Statistical Analysis Plan

Study Code	D6570C00002 (M-AS464-30)
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A 24-week Treatment, Randomised, Parallel-group, Double blinded, Double-Dummy, Multicenter Study to Assess the Efficacy and Safety of Aclidinium bromide/Formoterol fumarate compared with Individual Components and Placebo and Aclidinium bromide compared with Placebo when Administered to Patients with Stable Chronic Obstructive Pulmonary Disease

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Study Statistician

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Global Product Statistician

[redacted] Date

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Biometrics Team Lead

[redacted] Date

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
AB 400	Aclidinium bromide 400 µg
AB/FF 400/12	Fixed dose combination of aclidinium bromide 400 µg and Formoterol 12 µg
AE	Adverse Event
AESI	AE of Special Interest
ALP	Alkaline phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
AZBC	AstraZeneca Barcelona
BDI	Baseline Dyspnoea Index
BDRM	Blind Data Review Meeting
BID	Bis In Die (twice daily)
BMI	Body Mass Index
BTR	Best test review
bpm	Beats per minute
CAT	COPD Assessment Test
CI	Confidence Interval
CK	Creatine kinase
COPD	Chronic Obstructive Pulmonary Disease
COVID-19	Coronavirus Disease 2019
CR	Copy Reference
CRF	Case Report Form
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CVAC	Cardiovascular Adjudication Committee
DBL	Database Lock
DBP	Diastolic Blood Pressure

Abbreviation or special term	Explanation
DILI	Drug Induced Liver Injury
dp	Decimal places
ECG	Electrocardiogram
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
e-diary	Electronic diary
ENR	Expanded Normal Ranges
EOS	End of Study
EOT	End of Treatment
E-RS	EXACT-Respiratory Symptoms
EXACT	Exacerbations of Chronic Pulmonary Disease Tool
FDA	US Food Drug Administration
FDC	Fixed Dose Combination
FEV_1	Forced expiratory volume in 1 second
FF 12	Formoterol fumarate 12 µg
FVC	Forced Vital Capacity
g/L	Gram per litre
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HCRU	Health Care Resource Utilization
HLT	High Level Term
HR	Hazard Ratio
ICF	Informed Consent Form
ICS	Inhaled corticosteroids
IP	Investigational Product
ITT	Intention-to-Treat
IWRS	Interactive Web-response System
Kg	Kilograms
L	Litres
LABA	Long-acting β2 agonist
LAMA	Long-acting muscarinic antagonist

Abbreviation or special term	Explanation
LLN	Lower Limit of the Normal
LS	Least Square
m^2	Squared Meters
MCMC	Markov Chain Monte Carlo
mmHg	Millimeters of mercury
mmol/L	Millimoles per litre
MABA	Muscarinic antagonist β2 adrenoceptor agonist
MACE	Major Adverse Cardiac Event
MAR	Missing-At-Random
MAX	Maximum
MCID	Minimum Clinically Important Difference
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
µg	Microgram
MI	Multiple Imputation
MIN	Minimum
mL	Millilitre
MMRM	Mixed Model for Repeated Measures
MNAR	Missing-Not-At-Random
MOV	Maximum Observed Value
msec	Milliseconds
n	Number of subjects in analysis
N	Number of subjects in analysis set
N/A	Not Available
$nAUC_{0\text{-}3h}$	Normalised Area under curve from time 0 to 3 hours
NB	Negative Binomial
NMPA	National Medical Products Administration
OR	Odds Ratio
PCS	Potentially Clinically Significant
PD	Protocol Deviations

Abbreviation or special term	Explanation
PDE4	Oral phosphodiesterase type 4
PDS	Protocol Deviation Specification
PFT	Pulmonary Function Tests
PHL	Potential Hy's Law
pMDI	pressurized Metered Dose Inhaler
Post-IP	Post-treatment follow-up
PP	Per Protocol
PR interval	Duration in milliseconds between two R peaks of two consecutive QRS complexes
PT	Preferred Term
Q1	First Quartile
Q3	Third Quartile
QRS interval	Duration in milliseconds of the QRS complex
QT interval	Duration in milliseconds from the beginning of Q wave to the end of the T wave
QTcB	QT corrected using the Bazett formula
QTcF	QT corrected using the Fridericia formula
RR	Rate Ratio
RR interval	Time elapsed between two successive R waves of the QRS signal
SABA	Short-acting β2 agonist
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAMA	Short-acting muscarinic antagonist
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software, registered trademark of SAS Institute Inc.
SBP	Systolic Blood Pressure
SD	Standard Deviation
SDG	Standardised Drug Grouping
SE	Standard Error

Abbreviation or special term	Explanation
SGRQ	St George's Respiratory Questionnaire
SMQ	Standardised MedDRA Query
SI	International System Units
SOC	System Organ Class
TBD	To be defined
TBL	Total Bilirubin
TDI	Transition Dyspnoea Index
TEAE	Treatment-Emergent Adverse Event
TESAE	Treatment-Emergent Serious Adverse Event
TFLs	Tables Figures and Listings
ULN	Upper Limit of the Normal
WHO	World Health Organization

AMENDMENT HISTORY

Date	Brief description of change
June 2021	**Primary and secondary endpoints:** As per CSP amendment (refer to 'Version History (Version 4.0), Non-Substantial Changes to the Protocol' in the CSP), sex was dropped from all statistical models for primary (section 4.3.1), secondary (section 4.3.2) and additional efficacy (section 4.3.3) endpoints.
June 2021	**COVID-19 related analyses:** • Section 2.2 updated to include protocol deviations related to COVID-19 pandemic. • Disposition categories (section 3.1.1) updated to include disposition events related to COVID-19 pandemic. • Additional section (section 3.4) added to define disruptions due to the COVID-19 pandemic. • Section 4.2.1 updated to reflect changes in the summary table of important protocol deviations to use new corporate pandemic table and listing shells • Description of table for study treatment compliance and drug accountability (section 4.2.4) updated to instruct to present treatment compliance for all subjects and also separately for subjects affected and not affected by COVID-19. • New section 4.9 added detailing COVID-19 related analyses to be performed. These analyses are in alignment with AZ corporate pandemic TLF shells. • Section 8.2 (appendix 2) updated to included IPDs related to COVID-19.
May 2022	• Section 4.2.4 updated to include information on identifying adverse events of suspected/confirmed COVID-19 (required for producing table of study treatment compliance in subjects affected by COVID-19).

June 2021	**Minor changes to derivations and TLFs** • Derivation of expected overall intake of study medication (section 3.1.6) updated to use the first day the question on IP dose intake is activated in the e-diary after randomisation instead of Day 1 for subjects for whom a randomisation date had not been entered into the device. • Derivation of E-RS and use of daily rescue medication (section 3.2.3.4) updated to instruct to exclude last IP dose date for clarity. • A list of specific ECG parameters that can be flagged as potentially clinically significant has been added to section 3.3.5. • QTcB parameter has been added to ECG notable abnormality criteria in table 3.5 (section 3.3.5). • For subject disposition (section 4.2.1), denominators have been clarified for the table of subject recruitment by country and centre for the calculations of percentages for country and for centre. • For demography and baseline characteristics (section 4.2.2), the denominator to be used for calculation of percentages in all tables has been clarified. • For demography and baseline characteristics (section 4.2.2), specific parameters to be summarised for lung function data at screening have been added for clarity and the baseline definition added. • Reference to table of disallowed medication has been removed from the prior and concomitant medication section (section 4.2.3) as this table will no longer be presented. • Descriptions of the following adverse event tables (section 4.5.2) updated to remove inclusion of the number of TEAEs/related events in the top row of the table for consistency with AZ corporate standards: Most comment TEAEs (frequency of >1%); TEAEs by SOC, PT and maximum reported intensity; TEAEs by SOC, PT and investigator's causality assessment; TEAEs by SOC, PT and outcome. • Sorting order for table of non-serious TEAEs occurring in greater than 5% of subjects (section 4.5.2) updated to sort alphabetically by SOC and PT rather than alphabetically by SOC only. This is as per AZ corporate standards. • The sort order for the following adverse event tables (section 4.5.2) has been updated to align with AZ corporate standards (sorting by international order for system organ class and alphabetically for preferred term): TEAEs by SOC and PT; TEAEs by SOC, PT and maximum reported intensity; TEAEs by SOC, PT and investigator's causality assessment; TEAEs by SOC, PT and outcome; Non-serious TEAEs occurring in greater than 5% of subjects. For tables of AESIs and MACE by SMQ,

	SOC and PT, the sort order has been updated to alphabetically for SMQ, international order for SOC and alphabetically for PT. • For ECG (section 4.5.3), a new table has been added for the number and percentage of ECG abnormal findings not present at baseline. • Laboratory data, vital signs and ECG section (section 4.5.3) updated to include new listings of TEAEs for subjects with PCS values for lab data, vital signs and ECG. • Laboratory data, vital signs and ECG section (section 4.5.3) updated to include the following new lab and ECG tables/listings: number and percentage of subjects with a result classified as abnormally clinically relevant by the investigator (table); TEAEs for subjects with abnormal clinically relevant results (listing). Additionally, for ECG, a table displaying the distribution of the Global evaluation from the cardiologist has been added. • BMI removed as a subgroup for the subgroup analyses in section 4.7 (and from the SAS code in section 8.9, Appendix 9) as per the Changes of Analysis from Protocol table (section 6). This change was implemented due to concerns of insufficient numbers in some BMI categories in a Chinese population. • Forest plot described in the subgroup analyses section (section 4.7) updated to additionally present LS mean differences and 95% CIs to the right of the plot and number of subjects in each subgroup for a given treatment group with the corresponding change from baseline LS mean estimate at Week 24 to the left of the plot. • For the derivation of TDI focal score, section 8.3 (appendix 3) has been updated to clarify only to calculate when all TDI components are non-missing. • Section 8.7 (appendix 7) updated to clarify that only one of the 3 required data points needs to be present when calculating the 3-day rolling average of the EXACT daily scores. • Section 8.7 (appendix 7) updated to clarify that recovery from exacerbation can occur on a day where an EXACT Daily Score is missing, but it has been possible to calculate an EXACT Rolling Score.
May 2022	• Derivations of time since last COPD exacerbation and time since last hospitalization due to a COPD exacerbation updated to remove '+1' from the derivation, since these events occur before first IP dose. • Section 4.2.2 updated to instruct to also produce summaries of demographic, subject and disease characteristics for the ITT population.

	• Severity/intensity of HCRU exacerbations, defined in Section 8.7 (appendix 7), updated to be consistent with CSP. • General statement added to section 4.3.3.3 instructing to combine countries where the planned number of subjects is <5% (or n<=13 subjects per treatment group) for all models of COPD exacerbations. • Section 4.3.3.3 on Analysis of COPD exacerbations updated to clarify that countries with a small number of subjects may be combined to address issues of non-convergence in the logistic regression model.
June 2021	**Other minor changes:** • Removed instruction in section 3.1.5 to flag ICS as a disallowed mediation for Chinese subjects as disallowed medications are no longer presented. • Section 3.2.3.3 on COPD exacerbations updated to list COPD exacerbation efficacy variables and their definitions separately for HCRU and EXACT. • Preferred terms for 'unequal pupils' and 'edemas peripheral' have been corrected to 'pupils unequal' and 'oedema peripheral' respectively in definition of AESI table (table 3.2; section 3.3.2). • MedDRA version has been removed from footnote of definition of AESI table (table 3.2; section 3.3.2). • For descriptive summary statistics (section 4.1.3), further instructions on precision have been added, including the following: no decimal places (dp) should be presented for percentages of exactly 100%; round all summary statistics in PFT tables and lab tables to 3dp and 2dp respectively. • Sorting order for the medical and surgical history at screening tables in the demography and baseline characteristics section (section 4.2.2), has been updated to sort alphabetically by SOC and PT rather than alphabetically by SOC and decreasing frequency of PT. This is as per AZ corporate standards. • Description of tables related to prior COPD-related treatment, prior, concomitant and post-treatment medications in section 4.2.3 updated to refer to generic term rather than preferred term. • Instruction to use the Breslow approach for handling tied observations in the Cox proportional hazards model for time to first COPD exacerbation added to section 4.3.3.3. • The definition of 'at any visit' in the section on laboratory data, vital signs and ECG (section 4.5.3) has been updated for clarity. • Description of listing of key subject information for subjects with a treatment emergent PCS abnormality in haematology or biochemistry (section 4.5.3) updated to instruct to also flag values classed as clinically significant, as assessed by the investigator.

	• The handling of repeated and unscheduled assessments/visits (section 4.6.3) for efficacy analyses has been updated to clarify to exclude unscheduled/premature discontinuation data from statistical analyses for all efficacy data (excluding COPD exacerbations), rather than just for spirometry data. • Instruction to use CONTRAST statement in the PROC MIXED for the subgroup analyses (section 4.7) has be changed to use the LSMESTIMATE statement. • Further instructions for the ordering of variables within the VAR statement of the PROC MI for imputing non-monotone missing primary and secondary efficacy data (section 4.8.1) has been added for clarity. • Section on the copy reference approach (4.8.2) for multiple imputation of missing primary and secondary efficacy data updated to include and correct treatment arms of interest and corresponding reference arm to be used for all primary and secondary efficacy outcomes. • SAS code in section 8.9 (appendix 9) updated to reflect change to use LSMESTIMATE statement from CONTRAST statement.
May 2022	• The definition of 'at any visit' in the section on laboratory data, vital signs and ECG (section 4.5.3) has been reverted back to the original definition, as per edition 1.0 of the SAP.

1 STUDY DETAILS

This Statistical Analysis Plan (SAP) provides details of the statistical methods and variable derivations to be used in the analyses to assess the efficacy and the safety of the fixed dose combination (FDC) of Aclidinium Bromide/Formoterol Fumarate 400/12 µg compared with its individual components and placebo, when administered twice daily (BID) in patients with stable moderate-to-severe Chronic Obstructive Pulmonary Disease (COPD). This SAP will also be used for the analyses to assess the efficacy and the safety of the monotherapy Aclidinium Bromide 400 µg compared with placebo, when administered BID in patients with stable moderate-to-severe COPD.

In this study: AB/FF 400/12 represents a fixed dose combination (FDC) of 400 µg of Aclidinium bromide and 12 µg of Formoterol Fumarate (AB/FF 400/12), AB 400 represents a dose of 400 µg of Aclidinium bromide (AB 400), FF 12 represents a dose of 12 µg of Formoterol Fumarate (FF 12). All study treatments are administered BID via inhalation.

In addition to this SAP, a supplementary SAP for the China Sub-population will be done in a separate document.

1.1 Study Objectives

1.1.1 Primary objectives

To assess the bronchodilatory effect of Aclidinium bromide 400 µg /Formoterol fumarate 12 µg compared to individual components and placebo when administered twice daily via inhalation to COPD patients.

To assess the bronchodilatory effect of Aclidinium bromide 400 µg compared to placebo when administered twice daily via inhalation to COPD patients.

Primary Objective for AB/FF 400/12	**Endpoints**
To assess the bronchodilatory effect of AB/FF 400/12 compared to each of its individual components.	Change from baseline at Week 24 in: • 1-hour morning post-dose Forced Expiratory Volume in 1 second (FEV_1) of AB/FF 400/12 compared to AB 400 • Morning pre-dose (trough) FEV_1 of AB/FF 400/12 compared to FF 12
Primary Objective for Aclidinium Bromide 400	**Endpoints**
To assess the bronchodilatory effect of AB 400 compared to placebo.	• Change from baseline at Week 24 in morning pre-dose (trough) FEV_1 of AB 400 compared to placebo

1.1.2 Secondary objectives

To assess the benefits of Aclidinium bromide 400 µg /Formoterol fumarate 12 µg in COPD symptoms, disease-related health status and COPD exacerbations compared to placebo, when administered BID via inhalation to COPD patients.

To assess the benefits of Aclidinium bromide 400 µg in COPD symptoms, disease-related health status and COPD exacerbations compared to placebo, when administered BID via inhalation to COPD patients.

Secondary Objectives for AB/FF 400/12	Endpoints
To assess the effects of AB/FF 400/12 compared with placebo on the improvement of the patients' dyspnoea and disease-related health status.	• Transitional Dyspnoea Index (TDI) focal score at Week 24 of AB/FF 400/12 compared to placebo • Change from baseline at Week 24 in St George's Respiratory Questionnaire (SGRQ) total score of AB/FF 400/12 compared to placebo

Secondary Objectives for Aclidinium Bromide 400	Endpoints
To further characterize the efficacy of AB 400 compared to placebo on lung function.	• Change from baseline in peak FEV_1 at Week 24 of AB 400 compared to placebo.
To assess the effects of AB 400 compared with placebo on the improvement of the patients' dyspnoea and disease-related health status.	• TDI focal score at Week 24 of AB 400 compared to placebo • Change from baseline at Week 24 in SGRQ total score of AB 400 compared to placebo

1.1.3 Safety objectives

To evaluate the safety profile of Aclidinium bromide 400 µg /Formoterol fumarate 12 µg and Aclidinium bromide 400 µg in the same patient population.

Safety Objectives for AB/FF 400/12	
To assess the safety profile of AB/FF 400/12 compared to each of its individual components and placebo	• Adverse events • Clinical laboratory evaluations (haematology, biochemistry and serum pregnancy test) • Blood pressure • 12-lead Electrocardiogram (ECG)
Safety Objectives for Aclidinium Bromide 400	

To assess the safety profile of Aclidinium Bromide 400 compared to placebo	• Adverse events • Clinical laboratory evaluations (haematology, biochemistry and serum pregnancy test) • Blood pressure • ECG

1.2 Study Design

This is a 24-week treatment, multiple dose, randomised, parallel-group, double-blind, double-dummy, multicentre and multinational Phase III superiority trial. Enrolling countries are: China, India, Philippines, Taiwan and Vietnam.

The target population comprises males and non-pregnant/non-lactating females:

- Aged ≥40;
- Current or former smokers, with a cigarette smoking history of ≥10 pack-years;
- With a diagnosis of COPD prior to Visit 1 (screening) and a moderate-to-severe stage and stable airway obstruction (Global Initiative for Chronic Obstructive Lung Disease [GOLD], 2015): screening post-bronchodilator test FEV_1/forced vital capacity (FVC) < 70% and with $FEV_1 \geq 30\%$ and < 80% of the predicted normal value.

For further inclusion and exclusion criteria please refer to the Clinical Study Protocol (CSP).

The total duration of the trial for each patient is scheduled for approximately 28 weeks, including a run-in period of two weeks, followed by 24-week treatment period, and a final follow-up contact two weeks after last study dose. The study flow chart is shown in Figure 1-1, and details about the schedule of assessments are reported in Appendix 1.

Following a washout period for prohibited medication (with the duration varying from one day to one month, depending on the prohibited drug as per CSP), all subjects who have signed the informed consent form (ICF) will undertake a screening visit (Visit 1). At Visit 1, inclusion and exclusion criteria will be checked in terms of patient's medical history (including surgical, COPD and smoking history), review of prior medication, a physical examination, laboratory, vital sign and ECG measurements, and pulmonary function tests (spirometry forced manoeuvre and bronchodilator test).

Subjects fulfilling all inclusion/exclusion criteria at the time of the screening visit and who have done the required washout period of prohibited medication will enter a 14-day run-in period to assess patient's disease stability and baseline characteristics. At Visit 2, eligible subjects will be randomised and will start receiving the investigational product (IP).

Randomisation will be performed by strata using an Interactive Web-response System (IWRS). The stratification factors will be smoking status (current smokers vs. former smokers) and country (China, India, Philippines, Taiwan and Vietnam). Within each stratum, subjects will be randomised in a ratio 1:1:1:1 to one of the following 4 treatment arms:

- Aclidinium bromide 400 µg/Formoterol fumarate 12 µg (AB/FF 400/12)
- Aclidinium bromide 400 µg (AB 400)
- Formoterol fumarate 12 µg (FF 12)
- Placebo

The double-blind treatment period is expected to last 24 weeks with scheduled on-site clinical efficacy and safety assessments at Day 1 (Randomisation/Visit 2), Week 1 (Visit 3), Week 4 (Visit 4), Week 12 (Visit 5), Week 18 (Visit 6) and Week 24 (Visit 7).

During treatment, subjects are expected to take one puff of medication BID, one at 9am (±1 hour) and one at 9pm (±1 hour). Due to the study treatments being administered with different devices (Formoterol fumarate 12 µg and placebo via Turbuhaler and the other active treatments via Genuair), subjects will inhale a puff from both Genuair and Turbuhaler devices at each administration to keep the blind. At least one of these will be placebo (see Table 1-1).

Table 1-1. Schema of IP administration to ensure double-blind trial

Treatment Arm	Morning Inhalation (8-10 AM)	Evening Inhalation (8-10 PM)
AB/FF 400/12	1 puff of AB/FF 400/12 via Genuair 1 puff of placebo via Turbuhaler	1 puff of AB/FF 400/12 via Genuair 1 puff of placebo via Turbuhaler
AB 400	1 puff of AB 400 via Genuair 1 puff of placebo via Turbuhaler	1 puff of AB 400 via Genuair 1 puff of placebo via Turbuhaler
FF 12	1 puff of placebo via Genuair 1 puff of FF 12 via Turbuhaler	1 puff of placebo via Genuair 1 puff of FF 12 via Turbuhaler
Placebo	1 puff of placebo via Genuair 1 puff of placebo via Turbuhaler	1 puff of placebo via Genuair 1 puff of placebo via Turbuhaler

Rescue medication (salbutamol pressurized Metered Dose Inhaler (pMDI) 100 µg/puff) is permitted on an as-needed basis throughout the whole study. Maintenance COPD medication (inhaled, oral or parenteral corticosteroids up to a maximum of 10 mg/day or 20 mg every other day, and oral sustained release theophyllines at a maximum dose of 400 mg/day) will be also permitted during the study if the dose is stable for at least 4 weeks prior to Visit 1. Due to a change in the Chinese pharmacopeia (see clarification letter on March 23rd, 2018), Chinese subjects randomised after the 30th May 2018 will not be allowed to use any inhaled corticosteroid (ICS) as maintenance therapy.

