above.

For PIF at each resistance level (InCheck Device set to no resistance, resistance set equal to Turbuhaler S, and resistance set equal to ELLIPTA), the mean of triplicate pre-dose assessments at Visits 3 and 5 will be averaged as the subject level baselines. When missingness occurs, baseline will be handled as described above.

For IC, the average of the last pre-dose assessments at Visits 3 and 5 will be used as the subject level baselines. When missingness occurs, baseline will be handled as described above.

3.3 Efficacy Endpoints

3.3.1 Primary Efficacy Endpoints

There will be one primary endpoint, defined as follows:

- Peak change from baseline in FEV_1 within 4 hours post-dose following 1 week of treatment.

Peak change from baseline in FEV_1 within 4 hours post-dose is defined as the maximum of the FEV_1 assessments within 4 hours post-dosing at each visit minus baseline, provided that there are at least 2 non-missing values during the first 4 hours post-dose.

There will be no formal hypothesis testing for this pilot study, and exploratory hypotheses only will be evaluated.

3.3.2 Secondary Efficacy Endpoints

Secondary efficacy endpoints include five PFT endpoints, and three separate PIF endpoints, as follows:

- Area under the curve for change from baseline in FEV_1 from 0 to 4 hours (FEV_1 AUC0-4) following 1 week of treatment.
- Change from baseline in pre-dose FEV_1 following 1 week of treatment.
- Change from baseline in 2-hour post-dose inspiratory capacity (IC) following 1 week of treatment.
- Change from baseline in pre-dose PIF following 1 week of treatment.
    - InCheck Device set to no resistance
    - resistance set equal to Turbuhaler S
    - resistance set equal to ELLIPTA
- Change from baseline in 2-hour post-dose FEV_1 following the first dose.
- Change from baseline in 2-hour post-dose IC following the first dose.

FEV_1 AUC0-4 will be calculated using the trapezoidal rule and will be normalized by dividing by the time in hours from dosing to the last measurement included (typically 4 hours). Only one non-missing post-dose value is required for the calculation of AUC.

Change from baseline in pre-dose FEV_1 following 1 week of treatment is defined as the 45-minute pre-dose value following 1 week of treatment minus baseline. In subjects missing either of these pre-dose assessments, the value will be missing.

Change from baseline in 2-hour post-dose IC following 1 week of treatment will be defined as the 2-hour post-dose assessment of IC following 1 week of treatment minus baseline IC.

Change from baseline in pre-dose PIF following 1 week of treatment will be defined as the pre-dose PIF following 1 week of treatment minus baseline PIF.

Change from baseline in 2-hour post-dose FEV_1 following the 1st dose of treatment will be defined as the 2-hour post-dose assessment of FEV_1 following the 1st dose of treatment (Visit 3 or 5) minus baseline FEV_1.

Change from baseline in 2-hour post-dose IC following the 1st dose of treatment will be defined as the 2-hour post-dose assessment of IC following the 1st dose of treatment (Visit 3 or 5) minus baseline IC.

Each of the variables will be analysed for BFF MDI 320/9.6 µg and Symbicort Turbuhaler 320/9 µg treatment groups. Analysis will be similar to the primary endpoint analysis, but will be focused on estimation. Refer to section 4.2.4 for details.

3.4 Safety Endpoints

Adverse Events

Adverse Events (AEs), Serious Adverse Events (SAEs) and AEs leading to treatment discontinuation (DAEs) will be evaluated to meet the safety objectives of the study (Table 1). These endpoints will be collected in the adverse events eCRF.

Non-serious AEs will be collected from Randomization throughout the Treatment Period and including the washout and follow-up periods. SAEs will be recorded from the time of signing of informed consent form throughout the course of the study. AEs will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA).