Every evening from Visit 1 until the end of the study, subjects will be required to record on an electronic diary (e-diary) their daily intake of study (from Visit 2) and rescue medication, and to assess their symptoms via the Exacerbations of Chronic Pulmonary Disease Tool (EXACT) questionnaire. Subjects will also be provided with a paper diary to record any Adverse Event (AE), and the intake of any concomitant medication, which will be checked by the investigator at each on-site visit.

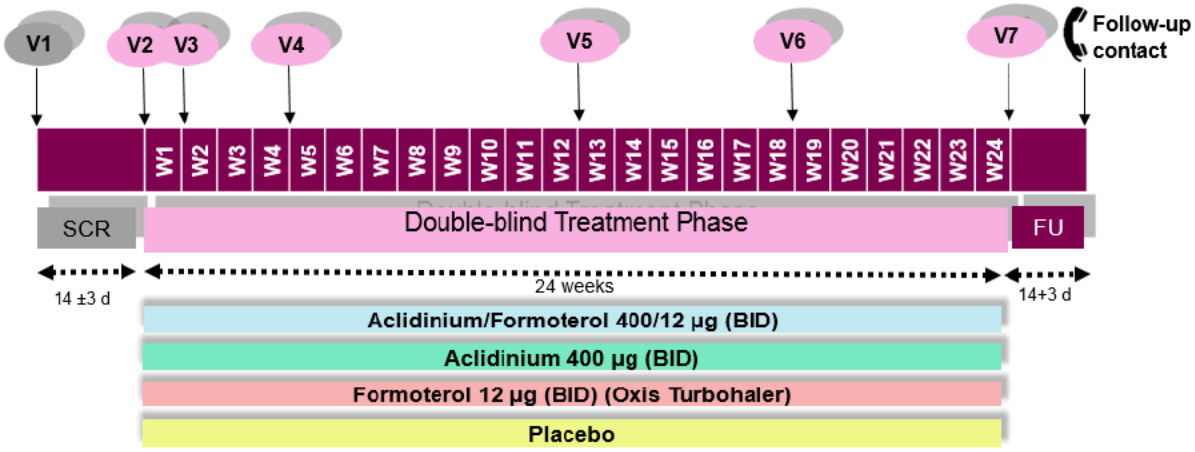
Subjects who prematurely discontinue treatment will participate in an End of Treatment (EOT) Visit for a final safety assessment, that includes a physical examination, laboratory tests, ECG and blood pressure measurements.

At the EOT visit, subjects will be invited to participate in a post-treatment (post-IP) follow-up period for the remainder of the planned study duration up until Week 24. Subjects who do not want to participate on the post-IP follow-up period will have to return the study material at EOT visit, which will be considered also the End of Study (EOS) visit. Subjects who accept the participation to the post-IP follow-up period may be administered other therapy. They will keep completing their paper diaries and e-diaries but the planned on-site visits will be replaced by telephone calls for the review of the paper diaries.

During the post-IP follow-up period the Serious Adverse Events (SAEs), COPD exacerbations and concomitant medication will be recorded. Their last contact (the EOS Visit) will, however, be at on-site for protocol defined measurements and to collect the study material. For these subjects, if the EOS visit is at Week 24, they are considered to have completed the study. If such a patient decides to discontinue from the post-IP follow-up period, they are considered to have discontinued from both treatment and study.

Subjects who complete the planned 24 weeks of treatment or prematurely discontinue from treatment and do not participate to the post-IP follow-up period, will undertake a final telephone contact, two weeks after last IP dose to follow-up any potentially new or ongoing AEs/COPD exacerbations and any medications used to treat them, as well as rescue medication usage.

Figure 1-1. Study flow chart



NOTES:
SCR = Screening; FU = Follow-up; d = days; v= visit; BID = Twice daily.

1.3 Number of subjects

Approximately 1515 patients will be screened in this study in order to achieve 1060 randomised patients, considering an estimated ineligibility rate of 30% prior to randomisation.

Based on previous data, a sample size of 265 randomised patients per group will provide at least 90% power to detect a statistically significant difference at week 24 of 100 mL between Aclidinium bromide 400 µg/Formoterol fumarate 12 µg and Aclidinium bromide 400 µg in change from baseline at 1-hour morning post-dose FEV_1, 65 mL between Aclidinium bromide 400 µg/Formoterol fumarate 12 µg vs Formoterol fumarate 12 µg in change from baseline morning pre-dose (trough) FEV_1, 100 mL between Aclidinium bromide 400 µg vs placebo in trough FEV_1, and 175 mL between Aclidinium 400 µg vs. placebo in peak FEV_1. Previous studies on the same drug and for the same spirometric endpoints showed a standard deviation of 230 mL

The sample size is driven by the comparison between Aclidinium bromide/Formoterol fumarate 400/12 µg vs. Formoterol fumarate 12 µg in morning pre-dose FEV_1, and the minimal detectable difference is 39 mL.

The same sample size will provide at least 90% power to detect a statistically significance difference at week 24 of at least 1-unit between Aclidinium bromide 400 µg/Formoterol fumarate 12 µg and Aclidinium bromide 400µg vs placebo in TDI focal score, assuming a SD of 3.5-units, and at least 4-unit difference in change from baseline in SGRQ total score assuming a SD of 13.5-unit for the same treatment comparisons.

All tests will be performed using two-sided tests at 5% significance level.

Nominal powers for primary and secondary efficacy variables are as follow:

	Step	Endpoint	Treatment Comparison	Nominal power (%)
Primary Endpoints	1	1-hour post-dose FEV_1	Aclidinium bromide/Formoterol fumarate 400/12 µg vs. Aclidinium bromide 400 µg	99
	2	Morning pre-dose FEV_1	Aclidinium bromide/Formoterol fumarate 400/12 µg vs. Formoterol fumarate 12 µg	90
	3	Morning pre-dose FEV_1	Aclidinium bromide 400 µg vs. placebo	99
Secondary Endpoints	4	Peak $FEV_1$1	Aclidinium bromide 400 µg vs. placebo	99
	5	TDI	Aclidinium bromide/Formoterol fumarate 400/12 µg vs. placebo	90
	6	TDI	Aclidinium bromide 400 µg vs. placebo	90
	7	SGRQ	Aclidinium bromide/Formoterol fumarate 400/12 µg vs. placebo	92
	8	SGRQ	Aclidinium bromide 400 µg vs. placebo	92

The order of the hierarchy of endpoints and treatment comparisons is detailed in Table 4-1.

2 ANALYSIS SETS

2.1 Definition of Analysis Sets

Analysis sets used in this study are defined in Table 2-1 and the use of them are explained below.

Table 2-1. Definition of analysis sets

Analysis Set	Definition/Criteria	Analysis Evaluated
Screening Analysis Set	Comprises of all subjects who signed the informed consent form and received a subject identification number.	• Screen subjects • Screen failures
Randomized Analysis Set	Comprises of all subjects who were randomized to a treatment arm.	• Patient disposition
Safety Analysis Set (SAF)	Comprises of all subjects in the Randomised Analysis Set who received at least one dose of study treatment.	• Safety data • Exacerbation data • Demographic and baseline characteristics
Intention-to-treat (ITT) Analysis Set	Comprises of all subjects in the Randomised Analysis Set who took at least one dose of IP and have a baseline FEV_1 Measurement.	• All efficacy data except exacerbations
Per Protocol Analysis Set (PP)	Comprises of all subjects in the ITT who a) met all inclusion/exclusion criteria liable to affect the efficacy assessment; b) have sufficient treatment compliance; and c) did not present serious deviations of the protocol that may affect efficacy. The precise reasons for excluding patients from the study populations will be fully defined and documented in the Blind Data Review Meeting (BDRM).	• Analysis of primary and secondary efficacy endpoints

For Randomised Analysis Set, ITT and PP, subjects will be classified to treatment arms according to their randomized treatment (planned treatment) and whether a patient is exposed to more than one IP study treatment during the study conduct will not change the classification. For the SAF, subjects will be classified using the actual treatment they received. A particular case will be applied to COPD exacerbations which will be analysed under the planned treatment for efficacy analyses. If a subject has received more than one study treatment, they will be included in the treatment arm which they received for a longer period.

Compliance to treatment should be 70% in individual inhaler for inclusion of a subject in the PP Analysis Set.

All randomised subjects (a total of 9 subjects) from study site 3512 will be excluded from the ITT and PP analysis sets due to significant deviations, which question the validity and integrity of the trial data generated from this site. These subjects will be included in the safety analysis set. Primary efficacy variables will be listed.

2.2 Violations and Deviations

The complete list of current protocol deviations (PDs) can be found in the Protocol Deviation Specification Form (PDS). This also includes PDs whose occurrence was impacted by the COVID-19 pandemic.

PDs will be considered as Important Protocol Deviations (IPDs) if 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, including the following:

- Key eligibility criteria not fulfilled but randomized
- Have insufficient study compliance (<70%)
- Withdrawal criteria fulfilled during the study but not withdrawn
- Incorrect study treatment or study dose received at any time during the treatment period
- Concomitant use of disallowed medications
- Other reasons which are identified by the study team as important.

Appendix 2 contains the full list of IPDs with flags to those which may result in the exclusion of a subjects from the PP analysis set. This includes IPDs related to COVID-19.

The final list of IPDs and the ones leading to a PP exclusion will be documented by the study team during a joint blind clinical review of data listings prior to Database Lock (DBL) and treatment unblinding (Blind Data Review Meeting - BDRM). Reasons for the PP exclusions will be documented in the BDRM minutes and a summary table and a listing will be produced by the categories of IPDs and by treatment group for the Clinical Study Report (CSR) as an appendix. Non-important PDs related to the COVID-19 pandemic will be listed separately.

3 PRIMARY, SECONDARY, AND ADDITIONAL VARIABLES

In this section, all study variables are described and/or derived.

3.1 Study Population

Study population summaries will include subject dispositions, demographic and baseline characteristics, medical history and physical examination at screening, disease characteristics at screening, prior, concomitant, and post-treatment medications, and treatment compliance.

Subjects are recruited in China, India, Philippines, Taiwan and Vietnam.

3.1.1 Subject Disposition

For each subject, the following disposition categories will be either collected in the Electronic Data Capture (EDC) system or derived:

- Enrolment status (Enrolled if subjects signed the ICF).
- Randomization Status (Randomized, Not-Randomized) and Reason for not being randomised (Screen failure [non-fulfilment of inclusion/exclusion criteria], Adverse event, Progressive disease, Withdrawal by subject, Lost to follow-up, Pregnancy, Other).
- Treatment Received (Treatment Received, Treatment Not Received) and Reason for not receiving treatment (Adverse event, Progressive disease, Lack of efficacy, Protocol deviation, Pregnancy, Withdrawal by Subject, Lost to Follow-up, Other).
- Treatment Completion Status (Treatment Completed, Treatment Discontinued) and Reason for Premature Discontinuation from the EOT Form (Adverse Event, Progressive Disease, Lack of efficacy, Protocol Deviation, Pregnancy, Withdrawal by Subject, Lost to Follow-up, Other). Discontinuation of treatment due to the COVID-19 pandemic will be recorded via a tick-box added to a new page in the EDC for any affected subjects.
- Study Completion Status (Study Completed, Study Withdrawn) and Reason for Study Withdrawal from the EOS Form (Adverse event, Progressive disease, Protocol deviation, Pregnancy, Withdrawal by Subject, Lost to follow-up, Other). Withdrawal from the study due to the COVID-19 pandemic will be recorded via a tick-box added to a new page in the EDC for any affected subjects.
- Follow-up contact Status (Follow-up contact made 14 days after last dose) after Week 24 (Visit 7) completed or when discontinued without going through the post-IP follow-up).

Subjects who complete the study are either subjects who made the Visit 7 (regardless of whether they made the follow-up phone contact at Week 26), or subjects who prematurely discontinue treatment but complete the post-treatment follow-up period until Visit 7 as it states in the EOS Form.

3.1.2 Demography

Demographic and subject characteristics (country, age, sex, race and ethnic population) will be collected at Screening (Visit 1). The subject characteristics height and weight will be collected as part of the subject physical examination.

The following variables will be derived:

- Age categorized (age group) as: ≥40 - <60; ≥60 - <70; ≥70.
- Body Mass Index (BMI) will be derived as continuous variable as weight in Kg divided by height in meter squared (Kg/m^2) and categorized (BMI group) as: Underweight (<18.5), Normal weight (≥ 18.5 and < 25), Pre-obese (≥ 25 and <30) and Obese (≥ 30).

3.1.3 Relevant Medical History and Physical Examination at Screening

Relevant medical history will be collected at Screening (Visit 1) and coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) dictionary.

A complete physical examination will be performed at Visit 1 and Visit 7. Relevant findings detected in physical examination at Visit 1 will be recorded under Medical History and those found at Visit 7 will be recorded under AE. Recorded medical History data will be split as medical history and surgical history. Based on whether these conditions are ongoing at the time of randomisation as recorded on the electronic case report form (eCRF), these conditions will be categorized as past (prior to screening) or current (ongoing at time of screening).

3.1.4 Disease Characteristics at Screening

The study population will be described using disease characteristics.

Smoking history at screening visit:

- Smoking status (current smoker/former smoker)
- Smoking consumption (number of pack-year)
- Smoking duration
  - Smoking duration (years): For former smokers is the difference between the year they stopped smoking and the year they started to smoke +1, and for current smokers the difference between the year of the screening visit and the year they started to smoke +1.

COPD history at screening visit:

- COPD severity derived per the 2015 GOLD classification of airflow limitation (using the post-bronchodilator FEV_1):
  - Stage I (mild): $FEV_1 \geq 80\%$ of the predicted normal values
  - Stage II (moderate): $FEV_1 \geq 50\%$ and $< 80\%$ of the predicted normal values
  - Stage III (severe): $FEV_1 \geq 30\%$ and $< 50\%$ of the predicted normal values
  - Stage IV (very severe): $FEV_1 < 30\%$ of the predicted normal values

- COPD severity derived per the GOLD classification of symptoms based on the COPD Assessment Test (CAT) at Baseline (Visit 2) and risk of exacerbation as collected in COPD history at Screening (Visit 1):
    - A: CAT Score<10, and ≤ 1 exacerbation not requiring hospitalization in the previous 12 months
    - B: CAT Score ≥10, and ≤ 1 exacerbation not requiring hospitalization in the previous 12 months
    - C: CAT Score <10, and ≥2 exacerbations or ≥1 exacerbation requiring hospitalization in the previous 12 months
    - D: CAT Score ≥10, and ≥2 exacerbations or ≥1 exacerbation requiring hospitalization in the previous 12 months

- COPD duration (years), will be computed as the year of screening visit and the year of diagnosis of COPD + 1
- Number of COPD exacerbations in the previous 12 months
- Time (days) since last COPD exacerbation, calculated as the difference between the date of resolution of last COPD exacerbation and the screening visit date
- Time (days) since last hospitalization due to a COPD exacerbation, calculated as the difference between the date of resolution of last COPD exacerbation and the screening visit date
- Chronic bronchitis and/or emphysema (yes/no)

Pulmonary function tests at screening visit:

- Absolute values of FEV_1 and FVC pre- and post-bronchodilator
- Percent of predicted FEV_1, and FVC pre- and post-bronchodilator
- Ratio FEV_1/ FVC (post- bronchodilator test)

Bronchodilator test:

- Mean absolute bronchodilator change and percentage of bronchodilator reversibility in FEV_1
    - Mean absolute bronchodilator change is the difference between pre- and post-bronchodilator FEV_1 values
    - The percentage of bronchodilator reversibility will be computed as: (Mean absolute bronchodilator change / Pre-bronchodilator FEV_1) x100.
- Percentage of subjects with bronchial reversibility (an increase in FEV_1 that is both ≥ 200 mL and 12% above the pre-bronchodilator FEV_1)

Baseline values at Day 1 (visit 2):

- Pulmonary function tests pre-IP at baseline
    - Absolute values of FEV_1, and FVC
    - Percent of predicted FEV_1, and FVC
- Signs and symptoms of health-related quality of life

- Total score of SGRQ and scores of the three dimensions
- Total score of Baseline Dyspnoea Index (BDI) and scores of the three components
- CAT (total) score

3.1.5 Prior, concomitant and post-treatment medications

Prior and concomitant medication will be collected by the investigator at each study visit using the information in the patient paper diaries.

Medications will be coded according to the latest World Health Organization (WHO) drug dictionary.

Prior medications:

- As recorded on the eCRF, includes any medication taken between 15 days prior to the ICF and the date of first IP dose, and will be summarised using the two categories below:
  - Any medication taken within 15 days prior to the ICF (included)
  - Any prior medication taken after the date of the ICF (excluded) to the day before the first IP dose (included)

Concomitant medications:

- Any drug that starts on or after the first IP dose up until the last IP dose (excluded) or started before the first IP dose and continued during the IP treatment period.

Post-treatment medication:

For subjects that discontinue from the IP and accept to participate in the post-treatment follow-up period

- Any drug collected during the follow-up period after last IP dose date.

Due to a change in the Chinese pharmacopeia, Chinese subjects randomised after the 30th May 2018 will not be allowed to use any ICS as concomitant maintenance therapy (see clarification letter on March 23rd, 2018).

Prior COPD-related treatment

Prior medication indicated for COPD only will be any medication for COPD taken prior to the ICF. Medications taken for COPD prior to the ICF signature will be identified as 'Prior COPD-related Treatment' and coded using the latest version of the AstraZeneca Barcelona COPD Standardised Drug Grouping (AZBC SDG) and categorized into the following therapeutic categories:

- Short-acting β2 agonists (SABA)*;
- Short-acting muscarinic antagonists (SAMAs)*;
- SABA + SAMA (FDC)*;
- Long-acting β2 agonists (LABA) *;
- Long-acting muscarinic antagonists (LAMA) *;
- LABA + LAMA (FDC)*;
- Inhaled corticosteroids (ICS)*;
- SABA + ICS (FDC) *;
- LABA + ICS (FDC) *;
- LAMA + ICS (FDC) *;
- LAMA + LABA + ICS (FDC) *;
- Muscarinic antagonist β2 adrenoceptor agonist (MABA);
- Systemic corticosteroid;
- Xanthines;
- Leukotriene modifiers;
- Oxygen;
- Oral phosphodiesterase type 4 (PDE4);
- Influenza vaccine;
- Cromones;
- Monoclonal Antibody;
- Others

All the above prior-COPD related treatment combinations are intended as FDC. For those medications marked with an asterisk, if subjects take more than one monotherapies or fixed-dose combinations forming a higher AZBC SDG therapeutic category, drugs will be combined and re-categorised to the maximum free-dose (free) drug combination (regardless of whether they are taken concomitantly to each other). For example, LABAs and LAMAs taken by the same subject as prior COPD-related treatment will be grouped into a new LABA + LAMA (free) category; subjects taking both an ICS + LABA (FDC) and a LAMA will be re-categorised into the LAMA + LABA + ICS (free) category. If a patient has taken any medications, it will be flagged in the patient data listing. See the programming Specs for the different groups.

Baseline ICS use will be flagged in the patient data listings for those subjects who use any ICS between Screening (Visit 1) and the first IP dose.

3.1.6 Study Treatment Compliance

The variables for treatment compliance are:

- Compliance with study treatment for Genuair
- Categorised compliance with study treatment for Genuair (Yes/No)
- Compliance with study treatment for Turbuhaler
- Categorised compliance with study treatment for Turbuhaler (Yes/No)
- Overall compliance (%) with study treatment
- Categorised overall compliance with study treatment (Yes/No)

A patient to be compliant they should have ≥70% compliance regardless of the inhaler. For overall compliance, the patient should be compliant with each of the inhalers

Compliance with study medication will be based on the study medication usage recorded by the patient in the bedtime e-diaries. Compliance (%) will be calculated for each device (Genuair and Turbuhaler) and overall as follows:

$$\frac{Actual\ \text{overall intake}}{\text{Expected overall } intake} * 100$$

where:

- Actual overall intake = sum of the daily numbers of puffs taken as recorded in the e-diary from Day 1 until the second-to-last IP dose day (because the morning IP dose of the very last day is not included in the e-diaries). For subjects discontinuing on Day 1 or Day 2, the actual overall intake will be the numbers of puffs taken on Day 1 as recorded on their e-diary.
- Expected overall intake = 2 puffs times the number of days between Day 1 (or the first day the question on IP dose intake is activated in the e-diary after randomisation) and the second-to-last IP dose day. For subjects discontinuing on Day 1 or Day 2, the expected overall intake will be 2 puffs.

The overall treatment compliance for both inhalers will be calculated as the average of the compliance rates of the two inhalers.

Drug accountability consists of the information on the provision and collection of the IP kits as recorded on the eCRF. Inhalers will be dispensed at Day 1 (Visit 2) and Week 12 (Visit 5) and will be collected at Week 12 (Visit 5) and Week 24 (Visit 7)/EOT. Drug accountability only includes information regarding the number of inhalers dispensed and collected as well as their status (used/unused/lost).

3.2 Efficacy Variables

The efficacy measurements are recorded in the study schedule in Appendix 1.