Only treatment emergent adverse events from the time of randomization onwards will be summarized. AEs will be assigned to the TP in which they first occurred, and summarized under the treatment group of that TP. AEs reported as starting during a Washout Period or follow-up period will be assigned to the last treatment received. If an AE has a missing or partial onset date, then the AE will be assumed treatment emergent, and assigned to the TP (or both TPs) where it could have possibly started.

Other Safety Assessments

No other safety data will be obtained during the course of the study.

3.5 Pharmacokinetic (PK) Endpoints

The pharmacokinetic of BFF MDI administered with a spacer and Symbicort Turbuhaler (DPI) will be assessed using plasma concentrations of budesonide and formoterol pre-dose and at various times post-dose on Visits 4 and 6. PK samples will be collected in the morning of Visit 4 and Visit 6 within 30 minutes prior to dosing and at 2, 5, 20, 30, and 40 minutes and 1, 2, 3, and 4 hours post-dose. The PK parameters calculated using pre-defined pre- and post-dose serial blood draws will include the following:

- Area under the plasma concentration time curve from 0 to 4 hours post-dose (AUC0-4)
- Time to maximum observed plasma concentration (tmax)
- Maximum observed plasma concentration (Cmax)
- The concentration at the end of the dosing interval (Ctrough)

- MDI/DPI treatment ratio for Cmax (TRCmax)
- MDI/DPI treatment ratio for AUC0-4 (TRAUC)
- MDI/DPI treatment ratio for Ctrough (TRCtrough)

Other PK parameters may be calculated, as appropriate.

3.6 Handling of Missing Data

All subjects who are randomized to treatment and receive at least one dose of study treatment and with post-baseline spirometry data from both treatment periods at Visits 4 and 6 will be defined as mITT set. Missing data, other than evaluable data defined in mITT set, is assumed to be missing at random. Therefore the primary analysis is defined such that within-subject comparisons can be made without needing to account for missing data. Any subjects excluded from this are not relevant to the per protocol estimand. A supportive analysis will also be conducted where all missing data is assumed to be missing at random. No imputation for entirely missing assessments is planned.

3.7 Handling of Re-Enrolments

Subjects who discontinued due to the COVID-19 related study hold may be invited to re-enroll into the study using a new subject identifier. The subject will be considered a returning subject if he/she signs the new ICF after study enrolment reopens. Only data obtained after the latest ICF will be used in analyses.

All available data from each study participation will be listed together, including both subject identifiers for patients re-enrolling. The records that are not used because of re-enrolment will be flagged in the listings.

4 ANALYSIS METHODS

The primary objective of this study is to assess the effects of BFF MDI administered with a spacer relative to Symbicort Turbuhaler on lung function, measured by peak forced expiratory volume in 1 second (FEV_1) within 4 hours post-dose at Week 1 post treatment, in subjects with COPD and low PIF.

The estimand of interest is the per protocol estimand. This is the effect of the randomized treatment in all subjects who are compliant with the protocol (no important protocol violations), including the use of randomized medication. This will enable estimation of the effects that could be attributed purely to device, rather than to adherence or other factors.

Analyses for the per protocol estimand will be conducted using the mITT Population where only data from subjects completing both treatment periods, without important protocol violations, will be utilized.

4.1 General Principles

4.1.1 Treatment Effect Assessment

For the efficacy analyses, BFF MDI administered with a spacer and Symbicort Turbuhaler will be assessed for Week 1 effects. The 95% confidence intervals (CIs) will be produced. P-values for differences between treatments, will be reported as two-sided to aid interpretation.

The modified Intent-to-Treat (mITT) Population will be considered the primary analysis population for efficacy. Sensitivity analyses for the primary endpoint will be conducted using the Intent-to-Treat (ITT) Population, if the data included in the ITT analysis set is different from the data included in the mITT analysis set.

Continuous efficacy variables will be summarized with descriptive statistics (the number of non-missing values, mean, standard deviation, median, minimum and maximum). Where PK data have been logarithmically transformed for analysis, the summary statistics on the back-transformed data will include the geometric mean and the coefficient of variation (calculated as $100\sqrt{[\exp(s^2)-1]}$, where s is the standard deviation of the data on the log scale). Categorical variables will be summarized with frequency counts and percentages, by treatment.