3.2.1 Primary Efficacy Variables

The primary efficacy variables and comparisons are the following:

- Change from baseline in 1-hour morning post-dose FEV_1 at Week 24 for comparison of AB/FF 400/12 and AB 400
- Change from baseline in morning pre-dose (trough) FEV_1 at Week 24 for the comparison of AB/FF 400/12 and FF 12
- Change from baseline in morning pre-dose (trough) FEV_1 at Week 24 for the comparison of AB 400 and placebo

Trough FEV_1 will be computed as the average of the two FEV_1 values at morning pre-dose. If one value is missing, then the remaining one will be used as the trough value.

Baseline of FEV_1 is defined as the average of the two FEV_1 values prior to the administration of the first dose of IP on Day 1. If one of the two values is missing, then the available one will be used as baseline value. If both values are missing, the Screening pre-bronchodilator value will be used as the baseline. Otherwise, the baseline value will be considered as missing.

The changes from baseline are calculated as:

- Change from Baseline = Post-dose Visit Value – Baseline

3.2.2 Secondary Efficacy Variables

The secondary efficacy variables and comparisons are the following:

- Change from baseline in peak FEV_1 at Week 24 for the comparison of AB 400 and placebo
- Improvement in TDI focal score at Week 24 for the comparison of AB/FF 400/12 and placebo
- Improvement in TDI focal score at Week 24 for the comparison of AB 400 and placebo
- Change from baseline in SGRQ total score at Week 24 for the comparison of AB/FF 400/12 and placebo
- Change from baseline in SGRQ total score at Week 24 for the comparison of AB 400 and placebo

TDI focal score is recorded as a comparison to BDI and no further derivation is required for 'Improvement in TDI'. The derivation of TDI focal score is given in Appendix 3.

Derivations for total score of SGRQ is given in Appendix 4. The baselines for SGRQ is the corresponding score derived from the data recorded on Day 1. If this score is missing, the baseline is considered as missing.

Peak FEV_1 is the highest value of FEV_1 recorded at that visit after the morning IP intake.

The change from baseline for SGRQ and FEV_1 variables are derived as:

- Change from Baseline = Post-dose Visit Value – Baseline

3.2.3 Additional Efficacy Variables

3.2.3.1 Pulmonary Function Test (PFT)

The additional PFT efficacy variables are:

- Changes from baseline in 1-h morning post-dose FEV_1 at Day 1 and Weeks 1, 4, 12, 18, and over 24 weeks on treatment
- Changes from baseline in morning pre-dose (trough) FEV_1 at Weeks 1, 4, 12, 18, and over 24 weeks on treatment
- Changes from baseline in peak FEV_1 at Day 1

- Changes from baseline in normalized Area Under the Curve (AUC) from 0 to 3 hours ($nAUC_{0\text{-}3h}$) FEV_1 at Day 1, and Week 24
- Absolute values and changes from baseline in FEV_1 at all visits by timepoint
- Changes from baseline in 1-h morning post-dose FVC at Day 1 and Weeks 1, 4, 12, 18, 24, and over 24 weeks on treatment
- Changes from baseline in morning pre-dose (trough) FVC at Weeks 1, 4, 12, 18, 24, and over 24 weeks on treatment
- Changes from baseline in peak FVC at Day 1 and Week 24
- Changes from baseline in normalized AUC from 0 to 3 hours ($nAUC_{0\text{-}3h}$) FVC at Day 1, and Week 24
- Absolute values and changes from baseline in FVC at all visits by timepoint
- Percentage change from baseline in 1-hour post-dose FEV_1 at Day1, at Weeks 1, 4, 12, 18, 24, and over 24 weeks on treatment
- Percentage change from baseline in morning pre-dose (trough) FEV_1 at Week 1, 4, 12, 18, 24, and over 24 weeks on treatment
- Percentage change from baseline in 1-hr post-doe FVC at Day1, at Weeks 1, 4, 12, 18, 24, and over 24 weeks on treatment
- Percentage change from baseline in morning pre-dose (trough) FVC at Weeks 1, 4, 12, 18, 24, and over 24 weeks on treatment

The baseline value for all the FEV_1 variables are the same as defined for the primary efficacy variables. The baseline for FVC variables are derived similarly using the values at morning pre-dose values or, if they are missing, using Screening value. The changes from baseline are calculated similar to the primary efficacy variables.

The mean normalized AUC from 0 to 3 hours for FEV_1 is derived using the following trapezoidal method formulae using time in hours:

$$nAUC_{0-3\text{h}}\ FEV_1 = \frac{1}{t_5 - t_0}\sum_{j=1}^{5}\left(t_j - t_{j-1}\right) * \frac{(FEV_{1(j)} + FEV_{1(j-1)})}{2}$$

where t_j (j = 0,1,2,3,4,5 for trough, 5 min, 30 min, 1h, 2h, and 3h, respectively) is the time (in hours) at the timepoint *j* at which FEV_1 is measured. The FEV_1 at timepoint *j=0* is the trough FEV_1 (and $t_0 = 0$). Note: on Day 1, this will be the baseline value.

At least two FEV_1 values must be available, one of which must be the trough FEV_1 and one FEV_1 value between 2h and 3h post-dose (extremes included). Otherwise, the $nAUC_{0\text{-}3h}$ will be considered missing.

For the derivation of AUC, all actual timepoints should be used, and should be given in hours.

The nAUC0-3h for FVC at Day 1 and Week 24 will be derived similarly.

3.2.3.2 Signs and Symptoms and Health-related Quality of Life

The BDI and TDI focal scores are derived together with the 3 following components:

- Functional impairment: the impact of breathlessness on the ability to carry out activities
- Magnitude of task: the type of task that causes breathlessness
- Magnitude of effort: the level of effort needed to evoke breathlessness

The SGRQ total scores are derived together with the following dimensions:

- Symptoms: the effect of respiratory symptoms, their frequency and severity
- Activity: activities that cause or are limited by breathlessness
- Impact: a range of aspects concerned with social functioning or psychological disturbances resulting from airways disease

The CAT is an 8-item questionnaire and the CAT score (total) has a scoring range of 0-40.

The higher scores of SGRQ and CAT indicate a greater deterioration of the COPD symptoms on the patient health status. A positive score in TDI indicates an improvement which increases with the value of score while a negative score indicates a deterioration which deteriorates further with the decrease of score value. The derivation of BDI and TDI focal scores and their three component-scores are detailed in Appendix 3. Details about the SGRQ questionnaire is given in Appendix 4. The CAT questionnaire is given in Appendix 5.

The baseline for TDI is BDI. The baselines for SGRQ and CAT scores will be the corresponding score derived for the questionnaire data recorded on Day 1. If derived score on Day 1 is missing, the baseline is considered as missing.

The Minimum Clinically Important Differences (MCID) are:

- TDI Focal Score: + 1 unit
- SGRQ Total Score: a reduction from baseline of at least 4 units
- CAT Total Score: a reduction from baseline of at least 2 units

The additional BDI/TDI, SGRQ and CAT efficacy variables are:

- Improvements in TDI focal score at Weeks 4 and 12 and three component scores at Weeks 4, 12, 24, and over 24 weeks on treatment.

- Number (%) of subjects who achieved a clinically meaningful difference in TDI focal score (improvement of ≥1 unit) at Weeks 4, 12, and 24.

- Change from baseline in SGRQ total score at Weeks 4 and12 and three dimension scores at Weeks 4, 12, 24, and over 24 weeks on treatment.

- Number (%) of subjects achieving a clinically meaningful improvement (≥4 units) compared with baseline in SGRQ total score at Weeks 4, 12, and 24.

- Change from baseline in the CAT score at Weeks 4, 12, 24, and over 24 weeks on treatment.

- Number (%) of subjects achieving a clinically meaningful improvement (≥2 units) in CAT score at Weeks 4, 12 and 24.

3.2.3.3 COPD Exacerbations

COPD exacerbations will be derived using the Health Care Resource Utilization (HCRU) and the EXACT tool.

HCRU exacerbations are derived based on the information recorded in the Adverse Event module of the eCRF. The date of onset and date of resolution will be extracted from eCRF data.

EXACT questionnaire is completed by subjects every study day before bed and has 14 questions. The EXACT Total score is computed across the 14 items and has a range of 0 to 100, with higher values indicating a more severe condition (Appendix 6). The onset date of a new EXACT exacerbation is the first day of the worsening of the baseline condition, where worsening is defined by an increase from baseline in the EXACT Daily Score of either ≥ 12 points for 2 consecutive days, or ≥ 9 points for 3 consecutive days. The date of onset and date of resolution for the exacerbation will be the dates started to meet these criteria and end to meeting them.

The following additional COPD exacerbation efficacy variables are based on HCRU (worsening of symptoms requiring a change in COPD treatment and/or hospitalization and/or emergency room treatment):

- Number (%) of subjects with at least 1 COPD exacerbation (any, mild, moderate, severe and moderate or severe).

Number of exacerbations will be set to zero for subjects with no exacerbations and further categorizated as 0, 1, ≥ 2 exacerbations.

- Total days of exacerbations (any, mild, moderate, severe and moderate or severe).

The duration of an exacerbation = date of recovery – date of onset +1. For the summary statistics, the duration will not be derived if either the date of onset or the date of recovery is completely or partially missing. The total days of exacerbation is the sum of all the durations of exacerbations experienced by the subject for a given severity.

- Time (days) to first COPD exacerbation (any, mild, moderate, severe and moderate or severe).

The time (in days) to the first exacerbation is derived as the time elapsed from the first IP dose date to the first exacerbation Onset Day (non-censored data) or the last IP dose date (censored data), whichever occurs first, + 1 day.

- Total risk time in years (any, mild, moderate, severe and moderate or severe).

The total-risk time in years for each patient will be calculated separately for each exacerbation type (HCRU: any, mild, moderate, severe and moderate or severe). It is defined as the time that a patient is at risk of an exacerbation of that type. For example, for an analysis of moderate or severe HCRU exacerbations, a subject is not at risk of experiencing a moderate or severe exacerbation during a moderate or severe exacerbation (or the seven days afterwards), but is at risk during a mild exacerbation (except for when both are combined into one exacerbation). For the while on treatment analysis (see Section 4.1.1), the total-risk time will be defined as the treatment exposure deducting both the summed duration of exacerbations during treatment exposure and seven days for each exacerbation reported by the patient. For the treatment policy analysis, the total-risk time will be defined as the time-on-study deducting both the summed duration of exacerbations while on-study and seven days for each exacerbation reported by the patient. In general, seven days should be deducted from the total-risk time for each exacerbation of that type. However, for exacerbations that end less than seven days prior to the end of treatment/study, this duration should be deducted instead. When deriving the duration of exacerbations, partially or completely missing Onset and Recovery Days will be imputed. For all Recovery Days occurring after the end of treatment, the date will be curtailed to the date of the last IP dose. For a patient in any exacerbation analysis for which the time-at-risk is calculated as being less than 1 day, it will be set to 1. The total risk time will be converted to years.

- Rate of COPD exacerbations per patient/year (any, mild, moderate, severe and moderate or severe).

The annual crude rate of exacerbation for each type will be estimated as the number of exacerbations of that type divided by the total risk time.

Derived from the EXACT questionnaire:

- Number (%) of subjects with at least 1 COPD exacerbation.

The derivation of number of subjects with at least 1 EXACT COPD exacerbation will be the same as for HCRU, as detailed above.

- Total days of exacerbations.

For EXACT, the event duration calculation requires the identification of the following parameters: (i) Onset; (ii) 3-day rolling average; (iii) Maximum Observed Value; (iv) Threshold for improvement; (v) Recovery. Further details of these parameters can be found in Appendix 7. The duration is calculated as the difference, in days, between the day of Onset and the day of Recovery. Recovery day is not included in the calculation of duration.

- Time (days) to first COPD exacerbation.

The derivation of time to first EXACT COPD exacerbation will be the same as for HCRU, as detailed above

- Total risk time in years.

A similar approach to that given for HCRU above will be used to derive total risk time in years for EXACT COPD exacerbations.

- Rate of COPD exacerbations per patient/year.

The annual crude rate will be calculated as the number of EXACT COPD exacerbations divided by the total risk time.

Appendix 7 provides further details on the derivation of both HCRU and EXACT exacerbation events.

For a COPD exacerbation to be counted as a separate event, it must be preceded by at least seven days in which no criteria for exacerbations is fulfilled. In case of relapse, the Recovery day for the resulting exacerbation is the Recovery day of the last episode and the onset day is the one from the first episode, and the severity of the resulting exacerbation will be that of the highest severity of the episodes.

For the while on treatment estimand, all exacerbations starting before the first IP dose or after the last IP dose will be excluded from the analysis and from the above calculations. For the policy estimand (on-study), all exacerbations starting before the first IP dose or after the last EOS visit date will be excluded from the analysis.

3.2.3.4 Daily COPD Symptoms (E-RS) and use of rescue medication

The E-RS scale is a part of the Exacerbations of Chronic Pulmonary Disease Tool (EXACT) questionnaire, which is composed by the following three domains:

- E-RS Breathlessness
- E-RS Cough and Sputum
- E-RS Chest Symptoms

The E-RS total score derived from 11 items of EXACT questionnaire (ranging from 0 to 40), quantifies the overall severity of respiratory symptoms, and 3 domain scores assesses breathlessness (derived sum of 5 items); cough and sputum (derived sum of 3 items); and chest symptoms (derived sum of 3 items).

The total E-RS score and the scores for the three domains are derived as detailed in Appendix 8. The higher scores of E-RS indicate a greater deterioration.

The additional COPD symptoms and use of recue medication variables are:

- Change from baseline in EXACT-Respiratory Symptoms (E-RS) total score and its three domains (breathlessness, cough & sputum and chest) for each period

comprised between two consecutive visits (Weeks 1, 4, 12, 18 and 24 and overall over 24 weeks).

The MCIDs for E-RS Breathlessness score, Cough and Sputum score and Chest Symptoms score are -1, -0.70, and -0.70, respectively. The MCID for the E-RS total score is based on a reduction from the baseline in at least 2 units. The following endpoint will be assessed:

- Number (%) of subjects with a clinically meaningful improvement in E-RS total score, and by domains for each period comprised between two consecutive visits (Weeks 1, 4, 12, 18 and 24 and overall over 24 weeks).

All subjects are provided salbutamol (salbutamol pMDI 100 μg/puff) as rescue medication. Subjects record every night the number of puffs of salbutamol taken within the last 24 hours by answering the question: *How many puffs of relief medication (salbutamol) have you inhaled in the last 24 hours (from yesterday when you went to bed until now)?*

The following endpoint will be assessed:

- Change from baseline in the use of rescue medication for each period comprised between two consecutive visits (Weeks 1, 4, 12, 18 and 24 and overall over 24 weeks).

The E-RS and the use of daily rescue medication are derived as the mean of all non-missing daily entries recorded between two consecutive (non skipped) scheduled visits (ending the night before the scheduled visit), or between a visit and the last IP date (excluded), if a patient withdrawn. Overall period is defined as a period between first dose and last IP dose (excluded). Missing values in daily rescue medication will not be imputed.

For E-RS and rescue medication, the baseline is defined as a 7-day interval before the first IP dose (ending the night before the first dose of IP), and will be calculated as the sum of scores/puffs divided by the total number of days with non-missing values reported that week. Baseline values will be computed only for those subjects recording at least 4 diary entries during this period. Otherwise the baseline score will be set to missing.

3.3 Safety Variables

3.3.1 Extent of Exposure and Study Duration

The variables analysed are:

- Duration of exposure to the IP calculated in days as:
  Date of the last IP dose - Date of the first IP dose +1.
- Categorised cumulative duration of exposure as: ≥ 1 day, ≥ 1 week, ≥ 4 weeks, ≥ 12 weeks, ≥ 18 weeks, and ≥ 24 weeks.
- Time in the study (duration of study) calculated in days as:
  Date of the last on-site visit - Date of randomisation +1.

- Categorised cumulative duration of study as: ≥ 1 day, ≥ 1 week, ≥ 4 weeks, ≥ 12 weeks, ≥ 18 weeks, and ≥ 24 weeks.

See Section 4.6.2 for definition of the last IP dose date.

3.3.2 Adverse Events

Adverse events (AE) will be coded using the latest MedDRA dictionary (version 23.0 or higher).

AEs will be categorised according to the following study periods:

- Pre-treatment AEs: started before first IP dose date
- Treatment-emergent AEs (TEAEs): AEs started on or after the date first IP dose until 15 days from the last IP dose date.
- Post-treatment AEs: AE started after 15 days from last dose

AEs with completely or partially missing start date/time and/or end date/time will be handled as detailed in Section 4.6.4 before flagging the AEs with the above categorisation. See Section 4.6.5 for imputation of missing severity and relationship to study drug.

The following durations will be derived as event date – first IP dose + 1:
- Days from first dose to onset of AE
- Days from last dose to onset of the AE
- Days from first dose to death
- Days from onset to resolution (duration of AE)
- Days from first dose to becoming serious

In case of the event date is prior to first IP dose, then the durations will be derived as event date – first IP dose.

Adverse Events of Special Interest (AESI) and Major Adverse Cardiovascular Events (MACE)

AEs of Special Interest (AESIs) will include cardiac, cerebrovascular, anticholinergic, pneumonia, and β_2-adrenergic events. AESI will be identified based on the categorisation of Standardised MedDRA Query (SMQ), System organ class (SOC), High Level Terms (HLTs) or Preferred Terms (PTs) as per Table 3-2.

The Cardiovascular Adjudication Committee (CVAC) is an independent external expert advisory panel responsible for applying a consistent and pre-specified set of criteria to determine if the reported potentially cardiovascular events are identified as Major Adverse Cardiovascular events (MACE). Adjudicated MACEs are composed by cardiovascular deaths (death due to acute myocardial infarction, sudden cardiac death, death due to heart failure or cardiogenic shock, death due to stroke, and death due to other cardiovascular cause), non-fatal myocardial infarction (MI) (Type 1: spontaneous; Type 2: demand type and procedure-related MI), and non-fatal stroke (ischemic, hemorrhagic, and undetermined).

Table 3-2. Definition of Adverse Events of Special Interest (AESI)

AESI Group	SMQ, SOC, HLT or PT	
Cardiac events	Ischemic Heart Disease:	
	• Myocardial infarction	Narrow search SMQ
	• Other Ischemic Heart Disease	Narrow search SMQ
	Tachyarrhythmias (supraventricular and ventricular tachyarrhythmias)	Narrow and broad search SMQ and the following additional PTs: tachycardia, heart rate increased and palpitations
	Cardiac failure	Narrow search SMQ
	Bradycardia	Narrow search SMQ Bradyarrhythmia terms, nonspecific and the following additional PTs: sinus arrest and sinus bradycardia
	Conduction defects	Narrow search SMQ
Cerebrovascular events	Hemorrhagic and Ischemic disorders:	
	• Haemorrhagic central nervous system vascular conditions	Narrow search SMQ
	• Ischaemic central nervous system vascular conditions	Narrow search SMQ
Anticholinergic events	Anticholinergic syndrome	Narrow and broad search SMQ
	Glaucoma	Narrow search SMQ
	Additional PTs: sinus tachycardia, supraventricular tachycardia, ventricular tachycardia, heart rate increased, palpitations, pupillary reflex impaired, pupils unequal, visual impairment, constipation, gastrointestinal obstruction, illeus paralytic, urinary tract infection, cystitis, urinary incontinence, incontinence, dysuria, urge incontinence, urine flow decreased, bladder irritation, oropharyngeal pain, dysphonia, laryngitis, pharyngitis, and throat irritation	
Pneumonia	All PTs that contain the term pneumonia	
β_2 adrenergic events	Hypertension	Narrow search SMQ
	Hyperglycaemia/new onset diabetes mellitus	Narrow search SMQ
	Tachyarrhythmias (incl supraventricular and ventricular tachyarrhythmias)	Narrow and broad search SMQ and the following additional PTs: tachycardia, heart rate increased, and palpitations
	Tremor (excl congenital)	Narrow search HLT
	Additional PTs: Anxiety, Nervousness, Insomnia, Headache, Dizziness, Vision blurred, Mydriasis, Dysgeusia, Throat irritation, Cough, Hypokalemia, Myalgia, Muscle spasms, Urinary retention, Urinary tract infection, Constipation, Oedema peripheral, Electrocardiogram QT interval abnormal, Electrocardiogram QT prolonged.	

AESI Group	SMQ, SOC, HLT or PT

3.3.3 Clinical Laboratory Tests

Laboratory assessments are expected at screening (baseline) and at the last on-site visit (at discontinuation of treatment and discontinuation or completion of study) and will include haematology, biochemistry and serum pregnancy test (only for women of childbearing potential).

All the collected laboratory variables can be found in Table 3-3 and are converted to the International System (SI) Units by the data management team for reporting purposes. See Section 4.1.12 for imputation rule of clinical laboratory data.

Laboratory values will be any values collected after the first dose, including in the post-treatment follow-up period.

For all haematology and biochemistry variables, changes from baseline will be calculated at any post-baseline study visits. The value recorded at Screening will be used as the baseline and if that value is missing, the baseline is considered as missing.

Potentially Clinically Significant (PCS) abnormalities in haematology and biochemistry will be identified using the expanded normal ranges (ENRs) and the notable abnormality limits of Table 3-3.

Each baseline and post-baseline value will be categorised as follows using the ENRs:

- Normal – if value falls within the ENR
- Low – if value is below the lower limit of ENR
- High – if value is above the upper limit of ENR

Post-baseline PCS abnormalities will be classified as follows:

- New - one of the below condition yields:
  - the value of the visit of interest is abnormal while its baseline value was normal
  - both baseline value and the value of the visit of interest are abnormal but the post-baseline is outside the ENR at the opposite extreme (*i.e.,* from low to high or vice versa)
- Worsened - one of the below condition yields:
  - the baseline value is high, and the ratio of the value at the visit of interest to the baseline is also above the upper limit of ENR;
  - the baseline value is low, and the ratio of the value at the visit of interest to the baseline is also below the lower limit of ENR;
- Notable - if value falls outside the limits of the notable abnormalities, having a baseline value that was within the notable abnormality limits.

Please note that while the categories of New and Worsened are mutually exclusive, a notable PCS can be also new or worsened at the same time.

Table 3-3. Expanded normal ranges and notable abnormalities for laboratory parameters

Laboratory Parameters	Expanded normal ranges		Notable abnormality ranges	
	xLLN [1]	xULN [2]	Lower Limit	Upper Limit
Haematology				
Haemoglobin	0.85	1.15	< 60 g/L	> 230 g/L
Haematocrit	0.85	1.15	< 24%	N/A
Erythrocytes (red blood cells)	0.85	1.15	N/A	N/A
Thrombocytes (platelets)	0.85	1.15	< 100 x 10^9/L	N/A
Leukocytes (white blood cells):				
Total Count	0.85	1.15	< 1 x 10^9/L	> 30 x 10^9/L
Neutrophils	0.85	1.15	< 0.5 x 10^9/L	N/A
Eosinophils	N/A	1.15	N/A	N/A
Basophils	N/A	1.15	N/A	N/A
Lymphocytes	0.85	1.15	N/A	N/A
Monocytes	N/A	1.15	N/A	N/A
Biochemistry				
Electrolytes:				
Sodium	0.95	1.05	< 115 mmol/L	> 165 mmol/L
Potassium	0.95	1.05	< 2.6 mmol/L	> 6.9 mmol/L
Calcium	0.85	1.15	< 1.25 mmol/L	> 3.25 mmol/L
Chloride	0.95	1.05	N/A	N/A
Inorganic phosphorous	0.85	1.15	N/A	N/A
Enzymes:				
Aspartate Aminotransferase (AST or GOT)	N/A	1.15	N/A	> 3xULN
Alanine Aminotransferase (ALT or GPT)	N/A	1.15	N/A	> 3xULN
Alkaline phosphatase (ALP)	N/A	1.15	N/A	> 3xULN
Gamma-glutamyl transferase (γGT)	N/A	1.15	N/A	> 3xULN
Lactate dehydrogenase (LDH)	N/A	1.15	N/A	> 3xULN

Laboratory Parameters	Expanded normal ranges		Notable abnormality ranges	
	xLLN [1]	xULN [2]	Lower Limit	Upper Limit
Creatine kinase (CK)	N/A	1.15	N/A	> 10xULN
CK-MM	N/A	1.15	N/A	> 10xULN
CK-MB	N/A	1.15	N/A	> 10xULN
CK-BB	N/A	1.15	N/A	> 10xULN
Substrates:				
Glucose	0.85	1.15	< 2.22 mmol/L	> 22.2 mmol/L
Total cholesterol	N/A	1.15	N/A	N/A
Triglycerides	N/A	1.15	N/A	N/A
Creatinine	N/A	1.15	N/A	> 265 µmol/L
Total bilirubin (TBL)	N/A	1.15	N/A	> 51.3 µmol/L
Total protein	0.85	1.15	< 20 g/L	> 90 g/L
Albumin	0.85	1.15	N/A	N/A
Uric acid	N/A	1.15	N/A	> 714 µmol/L
Blood urea nitrogen (BUN)	N/A	1.15	N/A	> 17.9 mmol/L

NOTES:
[1] xLLN = Factor multiplied by the Lower Limit of the Expanded Normal Range (LLN)
[2] xULN = Factor multiplied by the Upper Limit of the Expanded Normal Range (ULN)

The following increases in liver biochemistry observed in one active treatment group compared to the control group at any time during the study from first dose are signals of potential drug-induced liver injury (DILI):

- ALT/AST ≥ 3xULN and <5xULN
- ALT/AST ≥5xULN and <10xULN
- ALT/AST ≥10xULN and <20xULN
- ALT/AST ≥20xULN

The presence of one of the above DILI signals together with TBL ≥ 2xULN in which the elevation in transaminases precede or coincide with (that is, on the same day as) the elevation in TBL and irrespective of an increase in ALP in one active treatment group compared to placebo may be a signal of Potential Hy´s Law (PHL) (FDA, 2009).

For all the above DILI and PHL signals, the maximum value will be flagged.

3.3.4 Vital Signs

Systolic blood pressure (SBP) and diastolic blood pressure (DBP) are expected to be measured in millimeters of mercury (mmHg) as pre-morning dose and 1-hour post morning dose at each study visit except at Week 4. One single measurement will be also taken at the screening visit and at the last on-site visit (at week 24 [EOS] or EOT visit).

Changes from baseline will be calculated at each post-baseline visit and timepoint. The value recorded at morning pre-dose on Day 1 will be used as the baseline and if that value is missing Screening value will be used as the baseline. If both screening and Day 1 values are missing, then the baseline is considered as missing.

PCS abnormalities in blood pressure will be flagged if they meet either the high or low notable change criteria in Table 3-4.

Table 3-4. Criteria for notable changes in blood pressure

Parameter	Flag	Notable abnormality criteria
Systolic blood pressure (mmHg)	High	- Absolute value ≥ 180 and changes from baseline ≥ 20 OR - Absolute value ≥ 200 and baseline value < 200
	Low	- Absolute value ≤ 90 and changes from baseline ≤ -20 OR - Absolute value ≤ 75 and baseline value > 75
Diastolic blood pressure (mmHg)	High	- Absolute value ≥ 105 and changes from baseline ≥ 15 OR - Absolute value ≥ 115 and baseline < 115
	Low	- Absolute value ≤ 60 and changes from baseline ≤ -15 OR - Absolute value ≤ 40 and baseline value> 40

3.3.5 Electrocardiogram

A 12-lead Electrocardiogram (ECG) are expected to be collected in the morning as pre-dose and 1-hour post-dose at each study visit except at Week 4. One single measurement will be also taken at the screening visit and at the last on-site visit (at week 24 [EOS] or EOT visit).

Changes from baseline will be calculated at each post-baseline visit and timepoint, where relevant. Values recorded at morning pre-dose on Day 1 will be used as the baseline and if that value is missing Screening value will be used as the baseline. If both screening and Day 1 values are missing, then the baseline is considered as missing.

ECG values within each of heart rate, PR, QRS, QTcB and QTcF parameters will be flagged as PCS if they meet one of the criteria of Table 3-5, with criterion 1 being less severe than criterion 2.

Table 3-5. ECG notable abnormality criteria

Parameter	Criterion 1	Criterion 2
QTcB and QTcF interval	Absolute value > 480 msec OR Change from baseline > 30 msec	Absolute value > 500 msec OR Change from baseline > 60 msec
QRS interval	Absolute value ≥ 100 msec AND Percent change from baseline ≥ 25%	Absolute value ≥ 150 msec AND Baseline value < 150 msec
PR interval	Absolute values ≥ 200 msec AND Percent change from baseline ≥ 25%	Absolute value ≥ 250 msec AND Baseline value < 250 msec
Heart Rate:		
Tachycardia event	Absolute values ≥ 110 bpm AND Percent change from baseline ≥ 15%	Absolute values ≥ 120 bpm AND Baseline value < 120 bpm
Bradycardia event	Absolute values ≤ 50 bpm AND Percent change from baseline ≤ -15%	Absolute values ≤ 40 bpm AND Baseline value > 40 bpm

3.4 Additional Information on COVID-19

3.4.1 Disruption due to the COVID-19 Pandemic

A listing of subjects affected by the COVID-19 pandemic and a summary table of COVID-19 study disruptions will be produced.

A subject is considered to be affected by the COVID-19 pandemic if they experience a disruption to any of the following due to the pandemic:

- Scheduled visits
- Study drug disruption
- Discontinued treatment due to COVID-19
- Withdrew from study due to COVID-19

For all subjects affected by the pandemic, further details on the disruption will be collected as follows:

- Scheduled visits: For all scheduled visits disrupted by the pandemic, visit number, date of visit, reason for visit impacted by the pandemic (i.e. Subject Decision due to Pandemic Concerns or Other), visit status (i.e. visit Partially Completed/Fully Completed/Delayed/Not Done) and contact mode will be collected in a new module added to the EDC for collecting information on all visits affected by the pandemic.

- Study drug disruption: For each study drug-related disruption due to the pandemic, the start and stop date of the disruption will be collected in a new module added to the EDC for collecting information on the impact of the pandemic on administration of the study drug.

- Discontinuation of treatment/Withdrawal from study due to COVID-19: A new page will be added to the EDC with two tickboxes for collecting information on the following: (i) Discontinuation of the study drug due to the pandemic; (ii) Study discontinuation due to the pandemic.

4 ANALYSIS METHODS

All primary, secondary and additional efficacy endpoints will be analysed using ITT (except for COPD exacerbations). In addition, per protocol (PP) analyses will be performed for the primary and secondary endpoints. Safety data and COPD exacerbations will be analysed in the SAF analysis.

All personnel involved with the analysis of the study will remain blinded until DBL. Analyses will be performed by AstraZeneca.

4.1 General Principles

4.1.1 Study Estimands

The estimand will be based on the while on treatment approach where treatment estimates are analysed while subjects are taking the study medication, i.e., on-treatment during the IP intake period. The following five attributes describe the estimand that will be used to define the treatment effect of interest for all efficacy and sefety analyses:

- *Treatment Condition* = Randomized IP.

- *Population* = Patients with moderate to severe COPD, as per protocol-specified inclusion/exclusion criteria.

- *Patient-level outcome* = Change from baseline in primary and secondary endpoints at Week 24.

- *Intercurrent event (IE) handling* = While on treatment approach will be used to account for both intercurrent events by truncating at the time of the intercurrent event onset. Therefore, measurements of the endpoint until the time of the intercurrent events will be considered.

- *Summary measure* = Adjusted LSMeans obtained from MMRM model.

For COPD exacerbations, post treatment medications, and SAEs, in addition to the analysis based on while on treatment estimand, treatment policy estimand (on-study data) will be assessed. Treatment policy strategy considers events occurring during the IP intake and after the IP discontinuation. The while on treatment estimand will be the primary analysis for COPD exacerbations.

Generally, missing data are assumed to be Missing-At-Random (MAR).

The robustness of the results to potential departures from the underlying assumptions will be assessed through sensitivity analysis (see Section 4.11).

4.1.2 Last IP Dose Date

Last IP dose date

The date of the last IP dose is:

- the date recorded as the last date of IP at EOT for prematurely discontinued subjects
- the date recorded as the last date of IP at EOS for completed subjects

If any of the above are missing, the latest date recorded on bedtime e-diary where the subject confirms to have taken the IP will be used as the date of last IP dose.

4.1.3 Descriptive Summary Statistics

All data will be summarised by treatment group, study visit (including over 24 weeks on treatment) and timepoint, where applicable. The visit called 'over 24 weeks' will be calculated at subject level as the mean values of all treatment visits. The number of subjects in each treatment group of the analysis set used will be given in the column/row header as "(N=xx)". For the study population tables, the overall total summary column will be also reported.

The following standard descriptive statistics will be used:

- Categorical data will be summarized with frequency counts and percentages over the corresponding treatment group total N [n (%)]
  - Percentages will be rounded to one decimal place, unless the value is exactly equal to 100% (i.e. where the numerator is equal to the denominator), in which case there will be no decimal places
  - The total of all categories will be always reported and the category "Missing" will be added in case of observations not falling in any of the pre-defined categories.
  - Percentages for "Missing" will not be presented.

- Quantitative data will be summarized by the following statistics: number of non-missing values (n), arithmetic mean, standard deviation (SD), minimum (Min), first quartile (Q1), median, third quartile (Q3), and maximum (Max)
  - Except for tables of PFTs and lab data,minimum and maximum will be displayed with the same accuracy as the individual values

- Except for tables of PFTs and lab data, all other statistics will be rounded to one additional decimal place compared to the Min and Max, unless otherwise specified
- For PFT tables, all summary statistics will be rounded to three decimal places
- For tables of lab data, all summary statistics will be rounded to two decimal places

Rounding should be the last operation in the treatment of data. There should be no rounding of intermediate results during the calculation of any derived value.

4.1.4 Visits Reported and Statistical Comparisons for Efficacy

Unless otherwise specified, all statistical comparisons will be done by treatment group.

Results of all visits will be reported in all efficacy tables by treatment group (no total column will be shown in tables). Also, results over 24 weeks on treatment will be reported for PFT endpoints as shown in Section 3.2.3.1., daily COPD symptoms (E-RS), and use of rescue medication. As an exception, COPD exacerbations are reported along the entire treatment period.

All treatment effects will be estimated and presented in the tables. Primary and secondary treatment comparisons can be found in Table 4-1, and all remaining comparisons will be exploratory. Figures will only show the primary and secondary treatment comparisons.

All tests on treatment effects and all pairwise statistical comparisons will be two-sided superiority hypothesis tests presented along with their 95% Confidence Interval (CI) and p-value. The significance level will be set at 0.05. The types of statistical test used to generate the CIs and p-values should be included in a footnote.

All estimates and CIs will be presented to one more decimal place compared to the original individual data, if not otherwise specified. Actual p-values will be reported using three decimal places, or as '<0.001' if they are less than 0.001.

4.1.5 Other Statistical Considerations

All statistical analyses described in this SAP will be performed by the sponsor using the software SAS® version 9.4 or higher, whichever available at the time of analysis.

Tables, figures and Listings (TFLs) will be compiled in an Appendix to the CSR: tables, and figures will be appended in CSR Section 14, subject-level data listings will be in CSR Section 16.2. Every statistical inferential analysis on the primary and secondary endpoints (excluding sensitivity analyses) will be supported by the whole SAS output, which will be appended to Section 16.5 of the CSR.

Relevant data collected on the eCRF will be provided in subject-data listings sorted by unique subject identification number and visit and timepoint where available. Any exclusion of data from the analyses will be flagged in the subject-data listings.

4.2 Summary of Study Populations

Study population summaries will include subject dispositions, demographic and baseline characteristics, and treatment compliance.

4.2.1 Subject Disposition

Subjects will be counted for the Randomised Analysis Set, ITT and PP by randomised treatment and for SAF by treatment subjects actually received.

Number and percentage of subjects in each of the disposition categories of Section 3.1.1 will be tabulated by treatment group and overall for all subjects. Percentages will be calculated over the number of subjects randomised (with the exception of enrolment subjects for which only number will be shown). Enrolment, treatment completion status and study completion status will be summarised split into the following categories:

- Subjects enrolled
- Subjects randomised
- Subjects who received treatment
- Subjects who completed treatment (based on EOT form for discontinued subjects and EOS form at Week 24 for completed subjects)
- Subjects who completed study (based on EOS form) Subjects who made the follow-up contact 14 days after last dose

All disposition events and dates will be listed in two subject-data listings, one for subjects withdrawing from study and one for subjects completing the study.

A frequency table (counts and percentages) will be produced for the randomised analysis set to show the subject recruitment by country and centre. Number of subjects in each treatment group will be used as the denominator in the calculation of percentages for country. Total number of subjects in each country will be used as the denominator in the calculation of percentages for centre. Number and percentage of subjects by IWRS stratification factors at randomization (country and smoking status) will be also tabulated by treatment group and overall for the total randomised analysis set in a separate table. The whole randomisation scheme and randomisation numbers will be listed for all randomised subjects along with their actual received treatment in case, if different to what they were assigned at randomization.

For Important Protocol Deviations (IPD), the following will be presented in a single summary table: number and percentage of subjects with at least one IPD, including COVID-19 related IPDs; number and percentage of subjects with at least one COVID-19 related IPD only and number and percentage of subjects with at least one IPD excluding COVID-19 related IPDs. Each of these will be presented by PD coded term (Eligibility criteria not fulfilled, prohibited concomitant medication taken during the study, received incorrect investigational treatment/dose, Protocol-required procedure not adhered to and Other reasons) for each treatment group and overall for the total randomised analysis set. All IPDs will be listed for each subject and the PDs leading to the exclusions from the PP analysis set will be highlighted.

A separate listing of all COVID-19 related non-important PDs and other reported issues will also be produced. Other non-important PDs will not be included in the CSR.

Analysis sets defined in Section 2.1 and reasons for exclusion will be tabulated by treatment group and overall for the total randomized analysis set. Exclusions from each analysis set and related reasons will be also listed for each randomised subject.

4.2.2 Demography and Baseline Characteristics

Summaries of all collected and derived demographic, subject and disease characteristics will be produced by treatment group and for the overall SAF and ITT using the standard descriptive statistics for categorical and quantitative data. The number of subjects with data will be used as the denominator for calculating percentages.

- Demographic characteristics [age, age group, sex, race, ethnic population, and country]
- Subject characteristics [height, weight, BMI, and BMI group]
- COPD characteristics at screening [COPD severity derived with the GOLD categories for airflow limitation and based on symptoms and risk of exacerbation, COPD duration, time since last COPD exacerbation, time since last hospitalization due to a COPD exacerbation, number of COPD exacerbations in the previous 12 months (as continuous variable and as categorised variable up to maximum), history of chronic bronchitis and emphysema]
- Nicotine use at screening [smoking status, smoking consumption in pack-years, and smoking duration]
- Lung function data at screening [pre- and post-bronchodilator absolute (L) and percent predicted FEV_1, FVC and post-bronchodilator FEV_1/FVC Ratio (%), absolute (mL) and percent (%) bronchial reversibility and bronchial reversibility status] and at baseline [pre- and post-bronchodilator absolute (L) and percent predicted FEV_1, FVC]. For baseline, use the average of the 2 pre-dose timepoints on Day 1.
- BDI score (total score and scores of components), SGRQ score (total score and scores of dimensions) and CAT score at baseline

Demographic and subject characteristics will be listed together in a single subject-data listing.

Medical history and surgical history at screening will be summarised in two separate frequency tables in the SAF analysis set by treatment group and for the overall analysis set by SOC and PT. Results will be sorted alphabetically by SOC and PT. Medical and surgical history will be also presented together in a subject-data listing. The information about whether the condition is past or ongoing will be only listed. The version number of the MedDRA dictionary used will be shown as a footnote in every output.

4.2.3 Prior and Concomitant Medication

Prior medication (medication taken before ICF and medication taken after ICF and before first IP dose), prior COPD-related medication and all concomitant medication will be summarised

by treatment group in frequency tables produced in the Safety Analysis Set. The categorisation of medications given in Section 3.1.5 will be used for the summaries.

The number and percentage of subjects with prior COPD-related treatment will be tabulated by the AZBC SDG therapeutic categories of Section 3.1.5 (with the revised free- or fixed-dose combination). Prior and concomitant medication will be summarized by period, Anatomical Therapeutic Chemical 3 (ATC3) category and generic term. Results will be sorted alphabetically by ATC name and generic term. In all cases, if a patient uses more than 1 medication in a generic term, that patient will be counted only once in that generic term. The version number of the WHO DRUG dictionary used will be shown as a footnote.

Number and percentage of subjects taking prior, concomitant and post-treatment medications will be summarised overall, and by ATC3 text (or ATC2 if the ATC3 is missing), generic term, and treatment group for each period.

In all cases, if a patient uses more than 1 medication in a generic term, that patient will be counted only once in that generic term.

Completely or partially missing start and end dates will be imputed as per the rules of Section 4.3.4. See also the definition of last IP dose date in Section 4.1.2.

All prior and concomitant medications will be listed together in a subject-data listing. All tables and the subject-data listing will include medications taken for the treatment of COVID-19.

4.2.4 Study Compliance and Drug Accountability

The standard descriptive statistics will be presented for the compliance rates as continuous variable and for the compliance status for each inhaler and overall by treatment group and for ITT. Number and percentage of subject compliant with both devices will be also reported. The table will be produced with 3 subheadings: (i) Treatment compliance in all subjects; (ii) Treatment compliance in subjects not affected by COVID-19; (iii) Treatment compliance in subjects affected by COVID-19. This includes subjects with suspected/confirmed COVID-19 infection, as recorded on the adverse events page of the eCRF. Such adverse events will be identified from a narrow and broad search of the SMQ ‘COVID-19’.

Drug accountability will be only listed as recorded on the eCRF.

4.3 Efficacy Analysis

For the analysis of efficacy endpoints, in order to avoid any possible instability in the statistical modelling, if one level of a given factor represents only <5% of randomized subjects, the corresponding factor will be removed from all the inferential statistical models. However, this rule does not apply to randomization stratification factors.

4.3.1 Primary Efficacy Analysis

All primary efficacy endpoints will be analysed, using the ITT and the PP, by means of a mixed model for repeated measures (MMRM) adjusted for pre and post bronchodilator (salbutamol)

FEV_1 at screening visit, age, and baseline FEV_1 as covariates, and treatment group, country, smoking-status, visit, and treatment group-by-visit interaction as fixed effect factors.

The within-patient correlation will be modelled using the unstructured covariance matrix. The analysis will be performed based on all post baseline measurements using only the observed cases without imputation of missing values. If the model does not converge, then the compound symmetry covariance structure will be used. Restricted maximum likelihood method will be used. If the model still fails to converge, countries with too few subjects may be combined to address residual convergence issues. In this case, the country with smallest number of subjects in the analysis population will be merged with the next smaller country. This process will continue until the convergence is reached. If all the countries are to be merged to reach convergence, country term will be removed from the model.