4.1.2 Hypothesis Testing

There will be no formal hypothesis testing for this pilot study, and exploratory hypotheses only will be evaluated. There will be no type I error control for any endpoint.

4.1.3 Software

All statistical analysis will be conducted using SAS version 9.4, or other validated software as appropriate.

4.2 Analysis Methods

4.2.1 Disposition, Demographics and Baseline Characteristics

Descriptive summaries of disposition, demographics and baseline characteristics will be produced.

Disposition table will summarize the number of subjects who received each treatment, the number who completed 1 or 2 treatment periods and the number of early discontinuations.

Disposition tables will present data by the randomized treatment sequence. For re-enrolling subjects the latest randomization sequence will be used. An additional summary will be prepared for subjects who discontinued study due to the COVID-19 related hold, and show the number of subjects who re-enrolled and did not re-enroll.

The number of subjects in each analysis set will be summarized along with any reasons for exclusion.

Demographics and baseline characteristics at screening will be summarized descriptively, including COPD disease duration, disease severity, and COPD assessment test (CAT) score, as well as eosinophil count and whether receiving ICS at screening. The CAT is an 8-item Patient Reported Outcomes developed to measure the overall impact of COPD on health status [Jones, 2009, Appendix K]. A CAT total score is the sum of item responses. Scores range from 0-40 with higher scores indicative of greater COPD impact on health status. Subjects will complete the CAT at Visit 2 for screening purposes only. Pre- and post- bronchodilator spirometry parameters (and their percent predicted values) and reversibility to Ventolin HFA will be summarized using descriptive statistics based upon the assessments at Screening. Baseline spirometry, IC and PIF parameters will be summarized.

All demographic and baseline characteristic summaries will be presented by treatment group, and for all subjects in the ITT and mITT analysis sets. Subjects who had no assessments in TP 2 will not be summarized in the treatment group they were assigned to in TP 2. Thus, the treatment group summaries will potentially include fewer subjects than the ITT set.

4.2.2 Prior and Concomitant Medications

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

Concomitant medication is any medication reported as being taken after the start of the study medication in the study to the date prior to the last dose of study medication for the subject. A medication with an onset date on or after the last dose of study medication for the subject will not be considered concomitant, but will be considered a **Post-Treatment medication**.

It will be identified for each concomitant medication whether it was taken during treatment with BFF MDI administered with a spacer, Symbicort Turbuhaler, and during the washout, based on the definition of periods provided in section 1.2.

Any medication/treatment which cannot be identified as Prior, Concomitant, or Post-Treatment will be considered as being in each of the categories that are possible from the available information. For re-enrolling subjects, the determination of Prior, Concomitant and Post-Treatment will be relative to their latest study participation.

All medications will be assigned a preferred term and an ATC (Anatomic Therapeutic Class) term using the latest version of the World Health Organization Drug Dictionary (WHO-DD Global) available. Prior medications will be summarized according to whether they are COPD related or non-COPD related. For concomitant medications, summaries will be presented for those medications started during a treatment period and those started during the washout period, separately for COPD related or non-COPD related. All medications will be listed.

4.2.3 Exposure and Compliance

The number of days of exposure to each treatment (BFF MDI, Symbicort Turbuhaler) will be defined as ((End date of the last dose of IMP – Date of the first dose of IMP) + 1).
Exposure to IMP (BFF MDI, Symbicort Turbuhaler) will be summarized by actual treatment using the safety analysis set.

Percent compliance in a given TP is defined as (total number of IMP puffs of study treatment taken on a study day/total expected IMP puffs taken on a study day) averaged across all days in the TP) x 100.