Parameters will be estimated by means of the restricted maximum likelihood (REML) approach with the Newton-Raphson algorithm and using the Kenward-Roger approximation to estimate denominator degrees of freedom and adjust standard errors (Kenward and Roger, 1997). Missing data will not be imputed but modelled using the direct likelihood approach under the missing-at-random (MAR) assumption.

From the MMRM model, the estimated mean (least squares mean: LSMean) for each treatment and the estimated mean difference for each pairwise treatment comparison at all study visit be extracted from treatment-by-visit interaction in the model along with their standard errors (SEs) and two-sided 95% CIs, and the p-values corresponding to the between-treatment group differences. The results at Week 24 will be based on the treatment-by-visit interaction at Week 24 will be the primary efficacy results. Results over 24 weeks on treatment will also be reported, based on the treatment effect factor. Statistical comparisons will be two-sided hypothesis tests, and the overall significance level will set at 0.05.

Primary efficacy data will be summarized by visit (and overall over the 24 weeks on treatment) and by treatment group. No total column will be shown in tables.

Adjustment for multiplicity will be carried out for all primary endpoints as per Section 4.4.

4.3.2 Secondary Efficacy Analyses

Secondary efficacy endpoints will be analysed using the ITT and the PP.

Secondary efficacy endpoints will be analysed and summarized using MMRM models like for the primary endpoints, i.e., using the same covariance matrix, convergence rules, parameter estimation, and reported outputs.

Change from baseline in peak FEV_1 will be adjusted for pre and post bronchodilator (salbutamol) FEV_1 at screening visit, age, and baseline FEV_1 as covariates, and treatment group, country, smoking-status, visit, and treatment group-by-visit interaction as fixed effect factors.

MMRM analysis for TDI focal score and change from baseline in SGRQ total score at Week 24 will be adjusted by the corresponding baseline value (BDI or SGRQ at baseline) and age as

covariates, and treatment group, country, smoking-status, visit, and treatment group-by-visit interaction as fixed effect factors.

Adjustment for multiplicity will be carried out for all secondary endpoints as per Section 4.4.

4.3.3 Analysis of Additional Efficacy Endpoints

In addition to the primary and secondary efficacy analysis, the additional endpoints listed in Section 3.1.9 will also be analysed.

All the data for additional efficacy endpoints will be summarised using the ITT population (except for COPD exacerbations).

4.3.3.1 Analysis of Additional PFT Endpoints

This section provides the statistical methodology used to analyse all the additional efficacy endpoints listed in Section 3.1.9.1.

Additional PFT endpoints will be analysed and summarized using MMRM models like for the primary endpoints, i.e., using the same covariance matrix, convergence rules, parameter estimation.

The MMRM analyses used for the primary analysis will be performed for the above exploratory parameters by adjusting for pre and post bronchodilator (salbutamol) FEV_1 at screening visit, age, and baseline FEV_1 as covariates, and treatment group, country, smoking-status, visit, and treatment group-by-visit interaction as fixed effect factors.

For spirometric analysis by visit and timepoint, the statistical models will be specified as for the primary analysis, considering the specific time-point as the response. Note that for the 'visit' factor, only those visits whose timepoint was measured will be included.

4.3.3.2 Analysis of Signs and Symptoms and Health-related Quality of Life

This section provides the statistical methodology used to analyse all the additional efficacy endpoints listed in Section 3.1.9.2.

Change from baseline in TDI, SGRQ and CAT are analysed using the same MMRM model used for the secondary endpoints but using the appropriate baseline. All treatment effects and treatment comparisons will be estimated and 95% CIs and p-values will be presented.

The responder analysis, *i.e.* the analysis of the proportion of subjects achieving a MCID, at each study visit, will be done using the random-effect logistic regression model with random intercept to account for the variability between subjects. The models will be adjusted for age and the baseline score of the endpoint as continuous covariate, and smoking status, country, treatment, visit and treatment-by-visit interaction as fixed effects. The within-subject correlation will be modelled using the unstructured covariance matrix. If the model fails to converge, the compound symmetry covariance structure will be used instead. If the model still fails to converge, due to the country factor then the same approach as for the primary variable will be applied.

For each treatment arm, the odds will be presented along with the number of non-missing observations used in the estimation (n), the observed number and percentage of responders, and their two-sided 95% confidence intervals (CIs). ORs will be shown with their CIs and the two-sided p-value.

At each of these visits the odds and the odds ratio (OR) along with 95% CI and the p-value will be estimated using the treatment-by-visit interaction.

4.3.3.3 Analysis of COPD Exacerbations

This section provides the statistical methodology used to analyse all the additional efficacy endpoints listed in Section 3.1.9.3.

COPD exacerbations are derived using HCRU and EXACT as detailed in Section 3.2.3.4 and summary results will be produced for each category by treatment group as given below. When using the HCRU analysis, any, mild, moderate, severe, moderate-to-severe COPD exacerbation severities will be summarized descriptively but only any and moderate-to-severe will be reported for modelling purposes.

For all models used in the analysis of COPD exacerbations, any countries where the planned number of randomised subjects is less than 5% of the overall number of randomised subjects (equating to fewer than 13 subjects per treatment group) should be combined. If only one country meets this criteria, then it should be combined with the next smallest country.

While on treatment COPD Exacerbations:

The following analyses will be performed on the SAF for the COPD EXACT and HCRU exacerbation endpoints:

- Rate of COPD exacerbations per patient/year will be estimated using the negative binomial (NB) regression model.
- Number and percentage of subjects with at least one COPD exacerbation will be estimated using the logistic regression model.
- Time (days) to first COPD exacerbation through Week 24 will be analyzed using the Cox regression model.

For each treatment arm, the annual crude rate of exacerbation of each type (EXACT and HCRU) will be estimated as the number of exacerbations of that type divided by the total risk time.The rate of COPD exacerbations per years of exposure will be analysed and by means of NB regression models including age as a covariate, and baseline ICS use (use/no use of ICS as monotherapy within 15 days prior to the first dose date of the IP and continued after randomization), baseline COPD severity (mild/moderate vs. severe/very severe), smoking status (current/former smokers), country, prior history of exacerbation over 12 months before randomization (yes/no), treatment group as factors, and the log risk time in years as an offset. Treatment effects and pairwise treatment comparisons will be estimated by the event rates per patient-year and the Rate Ratio (RR) on the treatment coefficient, respectively.

For each treatment arm, estimated rates will be presented along with the number of non-missing observations used in the estimation (n), the number of events, the total risk time in years and their two-sided 95% Wald confidence intervals. RRs will be shown with their CIs and the two-sided p-value.

In the case of non-convergence, then a modified Poisson regression model with robust variance estimate using the sandwich method will be used instead. A scale parameter will be included in the Poisson model in case of evidence of overdispersion. The same SAS code of the NB model can be used, by changing the distribution and by adding the DSCALE option [SAS code: dist = poisson dscale] and by including a repeated statement for each subject [SAS code: repeated subject=USUBJID].

If the model still fails to converge, countries with too few subjects may be combined to address residual convergence issues. In this case, the country with smallest number of subjects in analysis population will be merged with the next smaller country. This process will continue until the convergence is reached. If all the countries are to be merged to reach convergence, then instead, country term will be removed from the model.

The number of subjects with at least one COPD exacerbation will also be analysed using a logistic regression model including age as a covariate, and baseline ICS use (use/no use of ICS as monotherapy within 15 days prior to the first dose date of the IP and continued after randomization), baseline COPD severity (mild/moderate vs. severe/very severe), smoking status (current/former smokers), country, prior history of exacerbation over 12 months before randomization (yes/no), and treatment group as factors. Frequency distribution (number and percentage) will also be reported.

Time (days) to first COPD exacerbation will be analysed through Cox Proportional Hazard model including age as a covariate, and baseline ICS use (use of ICS [yes/no] as monotherapy within 15 days prior to the first dose date of the IP and continued after randomization), baseline COPD severity (mild/moderate vs. severe/very severe), smoking status (current/former smokers), country, prior history of exacerbation over 12 months before randomization (yes/no), and treatment group as factors. The Breslow approach will be used for handling ties. Kaplan-Meier survival curves for any and moderate-to-severe exacerbations will be displayed for each treatment.

If a patient experiences a COPD exacerbation(s), the time to first event for while on treatment analysis will be derived as:

Time to event = date of onset of first exacerbation – date of first IP dose +1

Or if there are no exacerbations

Time to event = date of last IP dose – date of first IP dose +1

For each treatment, the following will be presented: number of non-missing observations used in the estimation (n), the observed number and percentage of subjects with at least one exacerbation and the median time-to-event in days. Median time-to-event will be estimated from the Cox model as the time at which the predicted survival=0.5. It will be set to NE (Non-estimable) if >50% of subjects are censored, and the median survival time cannot be determined.

Pairwise treatment comparisons will be estimated by Hazard Ratio (HR) and corresponding 95% CI and p-value.

For the logistic regression and Cox Proportional Hazard models, if the models fail to converge, countries with too few subjects may be combined to address residual convergence issues. In this case, the country with smallest number of subjects in analysis population will be merged with the next smaller country. This process will continue until the convergence is reached. If all the countries are to be merged to reach convergence, then instead, country term will be removed from the model(s).

Treatment policy (on-study) COPD exacerbations:

COPD exacerbations (HCRU Exacerbations and EXACT exacerbations) recorded during the study (i.e. during the treatment period and after discontinuation of study drug) will be analysed using the same methodology used for the while on treatment exacerbations.

For each type of exacerbation, all the analyses (the derivations of rate of exacerbations, the number (%) subjects with exacerbations, analysis of time to first exacerbation and estimation of odds and ORs) will be performed similarly and similar results will be presented.

Note that last on-site visit date is used instead of the last IP dose date as reference date to impute recovery dates according to the treatment policy approach. Duration of on-going exacerbations at last visit will be curtailed to the last visit date. For subjects with zero exacerbations, the time to the first exacerbation will be censored at the last on-site visit date.

4.3.3.4 Analysis of daily COPD Symptoms (EXACT-Respiratory Symptoms [E-RS])

This section provides the statistical methodology used to analyse all the additional efficacy endpoints listed in Section 3.1.9.4.

Change from baseline in E-RS score between two consecutive visits (Weeks 1, 4, 12, 18 and 24 and overall over 24 weeks) will be analysed using the same MMRM model used for the primary endpoints using the appropriate baseline and removing pre and post bronchodilator covariates. All treatment effect and treatment comparisons will be estimated and 95% CIs and p-values will be presented.

The responder analyses for the E-RS will be performed like the analyses performed for TDI, SGRQ and CAT (Section 4.3.3.2) and the results will be presented similarly.

4.3.3.5 Analysis of use of Rescue Medication

Subjects may be taking either salbutamol as rescue medications during the study period. Use of rescue medication is calculated as in Section 3.2.3.4.

Change from baseline in rescue medication (salbutamol) between two consecutive visits (Weeks 1, 4, 12, 18 and 24 and overall over 24 weeks) will be analysed using the same MMRM model used for the primary endpoints using the appropriate baseline and removing pre and post bronchodilator covariates. All treatment effect and treatment comparisons will be estimated and 95% CIs and p-values will be presented.

4.4 Multiplicity Adjustment Strategy

Hierarchical Strategy for Adjusting for Multiplicity:

Due to the presence of multiple study objectives and multiple comparisons (multiplicity), to control the family-wise type I error, the pre-specified sequence of testing of Table 4-1 will be carried out for all primary and secondary efficacy objectives (multiplicity hierarchical approach).

Any endpoint in the hierarchy following a non-statistically significant result at the 5% significance level will be reported for exploratory purposes and p-values will be only nominal and should be interpreted descriptively. Note that both primary variables for AB/FF 400/12 should overcome the statistical hierarchy (i.e., should be statistically significant) to meet the primary bronchodilator objective of the FDC.

Table 4-1. Multiplicity testing order of the primary and key secondary efficacy endpoints

Endpoints (at Week 24)		Treatment Comparison	Testing order in Hierarchy
Primary	Change from baseline in 1-hour post-dose FEV_1	AB/FF 400/12 vs. AB 400	1
	Change from baseline in morning pre-dose (trough) FEV_1	AB/FF 400/12 vs. FF 12	2
		AB 400 vs. placebo	3
Secondary	Change from baseline in peak FEV_1	AB 400 vs. placebo	4
	Improvements in TDI focal score	AB/FF 400/12 vs. placebo	5
		AB 400 vs. placebo	6
	Change from baseline in SGRQ total score	AB/FF 400/12 vs. placebo	7
		AB 400 vs. placebo	8

4.5 Safety Analysis

Safety data will be analysed in the SAF analysis.

Data will be summarized descriptively by randomised treatment group no total column will be shown in tables. No formal statistical hypothesis testing will be done for any safety objectives.

Safety analysis will include extent of exposure, AEs, laboratory data, vital signs and ECG. These safety data will be analysed using the SAF and subjects will be classified to treatments groups based on the actual treatment they have received.

Analysis of AEs will be performed using the while on treatment estimand. Treatment policy analyses will be also undertaken for serious adverse events, which will include events collected after treatment discontinuation.

4.5.1 Exposure to Treatment

For the extent of exposure, descriptive statistics of the duration of exposure and the duration of study (time in study) will be presented by treatment group. The derivations are given in Section 3.3.1.

Summary of cumulative duration of exposure and cumulative study duration will be presented by treatment group using the duration categories ≥ 1 day, ≥ 1 week, ≥ 4 weeks, ≥ 12 weeks, ≥ 18 weeks, and ≥ 24 weeks.

The information collected on the eCRF regarding the drug overdose will be only listed.

4.5.2 Adverse Events

The categorisation of AE given in Section 3.3.2 will be used for AE summary:

- Pre-treatment AEs: started before first IP dose date
- Treatment-emergent AEs (TEAEs): AEs started on or after the date first IP dose until 15 days from the last IP dose date.
- Post-treatment AEs: AE started after 15 days from last dose.

Pre-treatment AEs:

The pre-treatment AEs will be flagged in the AE listings.

Treatment-emergent AEs (TEAEs):

The following frequency distribution (subject counts and percentages, and number of events) tables of TEAEs will be produced by treatment group, SOC and PT, as appropriate. Subjects with multiple events in the same category are counted only once in that category and subjects with events belonging to multiple categories are counted in each of those categories. Multiple events in the same category are counted multiple times in that category. Multiple events belonging to more than 1 category are counted multiple times in each of those categories.

- TEAEs in any category:
  Frequency distribution of the following TEAE categories: “Any AE”, “Any TEAE”, “Any TEAE with outcome of death”, “Any SAE)”, “Any treatment-emergent SAE (TESAE)”, “Any TEAE leading to treatment discontinuation”, “Any treatment-emergent AESI”, “Any significant cardiac and cerebrovascular TEAE”, “Any anticholinergic TEAE”, “Any β2 adrenergic TEAE”, “Any pneumonia TEAE”, “Any MACE”.

- Most common TEAEs (frequency of >1%):
  Frequency distribution by PT of all the TEAEs with a total frequency of >1% (in any treatment group). PTs will be sorted by the descending frequency of the total column (even if not reported). The number of subjects with at least one TEAE will be reported in the top row of the table.

- TEAEs by SOC and PT:
  Frequency distribution (patient counts and percentages, and event counts and incidence rates) of the below groups of TEAEs (one table for each grouping) sorted by international order for SOC and alphabetically for PT. The number of subjects with at least one AE in the below categories and the number of related events will be reported as top row of the table.
    - Any TEAE
    - Any TEAE with outcome of death
    - Any TESAE
    - Any TEAE leading to discontinuation of IP

  Event rates per 1,000 patient-years of exposure is calculated as the number of subjects with at least one TEAE divided by the total number of years at risk for that TEAE multiplied by 1000. The number of years at risk is derived as the sum of the individual

durations of exposure as defined in Section 3.3.1, divided by 365.25. To each duration 15 days of follow-up will be added.

- TEAEs by SOC, PT and maximum reported intensity:

  Frequency distribution of the below groups of TEAEs (one table for each grouping) sorted by international order for SOC and alphabetical order for PT and "mild", "moderate", "severe" for intensity. The number of subjects with at least one TEAE in the category will be reported in the top row of the table.

  - Any TEAE
  - Any TESAE

- TEAEs by SOC, PT and investigator's causality assessment:

  Frequency distribution of the below groups of TEAEs (one table for each grouping) sorted by international order for SOC and alphabetical order for PT and "Not related and "Possibly Related" for causality. Each subject will be represented by the maximum reported causality for each PT. The number of subjects with at least one AE in each of the below category will be reported as top row of the table.

  - Any TEAE
  - Any TESAE

- TEAEs by SOC, PT and outcome:

  Frequency distribution of TEAE by SOC, PT and outcome, sorted by international order for SOC and alphabetical order for PT and "recovered/resolved", "recovering/resolving", "recovered/resolved with sequelae", "not recovered/not resolved", "fatal" for outcome. Each subject will be represented by the worst outcome for each PT. The number of subjects with at least one TEAE will be reported as top row of the table.

- Key subject information in listings:

  The following key information will be reported for each individual subject: treatment group, subject identifier, sex, age at screening visit, SOC, PT, term as reported by the investigator, treatment period (pre-, on-, or post-treatment) days from first dose to onset of AE, days from last dose to onset of the AE, whether subject received treatment for the AE, whether there is a reasonable possibility as assessed by the investigator that the AE is causally related to the IP.

  The output will be generated for the following AE groups:

  - Any AE with outcome of death (includes days from first dose to death)
  - Any TESAE (includes days from first dose to becoming serious, outcome, and action taken with IP. SAEs which are not TEAEs will be flagged)

- Any TEAE leading to discontinuation of IP (includes seriousness, outcome)

- Non-serious TEAEs occurring in greater than 5% of subjects:

  Frequency distribution by SOC and PT of all the TEAEs with a total frequency of >5% (in any treatment group) sorted by international order for SOC and alphabetically for PT. The number of subjects with at least one TEAE, the number of subjects with at least one non-serious TEAE and the number of subjects with at least one non-serious TEAE at the threshold cut-off greater than 5% will be reported in the top rows of the table.

- AESIs and MACE by SMQ, SOC and PT:

  Frequency distribution (patient counts, percentages and event rates) of the below groups of AEs (one table for each grouping) sorted by alphabetical order for SMQ, international order for SOC and alphabetically for PT. The number of subjects with at least one AE in the below categories will be reported as top row of the table.

  - Any treatment-emergent cardiac and cerebrovascular AESI
  - Any treatment-emergent anticholinergic AESI
  - Any treatment-emergent β_2 adrenergic AESI
  - Any treatment-emergent pneumonia AESI
  - Any treatment-emergent MACE

- Key AESI and MACE information in listings:

  The following information will be reported for each individual subject: treatment group, subject identifier, sex, age at screening visit, SMQ, SOC, PT, Adjudication Conclusion from Cardiovascular Adjudication Committee (CVAC), treatment period (pre-, on-, or post-treatment), treatment period (pre-, on-, or post-treatment), seriousness, intensity, whether there is a reasonable possibility as assessed by the investigator that the AE is causally related to the IP, outcome and action taken with IP . The output will be repeated for the following AE groups:

  - Any treatment-emergent cardiac and cerebrovascular AESI
  - Any treatment-emergent MACE

Treatment policy (on-study) SAEs:

The following summaries will be produced using a format similar to the corresponding TEAE summary:

- Any post-treatment SAE by SOC and PT
- Any post-treatment SAE by SOC, PT and maximum reported intensity
- Any post-treatment SAE by SOC, PT and investigator's causality assessment

All AEs and SAEs (including TEAEs and post-treatment AEs) will be listed and events flagged, as required. For all displays, the MedDRA version used will be shown as footnote.

4.5.3 Laboratory Data, Vital Signs and ECG

Absolute values and changes from baseline of all laboratory (haematology and biochemistry), vital signs and ECG parameters will be tabulated for each study visit and timepoint (if applicable) by treatment group using the standards descriptive statistics. For baseline, only absolute values will be summarized.

The number and percentage of ECG abnormal findings not present at baseline (rhythm, ectopy, conduction, morphology, myocardial infarction, ST segment, T wave and U wave observations) will be reported by finding, parameter, timepoint for each treatment group. Denominator for percentages will be the number of subjects with available baseline and at least one post-baseline assessment at a specific visit.

Contingency tables of the treatment-emergent potentially clinically significant abnormalities in haematology, biochemistry, vital signs and ECG will be produced: the number and incidence of subjects with at least one PCS shift from baseline will be summarised at each post-baseline study visit/timepoint and at any visit (*i.e.* at least once from start of treatment). Incidence rates will be calculated as the number of subjects in a specific PCS shift category over the number of subjects with a baseline value and an assessment made at the specific visit. For the laboratory parameters the shift categories will be: New / Decrease, New / Increase, Total New, Worsening / Decrease, Worsening / Increase, Total Worsening, Notable < Lower Limit, Notable > Upper Limit, Total Notable. The shift categories will be high and low for vital signs, and criterion 1 or criterion 2 for ECG.

Moreover, for each subject with a treatment-emergent PCS abnormality in haematology or biochemistry, the following key information will be tabulated: treatment group, subject identifier, sex, age at screening visit, study visit, abnormal laboratory variable name and SI unit, value, whether it is low (L) or high (H) according to the ENR, whether it is new or worsened, whether it is notable, and the related ENR, notable abnormalities range. For laboratory variables, values classified as clinically significant, as assessed by the investigator, will be flagged.

Listings of all TEAEs for subjects with PCS values for laboratory data; vital signs and ECG will also be provided. For laboratory data, the number and percentage of subjects with a result classified as abnormally clinically relevant by the investigator will be tabulated by study visit and treatment group for each parameter. In addition, a listing of TEAEs for subjects with abnormal clinically relevant results will be provided. For labs, the high and low alerts flagged by the investigator will not be listed, although they are collected on the eCRF.