The expected number of IMP (BFF MDI, Symbicort Turbuhaler) puffs is as follows:

- 2 puffs for a test day which is the last date of treatment.
- 4 puffs for the last date of treatment which is not a test day when an evening dose is taken.
- 2 puffs for the last date of treatment which is not a test day when an evening dose is not taken.
- 4 puffs on dates prior to the last date of treatment.

Treatment compliance will be categorized into 7 different groups depending on the degree of compliance: 0 – <20%, ≥20 – <40%, ≥40 – <70%, ≥70 – <90%, ≥90 – ≤110%, >110 – ≤130%, and >130%. Additionally, descriptive statistics (n, mean, standard deviation, median, minimum and maximum) will be provided for percent compliance by treatment group. Treatment compliance will also be listed.

Administration of study medication (including rescue Ventolin HFA) will be recorded on the paper diary provided to the subject.

Study treatment compliance will be checked at all visits. Treatment compliance will be verified through the subject reported IP intake from the paper diary. The dose indicator reading will additionally be checked for consistency, to verify that subjects took IP as reported. Dose indicator readings (to the nearest 10) and total inhalations reported in the paper diary will be recorded at the end of each treatment period. Dose indicator readings will be listed as 120+, 120, 110, 100, 90, 80, 70, 60, 50, 40, 30, 20, 10, and 0.

For re-enrolling subjects, exposure and compliance will be based on their latest study participation only.

4.2.4 Spirometry, PIF and IC Data

4.2.4.1 Primary Efficacy Analysis

Peak change from baseline in FEV_1 within 4 hours post-dose following 1 week of treatment

The peak change from baseline in FEV_1 will be analyzed in the mITT population using an analysis of covariance (ANCOVA) model with baseline FEV_1, PIF at screening (InCheck set at Turbuhaler S resistance) and reversibility to Ventolin HFA as continuous covariates and treatment, and period as categorical covariates. The model will include subject as a random effect to model correlation within subject across the study. The model will not include treatment sequence unless that term is determined to be important ($p<0.10$). Estimates of the difference between treatments, with 95% confidence intervals (CIs) will be reported. P-values will be produced to aid interpretation. If this model fit fails to converge, a linear model for the within-subject treatment difference will be considered.

Boxplots will be used for unadjusted endpoint values for both primary and secondary endpoints. Individual data points will be included in the boxplots. In addition, a paired line plot will be produced for the primary endpoint only.

4.2.4.2 Analysis of Secondary Efficacy Variables

FEV_1 AUC0-4 following 1 week of treatment, Change from baseline in pre-dose FEV_1 following 1 week of treatment, Change from baseline in 2-hour post-dose FEV1 following the 1st dose of treatment

FEV_1 based secondary endpoints will all use a similar model to the primary efficacy analysis.

Change from baseline in 2-hour post-dose IC following 1 week of treatment, Change from baseline in 2-hour post-dose IC following the 1st dose of treatment

IC based secondary endpoints will all use a similar model to the primary efficacy analysis, but with baseline IC used instead.

Change from baseline in pre-dose PIF following 1 week of treatment

PIF based secondary endpoints will use a similar model to the primary efficacy analysis, but with baseline PIF used instead, and without adjusting for PIF at screening (InCheck set at Turbuhaler S resistance).

At each visit, PIF will be measured with the InCheck Inspiratory Flow Measurement Device set to no resistance and then repeated with the resistance equal to Turbuhaler S and then equal to ELLIPTA. Change from baseline in pre-dose PIF with different resistances will be analyzed separately in a similar fashion.

Supportive analyses

A sensitivity analysis will be conducted for the primary endpoint in the ITT population using a similar ANCOVA model, if the data included in the ITT analysis set is different from the data included in the mITT analysis set. Sensitivity analyses will be considered in the ITT population for the secondary endpoints should the mITT and ITT populations differ substantially.

A subgroup analysis of subjects who completed the study entirely before vs entirely after the study being put on hold due to the COVID-19 pandemic will be carried out for the primary endpoint only using the mITT analysis set.