For ECG, the distribution of the Global evaluation from the cardiologist (interpretation variable) will be summarised by visit and timepoint (where applicable) with counts and percentages by treatment group. The number and percentage of patients with any ECG (performed within a visit) classified as abnormal clinically relevant by the investigator will be tabulated by visit, timepont, and treatment group. In addition, a listing of TEAEs for those patients included in the previous table will be provided.

4.5.4 Drug Induced Liver Injury (DILI) and Possible Hy's Law (PHL)

A contingency frequency table for the maximum treatment-emergent liver biochemistry value will be presented to assess the DILI and PHL criteria comparing ALT and AST categories (< 3xULN, ≥3xULN - <5xULN, ≥5xULN - <10xULN, ≥10xULN - <20xULN. ≥20xULN) versus the TBL categories (< 2xULN and ≥ 2xULN).

Furthermore, two scatter plots will be produced (one for ALT and one for AST) plotting the maximum post-baseline ALT/AST versus the maximum post-baseline TBL values, all expressed as xULN and on a log scale. Reference line will be added as dotted lines at 3xULN of ALT/AST and 2xULN of TBL, which will be explained in a footnote.

For subjects with ALT/AST ≥3xULN together with TBL ≥ 2xULN (regardless of the time-relationship between transaminases and TBL), the following key information will be tabulated: treatment group, subject identifier, sex, age at screening visit, study visit, treatment discontinuation day, ALT, AST, TBL, and ALP values, all expressed both in their SI-units and as xULN.

Pregnancy test data will be only listed and not summarized.

4.6 Statistical Considerations for Analyses

4.6.1 Graphical Representations and Plots

Graphical displays will be presented for primary and secondary endpoints in addition to the corresponding summary/analysis tables.

For example, the adjusted by-visit LS means of the primary and secondary variables will be plotted over time (in weeks) along with their 95% CIs. A reference horizontal line on zero will be also plotted to show the point of no change from baseline.

When plots are to be compared, the same scale (minimum and maximum axis values) will be used.

4.6.2 Selection of Spirometry Data (Best Test Review)

For all spirometric parameters, the Best Test Review (BTR) process done by a eResearch Technology clinical specialist will be utilized. Unacceptable values after BTR coded as BF410="YES" for FEV1 and FVC will be treated as missing.

4.6.3 Repeated and unscheduled assessments or visits

Efficacy analysis:

Repeated assessments/visits will be used for analysis. With the exception of COPD exacerbations, efficacy data obtained during unscheduled and premature discontinuation visits (at EOT or EOS visits) will not be statistically analysed, since they are aimed to patient monitoring purposes only. However, these data will be listed.

- For repeated assessments/visits, the spirometry observation from the last repeated assessment/visit will be used in statistical analyses (both pre and post IP intake).

- Questionnaires: In case of repeated questionnaires (SGRQ, TDI, CAT, E-RS, and rescue medication), the first one will be used for analysis.

Safety analysis:

Repeated assessments/visits will be used for analysis as follow:

- Before treatment intake: the last observation will be used in statistical analyses
- After treatment intake: the first observation will be used in statistical analyses
- Aberrant / non-interpretable values: the value will be excluded from the analyses
- For presentations that select a single 'at any visit' observation per subject (e.g., abnormal lab values over the course of the trial), scheduled and unscheduled visit data will be included in any table and plot.

Repeated, unscheduled, and early termination visits (EOT/EOS) assessments will be listed.

4.6.4 Imputing Missing Event Dates

Imputed dates will not be shown in subject-data listings and will not be used to calculate durations of events. The only purpose will be to categorise whether an event, such as an AE or a medication or an exacerbation, is treatment-emergent.

The following rules will be applied:

- When the start date and the end date are both incomplete, the imputation of the start date will be the first step.
- If the imputed start date is after the complete end date (or the date the AE becomes serious), then the start date will be set to the end date (or the date when the AE becomes serious).
- If the imputed end date is before the start date (imputed or non-imputed), then the end date will be set to the start date. If the end date is after the AE becomes serious (if applies), then the end date will be set to the date when the AE becomes serious.

Imputation rules for an event start date based on the first IP dose date

- If the start date is completely missing or only the year is missing, it will be imputed with the event end date/year or the first dose date/year, whichever occurs earlier. If the event start date is completely missing, the event end date is partially missing (only info of the month and year is available), and the first IP date is completely known (i.e., day/month/year):
    - If the first IP occurs on the same month and year than the event end date, then, use the first IP date to impute the event start date.
    - If the month of the event end date occurs firstly, then use the event end date considering the last day of that month (i.e. usually 30 or 31th) to impute the event start date.
- If the start year is not missing but the month is missing, then the following will be imputed:

  - if the start year is prior to the year of first dose, then December 31 will be used
  - if the start year is equal to the year of first dose, then the month and day of first dose will be assigned
  - otherwise, January 1 will be assigned to the missing fields
- If only the start day is missing, then the following will be imputed:
  - if month and year are the same as the first dose, then the day of the first dose will be assigned.
  - if the year is prior to the year of the first dose or the years are the same but the month is prior to first dose, then last day of the month will be used.
  - If the year is after the first dose date or the years are the same but the month is after to first dose, then first day of the month will be used.

Imputation rules for an event end date based on the last IP dose date

- If the end date is completely missing or only the year is missing, it will be imputed with the last dose date/year or the event start date/year, whichever occurs later. If the one which occurs later results to be the event start date but this date is partially missing, we will use this event start date with day = 1 (when only the day is missing) or January 1rst (when month and day are missing) to impute the event end date.
- If the end year is not missing but the month is missing, then the following will be imputed:

  - if the end year is prior to the year of last dose, then December 31 will be used
  - if the end year is equal to the year of last dose then the month and day of the last dose will be assigned
  - otherwise, January 1 will be assigned to the missing fields
- If only the end day is missing, then the following will be imputed:
  - if month and year are the same as the last dose, then the day of the last dose will be assigned
  - if the year is prior to of last dose or the years are the same but the month is prior to last dose, then last day of the month will be used
  - If the year is after last dose date or the years are the same but the month is after to last dose, then first day of the month will be used

If an analysis needs to be done using a treatment policy (on-study) approach (i.e. by including post-treatment data), the imputation of the end dates will be based on the last on-site visit date instead.

4.6.5 Imputation of Missing Data

In general, missing values in the efficacy endpoints will not be imputed (direct likelihood approach will be used). For the derivation of endpoints for summary tables and analysis, existing missing data will be imputed using the given methods below. Imputed values will not be shown in the subject-data listings.

Sensitivity analysis is given in Section 4.8.

Pre and Post- FEV_1 and FVC at Screening.

Screening FEV_1 pre- and post-bronchodilator will be imputed as follows:

- If pre-bronchodilator value (at screening visit) is missing, then the baseline value will be used as the pre-bronchodilator value.
- If post-bronchodilator value (at screening visit) is missing, it will be imputed after imputation is performed for pre-bronchodilator value. Missing post-bronchodilator value will be imputed by the pre-bronchodilator of the i*th* patient plus the mean absolute reversibility of all subjects (whole sample).

The same approach will be used for screening FVC pre- and post-bronchodilator.

Where it is necessary to impute the screening FEV_1 pre- and/or post-bronchodilator, the following PFT quantities at Screening will be imputed:

- FEV_1/FVC ratio pre-bronchodilator (%) derived as:
  100 x FEV_1 (pre-bronchodilator) / FVC (pre-bronchodilator)
- FEV_1/FVC ratio post-bronchodilator (%) derived as:
  100 x FEV_1 (post-bronchodilator) / FVC (post -bronchodilator)
- Screening absolute FEV_1 bronchial reversibility (mL) derived as:
  FEV_1 (post-bronchodilator) – FEV_1 (pre-bronchodilator)
- Screening percentage of FEV_1 bronchial reversibility (%) derived as:
  100 x [absolute FEV_1 bronchial reversibility / FEV_1 (pre-bronchodilator)]

Questionnaire Data

- Imputation methods for missing responses for the SGRQ are handled as described in Appendix 4.
- Details about how to handle the BDI and TDI scores are described in Appendix 3.

No other questionnaire data will be imputed.

Safety and Exacerbation Data

The following imputation will be done on AE data as well as on the HCRU COPD exacerbations for the summary statistics and inferential analyses:

- events with missing intensity will be imputed as severe.
- events with missing relationship to study drug will be deemed as definitely related.

The following imputation will be done on laboratory data (haematology and biochemistry) for the summary statistics and for the PCS categorisation:

- Any parameter value reported as '< xx.x' or '≤ xx.x' will be imputed with half of xx.x

- Any laboratory values reported as '> xx.x' or '≥ xx.x' will be imputed with 1.5 times xx.x

4.6.6 Professional duplicate subjects

Professional subjects are individuals who, in violation of protocol entrance criteria, enter into the study more than once at the same or in close succession.

During the trial, a Centralized Statistical Monitoring (CSM) Analysis Plan will be performed analyses performed. One of the objectives of the CSM analysis plan is to detect professional subjects.

Unless otherwise stated, data from the first instance of the patient entering the trial is used in analyses and summary tables. All data is listed for transparency, with flags for duplicate subjects to ensure clarity which records are in/out of the analysis.

For AEs, if a subject is on the same treatment throughout (across all instances), include all data in the analysis. If the patient is on different randomised treatments, the first instance of the subject entering the trial is used in analyses.

4.7 Subgroup Analyses

To explore the homogeneity of these results efficacy of AB/FF 400/12 and AB 400 over placebo across subgroups all the primary and secondary analyses will be carried out by the following subgroups:

- Sub-population (China and non-China)
- Sex (Male, Female)
- Age Group (< 65, ≥ 65 years old)
- Smoking Status (Current smoker, Former smoker)
- Screening Bronchodilator Reversibility (Reversible, Non-reversible)
- Baseline COPD Severity based on airflow limitation (mild-moderate, severe-very severe)
- Baseline ICS Use (Yes, No)

Information on how to derive the above categorisations can be found in Section 3. If less than 5% of subjects are included in a pre-specified subgroup category, categories may be combined or removed for a meaningful analysis. Subjects with missing values for the subgroup variables will be excluded from the subgroup analyses.

The descriptive and inferential analyses will be repeated by subgroup for the following main endpoints:

- Change from baseline in 1-h morning post-dose FEV_1 at Week 24
- Change from baseline in morning pre-dose FEV_1 at Week 24
- Change from baseline in peak FEV_1 at Week 24

- TDI focal score at Week 24
- Change from baseline in SGRQ total score at Week 24

For each endpoints, analysis will be performed using the same MMRM model described for the main analysis including the subgroup as a factor in the statistical model, if not already included. Also, in addition to the treatment-by-visit interaction term which is already included in the original model, treatment-by-subgroup, visit-by-subgroup, and treatment-by-visit-by-subgroup interactions will be added as fixed effect factors.

In addition, the estimate, 95% CI and p-value of testing the homogeneity between subgroup levels of AB/FF 400/12 vs. placebo, and AB 400 vs. placebo at Week 24, will be obtained through contrasts of hypothesis by using lsmestimate statement in PROC MIXED. The resulting SAS code and LSMESTIMATE statement for the comparisons between AB/FF 400/12 and AB 400 and placebo are provided in Appendix 9.

For each level of a subgroup, estimate of treatment effect and 95% CI and, for and the pairwise comparisons of AB/FF 400/12 versus placebo and AB 400 versus placebo the estimate of difference, 95% CI and p-value will be reported from the treatment-by-visit-by-subgroup interaction at Week 24. For the comparison between the two levels of each subgroup, estimate, 95% CI and p-value will be presented.

The adjusted LS Mean differences between AB/FF 400/12 versus Placebo and AB 400 versus Placebo at Week 24 in all subgroups will be shown in a single forest plot along with their 95% CIs. Values for the LS mean differences and 95% CI will be presented to the right of the plot. Within each forest plot, all the subgroup results will be compared to the results produced for the whole population (all subjects) which is extracted from the main analysis, that will be shown on the top of the plot. Number of subjects in each subgroup for a given treatment group, along with the corresponding change from baseline LS mean estimate at Week 24, will be presented to the left of the plot. The plot will show a reference vertical line on zero for the point of no treatment differences, with effect estimates on the right hand of the reference line favouring the fixed-dose combination. For the SGRQ total score, the interpretation of the results will be the opposite, with negative values on the left hand of the reference line favouring the active treatment.

All the above subgroup analyses are exploratory, and thus any statistically significant effect will be interpreted as nominally significant.

4.8 Sensitivity Analyses

Sensitivity analyses will be performed to assess the robustness of the analysis of primary and secondary continuous endpoints to the assumptions made when defining the while on treatment estimands for the study.

All sensitivity analyses will be performed on the ITT and performed using the multiple imputation (MI) model. The results of these analyses will provide information whether or not these assumptions have an impact on the main study conclusions.

4.8.1 Multiple Imputation Models

The missing values will be imputed for the sensitivity analyses on primary and secondary endpoints using MI.

The MI method can be summarised in three steps, imputation phase, analysis phase and pooling phase:

- Imputation phase

By means of the MI SAS procedure PROC MI, 25 copies of the original dataset will be simulated with random seed= 54321, where missing continuous endpoint values will be replaced with a 2-step imputation process.

The first step will be to impute non-monotone missing data ('holes' while on treatment) by treatment group. These will be imputed under the MAR assumption by means of a multivariate joint Gaussian imputation model using the stochastic Markov Chain Monte Carlo (MCMC) method. In the VAR statement of the PROC MI, screening and baseline variables should be ordered in such a way as to create a dataset with monotone missing values only following MCMC imputation. If there are no missing values for screening and baseline variables, then the suggested order is: pre-bronchodilator FEV_1 at screening; post-bronchodilator FEV_1 at screening; age; country; smoking status and then baseline value for PFT endpoints and age; country; smoking status and then baseline value for TDI and SGRQ endpoints.The second step is impute the remaining post-treatment discontinuation monotone missing values using a sequential (visit-by-visit) regression model based on the Copy Reference (CR) approach (Section 4.8.2) that assume that data are Missing-Not-At-Random (MNAR) (O´Kelly M, Ratitch B).

All imputation models should be at least as complex as the analysis model. All fixed effects used to adjust the analysis model will be therefore be included in the MCMC model and the sequential regression models. Since the MCMC method models all variables as continuous, it will be necessary to code all factors as numerical.

- Analysis phase

After the imputation phase, the same MMRM of the main analysis will be applied to the 25 fully imputed datasets to estimate the LS means and LS mean differences, one set of estimates for each imputed dataset.

- Pooling phase

The treatment effects and treatment differences for each visit from the results from 25 datasets will be combined to produce the study results, using the SAS procedure PROC MIANALYZE.

SAS code will be provided to the programmers for the MI algorithms.

4.8.2 Copy Reference (CR) Approach

The CR approach is a conditional sequential regression method based on the MNAR assumption that, after discontinuation, subjects in the experimental arm will no longer benefit from treatment and will be assumed to continue as if they were on the reference arm.

According to this approach, missing data in the treatment arm of interest at a certain visit will be imputed using the estimated means in the reference arm. For change from baseline at 1h post-dose FEV_1, the treatment arm of interest is AB/FF 400/12 and the reference arm will be AB 400. For change from baseline in trough FEV_1., the treatment arms of interest will be AB/FF 400/12 and AB 400 using reference arms of FF 12 and Placebo respectively. For change from baseline in peak FEV1, the treatment arm of interest will be AB 400, using Placebo as the reference arm. For TDI and SGRQ, the treatment arms of interest will be AB/FF 400/12 and AB 400, using Placebo as the reference arm for both. Imputation at each visit will be conditional on the subjects' outcomes observed or imputed at previous visit.

4.9 COVID-19 Analyses

For subjects in China, any date before 09 January 2020 is considered prior to the start of the COVID-19 pandemic, and any date on or following this time is considered post start of COVID-19 pandemic. For subjects in all other countries, any date before 11 March 2020 is considered prior to the start of the COVID-19 pandemic, and any date on or following this time is considered post start of COVID-19 pandemic.

4.9.1 Disruption due to the COVID-19 Pandemic

A summary table of disruptions due to COVID-19 will be produced for the Randomised Analysis Set and will display the number and percentage of subjects randomised prior to the start of the COVID-19 pandemic and post start of the COVID-19 pandemic by treatment group and for the overall total. For those randomised prior to the start of the pandemic, additional rows will be included to summarise the number and percentage no longer in the study at the start of the pandemic and the number and percentage still ongoing at the start of the pandemic.

Also included in this summary table will be the number and percentage of subjects with at least 1 disruption (i.e. visit impacted, study drug disrupted or discontinued, withdrawal from study) due to the COVID-19 pandemic by treatment group and for the overall total. For subjects with at least 1 disruption, the number and percentage will be additionally split by the following disruption categories:

- Scheduled visit impacted
- Study drug impacted
- Discontinued treatment due to COVID-19
- Withdrew from study due to COVID-19

A subject may experience more than one study disruption. Subjects experiencing more than one disruption for the same study characteristic (e.g. more than one visit disrupted) will be counted only once for that characteristic. Subjects experiencing disruptions across two or more study characteristics (e.g. visit disrupted and study drug disrupted) will be counted in all categories.

For all subjects affected by the COVID-19 pandemic, a listing of COVID-19 related disruptions to scheduled visits or study drug and discontinuation of study drug or withdrawal from study due to COVID-19 will be produced. For each disruption, further details on all items covered in Section 3.4.1 should be included.

5 INTERIM ANALYSIS

Not Applicable.

6 CHANGES OF ANALYSIS FROM PROTOCOL

Change	Rationale
Exploratory analyses of percent change from baseline for the primary and secondary endpoints are added.	Although differences in change from baseline may be seen for the given comparisons, this is to investigate relative changes in these endpoints.
COPD Exacerbations will be analysed in the SAF and not in the ITT.	Consistency with previous Aclidinium studies following an FDA recommendation.
The term 'Safety Analysis Set' is used instead of 'Safety Population' given in the CSP.	Safety Analysis Set is standard terminology for the analysis of data.
Comparison of AB 400 vs Placebo is explored descriptively, although not included in the CSP, using subgroup analysis on the primary and secondary efficacy variables.	To explore the homogeneity of AB 400 vs place in this patient population.
Definition of sub-population for Race is amended to 'Chinese and Non-Chinese' combining the subgroups based on Country.	To explore Chinese and non-Chinese results.
Subgroup for BMI group will not be used.	This change was implemented due to concerns of insufficient numbers in some BMI categories in a Chinese population.

Change	Rationale
CSP has the UK English version of SGRQ questionnaire. However, reporting of this questionnaire data will be based on the US English version. Please, refer to the CSP Appendix G and the Note to File dated 21 October 2019.	The database development, US English version of SGRQ questionnaire has been used using AZ standards.
Efficacy outputs 'over 24 weeks' on treatment are included	Exploratory analysis for completeness purposes.
CSP (sections 8.5.2 and 8.5.9) states that prior and concomitant medications will be categorized according to ATC classification and preferred term, but TFLs will actually present by ATC classification and generic term.	Updated to align with AZ corporate standards.

7 REFERENCES

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8 APPENDICES

8.1 Appendix 1: Schedule of Assessments

Table A-1. Study plan

Phase	Run-in (2 weeks) [1]	Double-blind Treatment (24 weeks)						Follow-up (2 weeks)	
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**EOT/ EOS**	**Phone Contact**
Week	**-2**	**0**	**1**	**4**	**12**	**18**	**24**	**N/A**	**26**
Day	**-14±3**	**1**	**7±3**	**28±3**	**84±3**	**126±3**	**168±3**	**N/A**	**182+3**
Informed Consent	C								
Medical, COPD and Smoking History	C								
Bronchodilator test [2]	C								
Inclusion/exclusion criteria	C	C							
Randomisation		P							
Physical exam [3]	C						C	C	
Laboratory analysis [4]	C						C	C	
ECG and Blood Pressure [5]	C	C	C		C	C	C	C	
Spirometry [6]		C	C	C	C	C	C		
Patient diaries [7]	P	P/R	P/R	P/R	P/R	P/R	C/R	C/R	
Rescue medication [8]	P	P	P	P	P	P	C	C	
AEs, COPD Exacerbations and prior/concomitant medication reviewed by investigator	C	C	C	C	C	C	C	C [9]	C
Drug accountability [10]		P			P/C		C	C	
CAT, BDI/TDI and SGRQ [11]		C		C	C		C		

Phase	Run-in (2 weeks) [1]	Double-blind Treatment (24 weeks)						Follow-up (2 weeks)	
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**EOT/ EOS**	**Phone Contact**
Week	**-2**	**0**	**1**	**4**	**12**	**18**	**24**	**N/A**	**26**
Day	**-14±3**	**1**	**7±3**	**28±3**	**84±3**	**126±3**	**168±3**	**N/A**	**182+3**

NOTES:
P = Provision/Dispensation, C = Collection/Test Performed, R = Investigator Review.
[1] Washout period for prohibited medication prior to Visit 1 and after the ICF signature from one day to one month, depending on the drug. See CSP for rules.
[2] Bronchodilator test will be done 10-15 minutes after the inhalation on 400 mcg of salbutamol through a Spacer device.
[3] Height and Weight only at Visit 1.
[4] Laboratory analysis includes haematology and biochemistry. Serum pregnancy test for women of childbearing potential only.
[5] ECG and Blood Pressure will be performed pre-morning dose and 1-hour post-morning dose. At Visit 1, EOT/EOS visit, only one test will be performed.
[6] Spirometry will consist of 2 pre-dose measurements performed 30 minutes apart and a series of post-morning dose tests. Post-morning dose spirometry at Visit 2 and Visit 7: at 5 and 30 min, and at 1, 2, 3 hours. At Visits 3, 4, 5 and 6 at 1h post-dose.
[7] Electronic and paper diaries filled-in by patients daily from Visit 1 until the follow-up visit: the e-diary (filled-in the evening) to record morning and evening number of doses of IP and rescue medication and to complete the EXACT questionnaire; the paper diary to record any new/changed AE and/or concomitant medication taken.
[8] If needed. Empty inhalers of rescue medication are collected throughout the study treatment, as applicable, if dispensed more than once.
[9] Only concomitant medication to treat AEs must be recorded at the follow-up contact.
[10] Drug accountability consists of dispensation/collection of the IP kit.
[11] Questionnaires should be assessed as pre-dose and before any test. The preferred completion order is: BDI (Visit 2) /TDI (following visits), CAT and SGRQ.