Subgroup analyses based upon PIF at screening with the Turbuhaler S resistance level will also be performed for primary and secondary endpoints. The groups will be defined using the stratification cut points (<40 L/min and ≥40 L/min); alternative thresholds will be used if necessary, based upon the observed distribution.

PIF thresholds with greatest separation of MDI vs. DPI effects will be investigated. To support this goal, scatter plots will be produced with baseline PIF on the X axis and the efficacy endpoint on the Y axis. Separate plots will be prepared for each resistance level for PIF as the X variable, and either change from baseline for MDI (primary endpoint only), change from baseline for DPI (primary endpoint only), or the difference between MDI and

DPI results (primary and secondary endpoints) as the Y variable. Pearson correlation coefficients will be calculated and added to each such plot.

4.2.5 Safety Data

Adverse events will be summarized by the number and percentage of subjects experiencing an event. Tables will show the overall incidence of AEs, and the incidence for each treatment. Treatment emergent adverse events from the time of randomization onwards will be summarized. AEs reported as starting during a Washout Period or follow-up period will be assigned to the last treatment received. For re-enrolling subjects, the treatment emergent status of AEs will be determined relative to their latest study participation.

AEs will be presented according to MedDRA preferred term and system organ class, using the latest version of MedDRA at the time of database lock. Summaries will be produced by intensity, seriousness, AEs leading to discontinuation, by causality assessment to study drug, and AEs leading to death. No hypothesis tests will be performed.

No other safety data will be obtained during the course of the study.

4.2.6 Pharmacokinetics (PK) data

4.2.6.1 Calculation or Derivation of PK Parameters

The PK analyses of the plasma concentration data for budesonide and formoterol will be performed by Covance, on behalf of the Clinical Pharmacokinetic Alliance, AstraZeneca R&D. PK parameters will be derived using non-compartmental methods in Phoenix® WinNonlin® Version 8.1 or higher. Individual treatment ratios for Cmax, Ctrough, and AUC0-4 will be derived by programming.

PK analysis will, where data allow, be carried out using actual elapsed times determined from the PK sampling and dosing times recorded in the database. If actual elapsed times are missing, nominal times may be used at the discretion of the PK Scientist with approval from the AZ Clinical Pharmacology Scientist (CPS).

For each PK sampling period, plasma concentrations that are non-quantifiable (NQ) from the time of pre-dose sampling (t=0) up to the time of the first quantifiable concentration will be set to a value of zero. After this time point, NQ plasma concentrations will be set to missing for all concentration profiles. Where 2 or more consecutive concentrations are NQ at the end of a profile, the profile will be deemed to have terminated and therefore any further quantifiable concentrations will be set to missing for the calculation of the PK parameters unless it is considered to be a true characteristic of the profile of the drug.

If an entire concentration-time profile is NQ, the profile will be excluded from the PK analysis.

Cmax, Ctrough, and tmax will be taken directly from the concentration-time profiles. Ctrough will be taken as the pre-dose concentration on Visit 4 and 6.

AUC0-4 will be calculated using the linear trapezoidal method when concentrations are increasing and the logarithmic trapezoidal method when concentrations are decreasing (linear up, log down). The minimum requirement for the calculation of AUC will be the inclusion of at least 3 consecutive plasma concentrations above the lower limit of quantification (LLOQ). Where there are just 3 quantifiable concentrations, at least 1 of these concentrations should follow the peak concentration.

Individual treatment ratios for Cmax, Ctrough, and AUC0-4 (TRCmax, TRCtrough, and TRAUC) will be calculated by dividing the parameter from the MDI treatment by the same parameter from the DPI treatment.

4.2.6.2 Statistical Analysis of PK Parameters

An analysis of covariance (ANCOVA) will be performed on the logarithmic transformation of Ctrough, Cmax and AUC0-4, from the PK Analysis Set. The ANCOVA model with treatment and period as categorical covariates, will include subject as a random effect to model correlation within subject across the study. Treatment sequence will not be included in the model unless that term is determined to be important ($p<0.10$). Ratios and 90% confidence intervals (CIs) for Cmax, Ctrough and AUC0-4 will be generated and produced by back transformation. Descriptive statistics of the untransformed tmax will be presented.