Protocol schedule for the Pulmonary Function Tests (PFTs)

Timepoints		Protocol Visits					
Time from morning dose	**Time (h)**	**Day 1**	**Week 1**	**Week 4**	**Week 12**	**Week 18**	**Week 24**
Pre-morning dose [1]	0	Y	Y	Y	Y	Y	Y
5 minutes	0.083	Y					Y
30 minutes	0.5	Y					Y
1 hour	1	Y	Y	Y	Y	Y	Y
2 hours	2	Y					Y
3 hours	3	Y					Y

Timepoints		Protocol Visits					
Time from morning dose	**Time (h)**	**Day 1**	**Week 1**	**Week 4**	**Week 12**	**Week 18**	**Week 24**
NOTES: [1] 2 measurements performed at -30 and 0 minutes pre-dose.							

8.2 Appendix 2: All Important Protocol deviations (IPDs) with those leading to exclusion from the Per Protocol analysis

There are 7 'PD Coded terms' for classifying IPDs:

- Inc/Excl criteria
- Disallowed medications
- IP admin/Study treat
- Procedures/Tests
- Developed discontinuation criteria but continued
- Informed Consent
- Other

Within each 'PD Coded Term' there is a detailed list of all 'IPD Terms' and the corresponding 'Description'. This classification can be found in the Protocol Deviations Specifications. In addition, the following table shows the criterion used to exclude terms 'Yes/No' from PP population. PP exclusion terms will be also applied to IPDs related with the COVID-19 outbreak (IPD terms PD082a, PD099a and PD118a in the table below).

PD Coded Term	IPD Term	Description	PP Exclusion
Inc/Excl criteria	PD001	Subject Randomized without fulfilling the inclusion criteria #1: Adult male or non-pregnant, non-lactating female patients aged ≥40	No
	PD002	Subject Randomized without fulfilling the inclusion criteria #2: Patients with a diagnosis of COPD (GOLD guidelines, 2015) prior to Visit 1 (screening)	Yes
	PD003	Subject Randomized without fulfilling the inclusion criteria #3: Moderate to severe stable COPD (Stage II or Stage III) at Visit 1: post-bronchodilator FEV_1 ≥30% and < 80% and FEV_1/FVC < 70%	Yes
	PD004	Subject Randomized without fulfilling the inclusion criteria #4: Current or former smokers with a smoking history of ≥ 10 pack-years	No
	PD005	Subject Randomized without fulfilling the inclusion criteria #5: Able to perform repeatable pulmonary function testing for FEV_1 at Visit 1(screening)	Yes
	PD006	Subject Randomized without fulfilling the inclusion criteria #6: Patients who understand the study procedures and are willing to participate in the study as indicated	No

		by signing the informed consent	
	PD008	Subject Randomized fulfilling the exclusion criteria #24: Patients unable to give consent, or patients of consenting age but under guardianship, or vulnerable patients	No
	PD009, PD010, PD011, PD014, PD015, PD016, PD017, PD018, PD019, PD020, PD021, PD025, PD027, PD030, PD134	Subject Randomized fulfilling the exclusion criteria #23: Patient did not undergo the required washout prior to V1 for different medications as specified in the Protocol Deviation Specification Form	No
	PD012, PD013, PD023, PD024, PD124, PD125, PD126	Subject Randomized fulfilling the exclusion criteria #23: Patient did not undergo the required washout prior to V1 for different medications as specified in the Protocol Deviation Specification Form	Yes
	PD031	Subject Randomized fulfilling the exclusion criteria #22: Patients treated with any investigational drug within 30 days (or 6 half-lives, whichever is longer) prior to screening	No
	PD034	Subject Randomized fulfilling the exclusion criteria #19: Any other	No

		serious or uncontrolled physical or mental dysfunction		
	PD035	Subject Randomized fulfilling the exclusion criteria #18: History of malignancy of any organ system (including lung cancer) within the past 5 years, other than basal or squamous cell skin cancer	No	
	PD036	Subject Randomized fulfilling the exclusion criteria #17: Known narrow-angle glaucoma, symptomatic bladder neck obstruction, acute urinary retention, symptomatic non-stable prostatic hypertrophy	No	
	PD037	Subject Randomized fulfilling the exclusion criteria #16: History of hypersensitivity reaction to inhaled anticholinergic drugs, sympathomimetic amines, inhaled medication or any component	No	
	PD038	Subject Randomized fulfilling the exclusion criteria #15: Patient with known non-controlled history of infection with human immunodeficiency virus and/or active hepatitis	No	
	PD039	Subject Randomized fulfilling the exclusion criteria #14: Abnormal liver function tests defined as AST, ALT, or total bilirubin ≥ 2.5 times	No	

		upper limit of normal ranges at screening	
	PD041	Subject Randomized fulfilling the exclusion criteria #12: QT corrected interval (QTc) using Fridericia formula (QTcF) (QTc=QT/RR1/3) >470 msec at Screening (Visit 1)	No
	PD042	Subject Randomized fulfilling exclusion criteria #11: Type I or uncontrolled Type II diabetes, uncontrolled hypo-or hyperthyroidism, hypokalaemia, hyperadrenergic state, uncontrolled or untreated hypertension	No
	PD043	Subject Randomized fulfilling the exclusion criteria #10: Clinically significant cardiovascular conditions	No
	PD046	Subject Randomized fulfilling the exclusion criteria #7: Patients who in the Investigator's opinion may need to start a pulmonary rehabilitation program during the study and/or patients who started/finished it within 3 months prior to screening	Yes
	PD047	Subject Randomized fulfilling the exclusion criteria #6: Clinically significant respiratory conditions other than COPD	Yes
	PD048	Subject Randomized fulfilling the exclusion	Yes

		criteria #5: Patients hospitalized for COPD exacerbation within 3 months prior to screening and during the run-in period	
	PD049	Subject Randomized fulfilling the exclusion criteria #4: Any respiratory tract infection or COPD exacerbation within 6 weeks prior to screening or during the run-in period	Yes
	PD050	Subject Randomized fulfilling the exclusion criteria #3: History or current diagnosis of asthma	Yes
	PD051	Subject Randomized fulfilling the exclusion criteria #2: Previous enrolment or randomisation in the present study	No
Disallowed medications	PD053a	Subject took prohibited medication at V2 or V7: Medication X YYYY*, Dose XX, Frequency XX taken between DD-MMM-YYYY and DD-MMM-YYYY	Yes
	PD129	Subject receiving a restricted medication X YYYY*, changed either daily dose, dosing schedule, formulation or treatment during the course of the trial with reason other than COPD exacerbation	Yes
IP admin/Study treat	PD054	The subject did not follow the dose regimen for the	No

		IMP according to the protocol taking more IMP doses than expected: >125 % of expected doses taken	
	PD055	Patient received expired IMP kit	Yes
	PD056	The IMP was not stored according to the temperature conditions stated in the protocol and the IMP manuals, AND This IMP was given to a subject	Yes
	PD058	The subject did not follow the dose regimen for the IMP according to the protocol: <70 % compliance	Yes
	PD059	Subject was dispensed/administered the wrong kit of medication (kit xx dispensed instead of kit yy)	Yes
	PD060	Patient is a screening failure, however patient received study drug	Yes
Procedures/Tests	PD070	SAE was not reported within 24 hours as per the protocol requirement	No
	PD073	ECG assessments were not performed at Visit 1 and not available in source document but patient was randomized	No
	PD074	Pre-dose ECG assessments were not performed at Visit 2 and not available in source document	No

	PD077	Blood pressure assessments were not performed at Visit 1 and not available in source document but patient was randomised	No
	PD078	Pre-dose Blood pressure assessments were not performed at Visit 2 and not available in source document but patient was randomised	No
	PD082, PD082a	Patient is randomised but the Pregnancy Test was not done at Visit X for a female patient of childbearing potential	No
	PD083	Pre dose Spirometry was not done at Visit 1 but patient was randomised	No
	PD084	Pre dose Spirometry was not done at Visit 2 but patient was randomised	No
	PD087	The Laboratory analysis (haematology and/or biochemistry) was not done at Visit 1 but patient was randomised	No
	PD091	Physical exam not done at Visit 1 but patient was randomised	No
	PD092	Bronchodilator test not done at Visit 1 but patient was randomised	No
	PD098	Patient relief medication is not dispensed according to the protocol (upon ICF signature and as needed during the whole duration of the trial)	No

	PD099, PD099a	Test xx was not performed according to the instructions given in the standard guidelines or per protocol requirements	No
	PD107	There is no baseline FEV_1 result available for a randomised patient	Yes
	PD108	There is no baseline FVC result available for a randomised patient	No
	PD109	There is no post -baseline FEV_1 result available for a randomised patient	Yes
	PD110	There is no post-baseline FVC result available for a randomised patient	No
	PD111	Visit 3/4/5/6 performed while patient was affected by any mild COPD exacerbation or within 2 weeks after mild COPD exacerbations recovery	No
	PD112	Visit 3/4/5/6 performed while patient was affected by any moderate or severe COPD exacerbation or within 4 weeks after moderate/severe COPD exacerbations recovery	No
	PD113	Patient performed Visit 7 (efficacy assessments) while affected by a COPD exacerbation	Yes
	PD115	Patient randomized in the wrong stratus strata (data from RTSM)	No
	PD118, PD118a	Visit 7 is missing for a patient completing the treatment	No

Developed discontinuation criteria but continued	PD123	The pregnancy Test at Visit X was positive and patient was not withdrawn from the study	No
Informed Consent	PD128	Subject started study related procedures before signing the ICF: More than 1-day between stopping medications and ICF signature date	No
Other	PD120	GCP breach: any critical issue that may jeopardize the data reliability such as evidences of bad use of users credentials to access the electronic data collection tools, missing source documents or medical notes, clear evidences of data/documents/signatures falsification, etc	No
	PD121	GCP breach: any critical issue related to the patients confidentiality (i.e. full name of the patient included in the databases)	No
	PD122	GCP issue: poor quality of medical notes, a lot of missing data in medical notes, investigator did not review/sign tests results, investigator did not check treatment compliance or did not complete drug accountability, investigator did not follow-up a clinically significant abnormality to guarantee the patient safety, etc	No

8.3 Appendix 3: Baseline and Transition Dyspnoea Indexes (BDI & TDI)

An independent interviewer will ask the patients open-ended questions related to their dyspnoea and will arbitrarily assign an impairment severity score for three components, that are functional impairment, magnitude of task and magnitude of effort. Individual component scores are presented in Table A-2. All alphanumeric values of the BDI and TDI component scales will be coded as missing when calculating the scores.

The BDI and TDI focal scores are derived as sum of the individual component scores. The BDI focal score can range from 0 and 12, with higher scores indicating a lower severity of breathlessness. The TDI focal score can vary from -9 to +9, with negative values indicating a worse deterioration in dyspnoea, 0 showing no change from baseline and positive values associated to a post-baseline improvement.

Table A-2. Grades for the BDI and TDI components

		Dyspnoea Components		
	Grade	**Functional impairment**	**Magnitude of task**	**Magnitude of effort**
BDI	4	No Impairment	Extraordinary	Extraordinary
	3	Slight Impairment	Major	Major
	2	Moderate Impairment	Moderate	Moderate
	1	Severe Impairment	Light	Light
	0	Very Severe Impairment	No Task	No Effort
	W [1]	Amount Uncertain		
	X [2]	Unknown		
	Y [3]	Impaired for Reasons Other than Shortness of Breath		
TDI	- 3	Major Deterioration		
	- 2	Moderate Deterioration		
	- 1	Minor Deterioration		
	0	No Change		
	+ 1	Minor Improvement		
	+ 2	Moderate Improvement		
	+ 3	Major Improvement		
	Z [4]	Further Impairment for Reasons Other than Shortness of Breath		

NOTES:
[1] Subject is impaired but no information on the severity can be obtained.
[2] There is insufficient information to determine if the subject is impaired.
[3] Patient's impairment is due to factors other than respiratory.
[4] The post-baseline dyspnoea cannot be rated.

In case of one (or more) component is missing the BDI will be classified as X, and TDI will be not calculated. The TDI focal score will only be calculated when all TDI components are non-missing.

8.4 Appendix 4: SGRQ questionnaire

As per the Note to File dated 21 October 2019, while the original UK English version of the SGRQ is attached to the CSP (Appendix G), the version used in the study database and described in this section is the US English version.

The SGRQ is composed of 50 items split into 17 parts, from which the following dimension scores will be derived:

- Symptoms Score: derived from questions 1-8
- Activity Score: derived from questions 11, 15
- Impact Score: derived from questions 9-10, 12-14, 16-17

For each of the above SGRQ dimensions, the score is derived in the below 4 steps:

- Sum up the weights for all questions with a response (sum of weights of positive items).
- Sum up the weights for all questions with a missing response (sum of weights of missing items)
- Deduct the possible maximum sum of weights from the sum of weights of missing items obtained at bullet point 2), where the maximum sum of weights for each dimension is:
    - Symptoms: 662.5
    - Activity: 1209.1
    - Impacts: 2117.8
- Divide the sum of weights of positive items derived at bullet point 1) by the adjusted sum of weights for all items derived at bullet point 3):

$$Score = 100x\frac{Sum\ of\ weights\ for\ positive\ items\ in\ dimension}{Adjusted\ sum\ of\ weights\ for\ all\ items\ in\ dimention}$$

The SGRQ total score is calculated in a similar way:

$$Score = 100x\frac{Sum\ of\ weights\ for\ positive\ items\ in\ the\ questionnaire}{Adjusted\ sum\ of\ weights\ for\ all\ items\ in\ the\ questionnaire}$$

The maximum sum of weights for the questionnaire (total) is: 3989.4

SGRQ total score summarizes the overall impact of COPD on patients' quality of life. If any of the component scores is missing, total score will not be derived.
SGRQ scores range from 0 to 100, with higher SGRQ scores indicating a higher deterioration in patients' health status.

Missing items will not be imputed except for the following cases and imputation will be performed before the derivation of scores:

- If the response of question 6 is missing and the answer of question 5 is "no attacks", then the question 6 response will be imputed to "less than a day".

- If the four items of question 14 are missing, their responses will be imputed to "false".
- If more than 2 items of the Symptoms dimension have missing response, the Symptom Score will be set to missing.
- If more than 4 items of the Activity dimension have missing response, the Activity Score will be set to missing.
- If more than 6 items of the Impacts dimension have missing response, the Impacts Score will be set to missing.

NOTES:
[1] If the response of question 6 is missing and the answer of question 5 is "no attacks", then the question 6 response will be imputed to "less than a day".
[2] If the four items of Section 5 are missing, their responses will be imputed to "false".

US SGRQ item scoring system

Part	Question	Answer	Score
1	Over the past 4 weeks, I have coughed	Almost every day	80.6
		Several days a week	63.2
		A few days a month	29.3
		Only with respiratory infections	28.1
		Not at all	0.0
2	Over the past 4 weeks, I have brought up phlegm (sputum)	Almost every day	76.8
		Several days a week	60.0
		A few days a month	34.0
		Only with respiratory infections	30.2
		Not at all	0.0
3	Over the past 4 weeks, I have had shortness of breath	Almost every day	87.2
		Several days a week	71.4
		A few days a month	43.7
		Only with respiratory infections	35.7
		Not at all	0.0
4	Over the past 4 weeks, I have had wheezing attacks	Almost every day	86.2
		Several days a week	71.0
		A few days a month	45.6
		Only with respiratory infections	36.4
		Not at all	0.0
5	How many times during the past 4 weeks have you suffered from severe or very unpleasant respiratory attacks? [1]	more than 3 attacks	86.7
		3 attacks	73.5
		2 attacks	60.3
		1 attack	44.2
		no attacks	0.0
6	How long did the worst respiratory attack last? (Go to Question 7 if you did not have a severe attack) [1]	a week or more	89.7
		3 or more days	73.5
		1 or 2 days	58.8
		less than a day	41.9
7	Over the past 4 weeks, in a typical week, how many good days (with few respiratory problems) have you had?	No good days	93.3
		1 or 2 good days	76.6
		3 or 4 good days	61.5
		nearly every day was good	15.4
		every day was good	0.0
8	If you wheeze, is it worse when you get up in the morning?	No	0.0
		Yes	62.0
9	How would you describe your respiratory condition?	The most important problem I have	83.2
		Causes me quite a lot of problems	82.5
		Causes me a few problems	34.6

Part	Question	Answer	Score
		Causes no problem	0.0
10	If you have ever held a job, my respiratory problems	made me stop working altogether	88.9
		interfere with or made me change my job	77.6
		do not affect my job	0.0
11	**These are questions about what activities usually make you feel short of breath these days**		
	Sitting or lying still	True	90.6
		False	0.0
	Washing or dressing yourself	True	82.8
		False	0.0
	Walking around the house	True	80.2
		False	0.0
	Walking outside on level ground	True	81.4
		False	0.0
	Walking up a flight of stairs	True	76.1
		False	0.0
	Walking up hills	True	75.1
		False	0.0
	Playing sports or other physical activities	True	72.1
		False	0.0
12	**These are more questions about your cough and shortness of breath these days.**		
	Coughing hurts	True	81.1
		False	0.0
	Coughing makes me tired	True	79.1
		False	0.0
	I am short of breath when I talk	True	84.5
		False	0.0
	I am short of breath when I bend over	True	76.8
		False	0.0
	My coughing or breathing disturbs my sleep	True	87.9
		False	0.0
	I get exhausted easily	True	84.0
		False	0.0
13	**These are questions about other effects that your respiratory problems may have on you these days**		
	My coughing or breathing is embarrassing in public	True	74.1
		False	0.0
	My respiratory problem is a nuisance to my family, friends, or neighbors	True	79.1
		False	0.0
	I get afraid or panic when I cannot catch my breath	True	87.7
		False	0.0
	I feel that I am not in control of my respiratory problems	True	90.1
		False	0.0
		True	82.3

Part	Question	Answer	Score
	I do not expect my respiratory problem to get any better	False	0.0
	I have become frail or an invalid because of my respiratory problem	True	89.9
		False	0.0
	Exercise is not safe for me	True	75.7
		False	0.0
	Everything seems too much of an effort	True	84.5
		False	0.0
14 [2]	**These are questions about your respiratory treatment.**		
	My treatment does not help me very much	True	88.2
		False	0.0
	I get embarrassed using my medication in public	True	53.9
		False	0.0
	I have unpleasant side effects from my medication	True	81.1
		False	0.0
	My treatment interferes with my life a lot	True	70.3
		False	0.0
15	**These are questions about how your activities might be affected by your respiratory problems.**		
	I take a long time to get washed or dressed	True	74.2
		False	0.0
	I cannot take a bath or shower, or I take a long time to do it	True	81.0
		False	0.0
	I walk slower than other people my age, or I stop to rest	True	71.7
		False	0.0
	Jobs such as housework take a long time, or I have to stop to rest	True	70.6
		False	0.0
	If I walk up one flight of stairs, I have to go slowly or stop	True	71.6
		False	0.0
	If I hurry or walk fast, I have to stop or slow down	True	72.3
		False	0.0
	My breathing makes it difficult to do things such as walk up hills, carry things upstairs, light gardening such as weeding, dance, bowl or play golf	True	74.5
		False	0.0
	My breathing makes it difficult to do things such as carry heavy loads, dig in the garden or shovel snow, jog or walk briskly (5 miles per hour), play tennis or swim	True	71.4
		False	0.0
	My breathing problem makes it difficult to do things such as very heavy manual work, ride a bike, run, swim fast, or play competitive sports	True	63.5
		False	0.0
16	**We would like to know how your respiratory problems usually affect your daily life**		
	I cannot play sports or do other physical activities	True	64.8
		False	0.0

Part	Question	Answer	Score
	I cannot go out for entertainment or recreation	True	79.8
		False	0.0
	I cannot go out of the house to do the shopping	True	81.0
		False	0.0
	I cannot do household chores	True	79.1
		False	0.0
	I cannot move far from my bed or chair	True	94.0
		False	0.0
17	Now, would you check (one only) which you think best describes how your respiratory problem affects you?	Does not stop me from doing anything	0.0
		Stops me from doing one or two things	42.0
		Stops me from doing most of the things	84.2
		Stops me from doing everything	96.7

NOTES:
[1] If the response of question 6 is missing and the answer of question 5 is "no attacks", then the question 6 response will be imputed to "less than a day".
[2] If the four items of question 14 are missing, their responses will be imputed to "false".

SGRQ Questionnaire (US English Version)

ST. GEORGE'S RESPIRATORY QUESTIONNAIRE
ENGLISH FOR THE UNITED STATES

ST. GEORGE'S RESPIRATORY QUESTIONNAIRE (SGRQ)

This questionnaire is designed to help us learn much more about how your breathing is troubling you and how it affects your life. We are using it to find out which aspects of your illness cause you the most problems, rather than what the doctors and nurses think your problems are.