4.2.6.3 Presentation of PK Data

All PK concentration, parameter summaries and statistical analyses will be presented for the PK Analysis Set, unless otherwise specified. The PK concentration and parameter listings will be presented for the Safety Analysis Set and will include all reportable individual PK results. Individual PK concentration and parameter data for any subjects not included in the PK Analysis Set or excluded from the descriptive summary tables, figures and/or inferential statistical analyses will be included in the listings and flagged with an appropriate footnote.

PK Concentration Listings

A listing of individual PK blood sample collection times, derived sampling time deviations and concentrations for all analytes at each protocol scheduled time-point will be presented for all subjects who have been dosed. Listings will be presented by Treatment/Visit.

PK Concentration Descriptive Statistics

For each analyte, plasma concentrations for each scheduled time-point will be summarized by Treatment using appropriate descriptive statistics. Individual concentrations with time deviations of greater than ±10% from the protocol scheduled time, will be used in the PK analysis but will be flagged for exclusion from the summary tables and corresponding figures.

The following descriptive statistics will be presented for plasma concentrations:

- n (number of observations)
- n below LLOQ (Lower Limit of Quantification)
- geometric mean (gmean)
- geometric coefficient of variance (%) (gCV)
- gmean ± geometric standard deviation (gmean + gSD and gmean - gSD)
- arithmetic mean (mean)
- arithmetic standard deviation (SD)
- median
- minimum (min)
- maximum (max)

The gmean is calculated as $\exp(\mu)$, where μ is the mean of the data on the natural log scale.

The gCV is calculated as $100 \times \text{sqrt}[\exp(s^2)-1]$, where s is the SD of the data on the natural log scale.

The gmean ± gSD (gmean-gSD and gmean+gSD) are calculated as $\exp[\mu \pm s]$.

Protocol scheduled times will be used to present the PK concentration summary tables and corresponding gmean concentration-time figures.

Handling of Non-Quantifiable Concentrations

Individual concentrations below the LLOQ of the bioanalytical assay will be reported as NQ in the listings with the LLOQ defined in the footnotes of the relevant TFLs. Individual plasma concentrations that are Not Reportable will be reported as NR and those that are missing will be reported as NS (No Sample) in the listings. Plasma concentrations that are NQ, NR or NS will be handled as follows for the provision of descriptive statistics:

- Any values reported as NR or NS will be excluded from the summary tables and corresponding figures.

- At a time-point where less than or equal to 50% of the concentration values are NQ, all NQ values will be set to the LLOQ, and all descriptive statistics will be calculated accordingly.
- At a time-point where more than 50% (but not all) of the values are NQ, the gmean, gmean ± gSD and gCV% will be set to NC (not calculable). The maximum value will be reported from the individual data, and the minimum and median will be set to NQ.
- If all concentrations are NQ at a time point, no descriptive statistics will be calculated for that time point. The gmean, minimum, median and maximum will be reported as NQ and the gCV% and gmean ± gSD as NC.
- The number of values below LLOQ (n < LLOQ) will be reported for each time point together with the total number of collected values (n).

Three observations > LLOQ are required as a minimum for a plasma concentration or PK parameter (e.g. Cmax) to be summarized. Two observations > LLOQ are presented as minimum and maximum with the other descriptive statistics as NC.

PK Parameter Listings

All reportable PK parameters will be listed for each subject by Treatment/Visit, for each analyte separately.

PK Parameter Descriptive Statistics

All PK parameters will be summarized for each analyte by Treatment using appropriate descriptive statistics. The descriptive statistics for all PK parameters will presented n, gmean, gCV(%), mean, SD, median, min and max with the exception of tmax which will present n, median, min and max.

Three values are required as a minimum for PK parameters to be summarized. Two values are presented with n, min and max with the other descriptive statistics as NC.

If one or more values for a given parameter is zero (or imputed with zero), then no geometric statistics will be calculated for that parameter and the results for geometric statistics will be set to NC.

Graphical Presentation of PK data

All gmean plots or overlaying individual plots showing all subjects by treatment will be based on the PK Analysis Set. Individual plots by subject will be based on the Safety Analysis Set. Scatter plots for individual PK parameters versus Treatment will present both summary

parameter data and individual subject parameter data for each Treatment including only subjects in the PK Analysis Set.

For consistency, the plasma concentration values used in the gmean data graphs will be those given in the descriptive statistics summary table for each time point.

For gmean concentration-time plots, NQ values will be handled as described for the descriptive statistics; if the geometric mean is NQ, the value plotted will be zero for linear plots and missing for semi-logarithmic plots. Any gmean±gSD error bar values that are negative will be truncated at zero on linear concentration-time plots and omitted from semi-logarithmic plots.

For individual plots, plasma concentrations which are NQ prior to the first quantifiable concentration will be set to a value of zero (linear plots only). After the first quantifiable concentration, any NQ plasma concentrations will be regarded as missing.

Data permitting, the following figures may be presented as appropriate:

- Gmean plasma concentration-time data (with ±gSD error bars) by analyte with both treatments overlaid on the same plot in both linear and semi-logarithmic scales using scheduled post-dose time.
- Individual subject plasma concentration-time data graphically presented in both linear and semi-logarithmic scales using actual time post-dose as:
  - By subject with both treatments overlaid on the same plot for each analyte
  - Combined individual plots by treatment with all subjects overlaid on the same plot for each treatment
- Individual ratios of MDI/DPI treatments for Cmax, Ctrough and AUC0-4 plotted by parameter and will include the gmean ratio and 90% confidence interval for each analyte.

Precision and Rounding Rules for Pharmacokinetic Data

PK concentration data listings will be presented to the same number of significant figures as the data received from the bioanalytical laboratory (usually to 3 significant figures) and against the same units as received.

PK concentration descriptive statistics will all be presented to 4 significant figures with the exception of the min and max which will be presented to 3 significant figures and n and n<LLOQ which will be presented as integers.

PK parameter listings will be presented according to the following rules:

- Cmax and Ctrough: present to the same number of significant figures as received from the bioanalytical laboratory
- tmax: present as received in the data, usually to 2 decimal places
- AUC0-4, TRCmax, TRCtrough and TRAUC: present to 3 significant figures

The descriptive statistics for all PK parameter data will all be presented to 4 significant figures with the exception of the min and max which will be presented to 3 significant figures apart from the following:

- tmax: present as received in the data, usually to 2 decimal places
- number of values (n): present as an integer

4.2.7 Assumptions checks and removal of outliers

The logarithmic transformations will be required for certain PK data. If data are transformed via the natural logarithm prior to analysis, the adjusted mean estimates and confidence intervals from the linear models will be exponentiated back for presentation. As such, the treatment effect for these endpoints will be presented as a ratio.

The distributional assumptions will be assessed via visual inspection of residuals and consideration of alternatives if necessary.

5 INTERIM ANALYSES (NOT APPLICABLE)

No interim analyses are planned in this study.

6 CHANGES OF ANALYSIS FROM PROTOCOL

No changes of analysis from the protocol are made. For mITT population definition, protocol states “Data judged to be impacted by major protocol violations will be excluded”, but given the updated terminology now used for protocol deviations the SAP clarifies this as “data judged to be impacted by important protocol violations will be excluded”.

7 REFERENCES

Jones PW, Harding G, Berry P, et al. Development and first validation of the COPD Assessment Test. Eur Respir J 2009;34:648-654.

8 APPENDIX (NOT APPLICABLE)

SIGNATURE PAGE

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