Please read the instructions carefully and ask if you do not understand anything. Do not spend too long deciding about your answers.

Before completing the rest of the questionnaire:

Please check one box to show how you describe your current health:

Very good	Good	Fair	Poor	Very poor
☐	☐	☐	☐	☐

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continued…

St. George's Respiratory Questionnaire
PART 1

Please describe how often your respiratory problems have affected you over the past 4 weeks.

		Please check (✓) *one box for each question*: almost every day	several days a week	a few days a month	only with respiratory infections	not at all
1.	Over the past 4 weeks, I have coughed:	☐	☐	☐	☐	☐
2.	Over the past 4 weeks, I have brought up phlegm (sputum):	☐	☐	☐	☐	☐
3.	Over the past 4 weeks, I have had shortness of breath:	☐	☐	☐	☐	☐
4.	Over the past 4 weeks, I have had wheezing attacks:	☐	☐	☐	☐	☐

5. How many times during the past 4 weeks have you suffered from severe or very unpleasant respiratory attacks?

Please check (✓) *one*:
- more than 3 times ☐
- 3 times ☐
- 2 times ☐
- 1 time ☐
- none of the time ☐

6. How long did the worst respiratory attack last?
(Go to Question 7 if you did not have a severe attack)

Please check (✓) *one*:
- a week or more ☐
- 3 or more days ☐
- 1 or 2 days ☐
- less than a day ☐

7. Over the past 4 weeks, in a typical week, how many good days (with few respiratory problems) have you had?

Please check (✓) *one*:
- No good days ☐
- 1 or 2 good days ☐
- 3 or 4 good days ☐
- nearly every day was good ☐
- every day was good ☐

8. If you wheeze, is it worse when you get up in the morning?

Please check (✓) *one*:
- No ☐
- Yes ☐

St. George's Respiratory Questionnaire
PART 2

Section 1

How would you describe your respiratory condition?

	Please check (✓) *one*:
The most important problem I have	☐
Causes me quite a lot of problems	☐
Causes me a few problems	☐
Causes no problems	☐

If you have ever held a job:

	Please check (✓) *one*:
My respiratory problems made me stop working altogether	☐
My respiratory problems interfere with my job or made me change my job	☐
My respiratory problems do not affect my job	☐

Section 2

These are questions about what activities usually make you feel short of breath <u>these days</u>.

	For each statement please check (✓) ***the box*** that applies to you ***these days***: True	False
Sitting or lying still	☐	☐
Washing or dressing yourself	☐	☐
Walking around the house	☐	☐
Walking outside on level ground	☐	☐
Walking up a flight of stairs	☐	☐
Walking up hills	☐	☐
Playing sports or other physical activities	☐	☐

St. George's Respiratory Questionnaire
PART 2

Section 3

These are more questions about your cough and shortness of breath <u>these days</u>.

	For each statement please check (✓) ***the box*** that applies to you ***these days***: True	False
Coughing hurts	☐	☐
Coughing makes me tired	☐	☐
I am short of breath when I talk	☐	☐
I am short of breath when I bend over	☐	☐
My coughing or breathing disturbs my sleep	☐	☐
I get exhausted easily	☐	☐

Section 4

These are questions about other effects that your respiratory problems may have on you <u>these days</u>.

	For each statement, please check (✓) ***the box*** that applies to you ***these days***: True	False
My cough or breathing is embarrassing in public	☐	☐
My respiratory problems are a nuisance to my family, friends or neighbors	☐	☐
I get afraid or panic when I cannot catch my breath	☐	☐
I feel that I am not in control of my respiratory problems	☐	☐
I do not expect my respiratory problems to get any better	☐	☐
I have become frail or an invalid because of my respiratory problems	☐	☐
Exercise is not safe for me	☐	☐
Everything seems too much of an effort	☐	☐

Section 5

These are questions about your respiratory treatment. If you are not receiving treatment go to section 6.

	For each statement, please check (✓) ***the box*** that applies to you ***these days***: True	False
My treatment does not help me very much	☐	☐
I get embarrassed using my medication in public	☐	☐
I have unpleasant side effects from my medication	☐	☐
My treatment interferes with my life a lot	☐	☐

St. George's Respiratory Questionnaire
PART 2

Section 6

These are questions about how your activities might be affected by your respiratory problems.

	For each statement, please check (✓) ***the box*** that applies to you ***because of your respiratory problems***: True	False
I take a long time to get washed or dressed	☐	☐
I cannot take a bath or shower, or I take a long time to do it	☐	☐
I walk slower than other people my age, or I stop to rest	☐	☐
Jobs such as household chores take a long time, or I have to stop to rest	☐	☐
If I walk up one flight of stairs, I have to go slowly or stop	☐	☐
If I hurry or walk fast, I have to stop or slow down	☐	☐
My breathing makes it difficult to do things such as walk up hills, carry things up stairs, light gardening such as weeding, dance, bowl or play golf	☐	☐
My breathing makes it difficult to do things such as carry heavy loads, dig in the garden or shovel snow, jog or walk briskly (5 miles per hour), play tennis or swim	☐	☐
My breathing makes it difficult to do things such as very heavy manual work, ride a bike, run, swim fast, or play competitive sports	☐	☐

Section 7

We would like to know how your respiratory problems <u>usually</u> affect your daily life.

	For each statement, please check (✓) ***the box*** that applies to you ***because of your respiratory problems***: True	False
I cannot play sports or do other physical activities	☐	☐
I cannot go out for entertainment or recreation	☐	☐
I cannot go out of the house to do the shopping	☐	☐
I cannot do household chores	☐	☐
I cannot move far from my bed or chair	☐	☐

St. George's Respiratory Questionnaire

Here is a list of other activities that your respiratory problems may prevent you from doing. (You do not have to check these, they are just to remind you of ways your shortness of breath may affect you):

Going for walks or walking the dog

Doing activities or chores at home or in the garden

Sexual intercourse

Going to a place of worship, or a place of entertainment

Going out in bad weather or into smoky rooms

Visiting family or friends or playing with children

Please write in any other important activities that your respiratory problems may stop you from doing:

.....

.....

.....

.....

Now please check the box (one only) that you think best describes how your respiratory problems affect you:

It does not stop me from doing anything I would like to do ☐

It stops me from doing one or two things I would like to do ☐

It stops me from doing most of the things I would like to do ☐

It stops me from doing everything I would like to do ☐

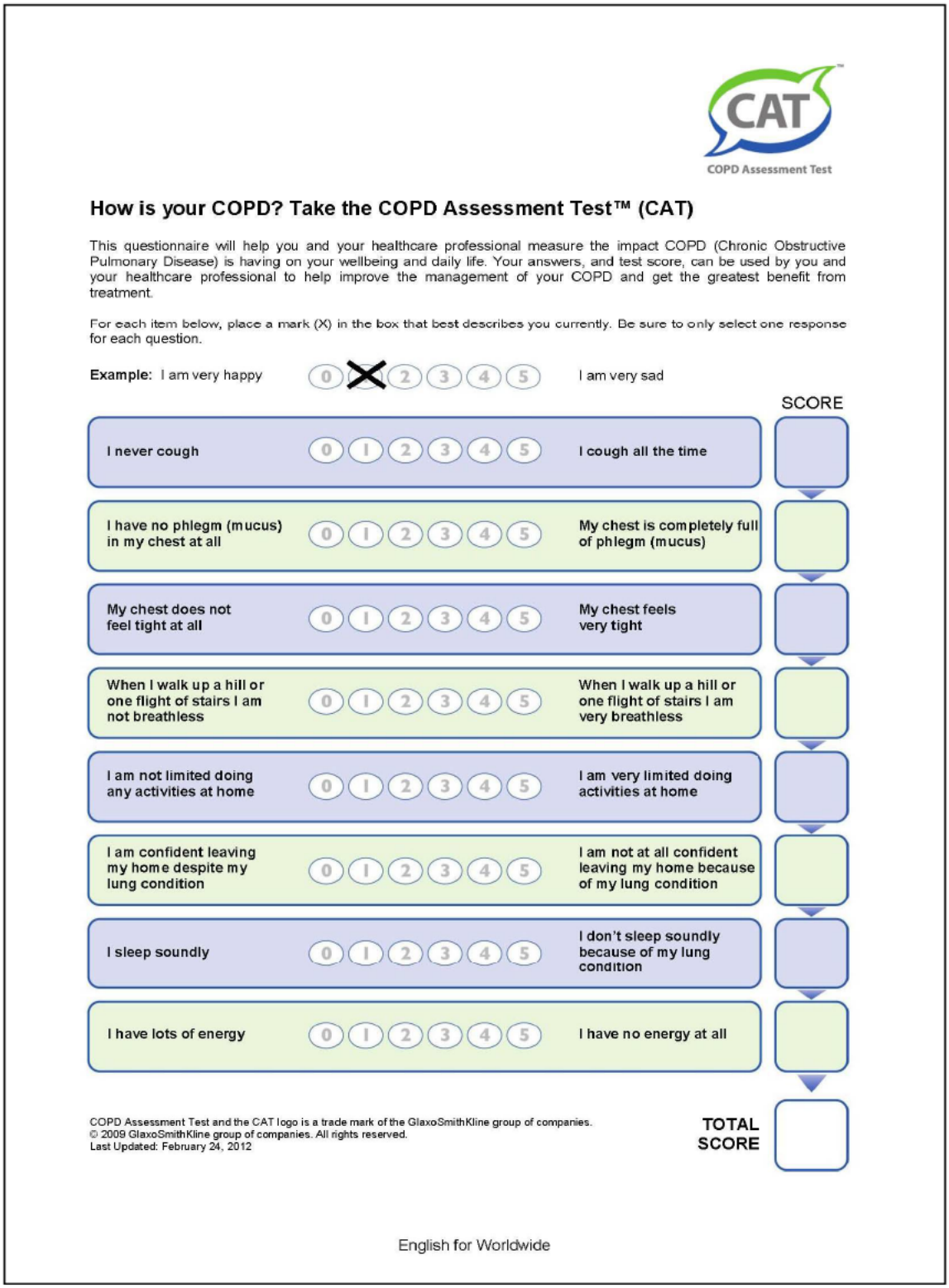
Thank you for completing this questionnaire. Before you finish would you please make sure that you have answered all the questions.

8.5 Appendix 5: COPD Assessment Test (CAT)

Patient-completed questionnaire assessing globally the impact of COPD (cough, sputum, dysnea, chest tighteness) on health status. The questionnaire has 8 item (one question assessing impact on sleep).

Range of CAT scores from 0–40. Higher scores denote a more severe impact of COPD on a patient's life. The difference between stable and exacerbation patients was five units. No target score represents the best achievable outcome.

In case of one (or more) question is missing, the CAT will be kept as missing and not calculated.



CAT
COPD Assessment Test

How is your COPD? Take the COPD Assessment Test™ (CAT)

This questionnaire will help you and your healthcare professional measure the impact COPD (Chronic Obstructive Pulmonary Disease) is having on your wellbeing and daily life. Your answers, and test score, can be used by you and your healthcare professional to help improve the management of your COPD and get the greatest benefit from treatment.

For each item below, place a mark (X) in the box that best describes you currently. Be sure to only select one response for each question.

Example: I am very happy 0 X 2 3 4 5 I am very sad

			SCORE
I never cough	0 1 2 3 4 5	I cough all the time	
I have no phlegm (mucus) in my chest at all	0 1 2 3 4 5	My chest is completely full of phlegm (mucus)	
My chest does not feel tight at all	0 1 2 3 4 5	My chest feels very tight	
When I walk up a hill or one flight of stairs I am not breathless	0 1 2 3 4 5	When I walk up a hill or one flight of stairs I am very breathless	
I am not limited doing any activities at home	0 1 2 3 4 5	I am very limited doing activities at home	
I am confident leaving my home despite my lung condition	0 1 2 3 4 5	I am not at all confident leaving my home because of my lung condition	
I sleep soundly	0 1 2 3 4 5	I don't sleep soundly because of my lung condition	
I have lots of energy	0 1 2 3 4 5	I have no energy at all	
		TOTAL SCORE	

Last Updated: February 24, 2012

English for Worldwide

8.6 Appendix 6: EXACT and raw score assignment

An EXACT Total score is computed for each day of diary collection. The EXACT Total score is based on a logit scoring system with conversion to a 0 to 100 scale for ease of interpretation and use. To compute the EXACT Total score:

1. Sum the raw scores of the 14 EXACT items (Table A-4a). Raw scores are assigned to each EXACT item response. Each "raw summed score" has its corresponding EXACT Total score.
2. For each "raw summed score", find the corresponding EXACT Total score (Table A-4b), which can range on a scale from 0 to 100 (Raw summed score to scale score conversion table for EXACT Total Score)
3. Daily EXACT Total scores of 0 are set to missing.
4. Where no diary entry exists for a given day, enter missing for the EXACT Total score computation.

Table A-4a. Raw item scoring system of the EXACT questionnaire

Item	Question	Answer	Raw Score
1	Did your chest feel congested today?	Not at all	0
		Slightly	1
		Moderately	2
		Severely	3
		Extremely	4
2	How often did you cough today?	Not at all	0
		Rarely	1
		Occasionally	2
		Frequently	3
		Almost constantly	4
3	How much mucus (phlegm) did you bring up when coughing today?	Not at all	0
		A little	1
		Some	1
		A great deal	2
		A very great deal	3
4	How difficult was it to bring up mucus (phlegm) today?	Not at all	0
		Slightly	1
		Moderately	2
		Quite a bit	3
		Extremely	4
5	Did you have chest discomfort today?	Not at all	0
		Slight	1
		Moderate	2
		Severe	3
		Extreme	4
6	Did your chest feel tight today?	Not at all	0
		Slightly	1
		Moderately	2

Item	Question	Answer	Raw Score
		Severely	3
		Extremely	4
7	Were you breathless today?	Not at all	0
		Slightly	1
		Moderately	2
		Severely	3
		Extremely	4
8	Describe how breathless you were today:	Unaware of breathlessness	0
		Breathless during strenuous activity	1
		Breathless during light activity	2
		Breathless when washing or dressing	3
		Present when resting	3
9	Were you short of breath today when performing your usual personal care activities like washing or dressing?	Not at all	0
		Slightly	1
		Moderately	2
		Severely	3
		Extremely	3
		Too breathless to do these	4
10	Were you short of breath today when performing your usual indoor activities like cleaning or household work?	Not at all	0
		Slightly	1
		Moderately	2
		Severely	3
		Extremely	3
		Too breathless to do these	3
11	Were you short of breath today when performing your usual activities outside the home such as yard work or errands?	Not at all	0
		Slightly	1
		Moderately	2
		Severely	3
		Extremely	3
		Too breathless to do these	3
12	Were you tired or weak today?	Not at all	0
		Slightly	1
		Moderately	2
		Severely	3
		Extremely	4
13	Last night, was your sleep disturbed?	Not at all	0
		Slightly	1
		Moderately	2
		Severely	3
		Extremely	4
14	How scared or worried were you about your lung problems today?	Not at all	0
		Slightly	1
		Moderately	2
		Severely	3
		Extremely	3

Table A-4b. Scale conversion from the daily raw summed scores to the daily EXACT score

EXACT Raw Score	EXACT Daily Score	EXACT Raw Score (continued)	EXACT Daily Score (continued)
0	- [1]	26	50
1	8	27	51
2	13	28	52
3	17	29	53
4	20	30	54
5	23	31	55
6	25	32	57
7	27	33	58
8	28	34	59
9	30	35	60
10	31	36	61
11	33	37	63
12	34	38	64
13	36	39	65
14	37	40	67
15	38	41	68
16	39	42	70
17	40	43	72
18	41	44	73
19	42	45	75
20	43	46	77
21	44	47	80
22	46	48	83
23	47	49	87
24	48	50	92
25	49	51	100

NOTES:
[1] EXACT daily scores of 0 will be set as missing.

8.7 Appendix 7: Derivation of COPD Exacerbations

Health Care Resource Utilization (HCRU) Exacerbations

HCRU exacerbations are evaluated by the investigator and recorded in the AE form of the EDC system at each protocol visit based on the information provided in the patients´ electronic and paper diaries.

The intensity will be based on the following actions taken as recorded on the eCRF:

- **Mild**: Increase of COPD symptoms during at least 2 consecutive days, self-managed by the patient at home by increasing usual COPD medication (short-acting and/or inhaled corticosteroid used.
- **Moderate**: Increase of COPD symptoms during at least 2 consecutive days, which does not lead to hospitalization but is treated with antibiotics and/or systemic corticosteroids or an increase in dose of systemic corticosteroids.
- **Severe**: Increase in COPD symptoms during at least 2 consecutive days, which leads to hospitalization (overnight stay at hospital or emergency room) or death.

If the above severity classes cannot be derived, intensity will be imputed as severe.

The Onset Day and the Recovery Day are the AE start and stop dates recorded on the eCRF.

For a COPD exacerbation to be counted as a separate event, it must be preceded by at least seven days in which no criteria for exacerbations is fulfilled. In case of relapse, the Recovery day for the resulting exacerbation is the Recovery day of the last episode and the onset day is the one from the first episode, and the severity of the resulting exacerbation will be that of the highest severity of the episodes.

Exacerbations of Chronic Pulmonary Disease Tool (EXACT)

EXACT exacerbations are symptom-based exacerbations derived using the daily EXACT questionnaire.

The following parameters must be derived:

- EXACT Daily Scores

  From the first IP dose date onwards.

- EXACT Baseline Score

  The mean of the EXACT Daily Scores recorded 7 days before the first IP dose day (excluded). If fewer than 4 days of data are available, the score will be set to missing.

- Onset Day

  The first day (Day 1) of the worsening of the baseline condition, where worsening is defined by an increase from baseline in the EXACT Daily Score of either ≥ 12 points for 2 consecutive days, or ≥ 9 points for 3 consecutive days.

- EXACT Rolling Scores

  3-day (Day_{x-1}, Day_x, and Day_{x+1}) rolling averages of the EXACT Daily Scores from the Onset Day until last possible day. Only one of the 3 data points need to be present for this computation and therefore, a rolling average can still be calculated on days where EXACT Daily Scores are missing. The rolling mean for the Onset Day will only include Day 1 and Day 2.

- Maximum Observed Value (MOV)

  The highest EXACT Rolling Score within 14 days from the Onset Day.

- Recovery Day

The first day of the 7-day recovery period, where recovery is defined by a decrease from the MOV in the EXACT Rolling Score ≥ 9 points for 7 consecutive days. It is permitted for days where an EXACT Daily Score is missing, but an Exact Rolling Score is calculable, to be considered as the recovery day if the criteria for recovery, based on the MOV and EXACT Rolling Score, is met.

The occurring of a score increase meeting the onset definition of point 3) identifies an EXACT exacerbation.

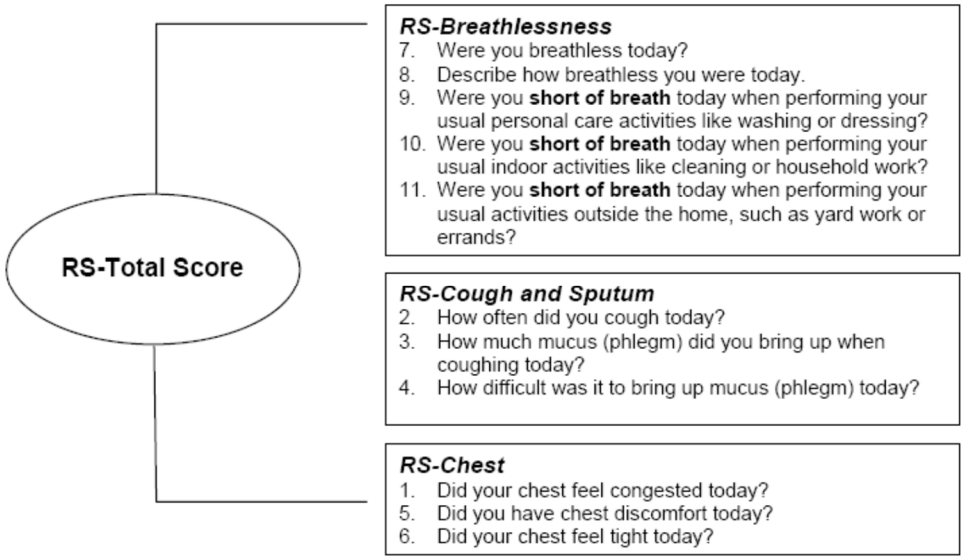
For a COPD exacerbation to be counted as a separate event, it must be preceded by at least seven days in which no criteria for exacerbations is fulfilled. In case of relapse, the Recovery day for the resulting exacerbation is the Recovery day of the last episode and the onset day is the one from the first episode, and the severity of the resulting exacerbation will be that of the highest severity of the episodes.

The patient EXACT Baseline Score is reset following each exacerbation as the mean of the EXACT Daily Scores during the 4th week following recovery (22-28 days after the Recovery Day), with a required of minimum of 4 days of data. If the subject experiences new events (i.e. score increases meeting the onset criteria) during this 4-week period, the EXACT Baseline Score will be calculated during the 4th week following the recovery from that last event. If no exacerbations occur, the EXACT Baseline Score will be reset every 28 exacerbation-free days. If less than 4 days data are available the baseline will not be re-established and the previous baseline will be used instead.

8.8 Appendix 8: Annotated E-RS for Raw Score Assignment

The following domain scores will be derived:

- E-RS Breathlessness score: sum the raw scores of questions 7-11 (ranging 0-17)
- E-RS Cough and Sputum score: sum the raw scores of questions 2-4 (ranging 0-11)
- E-RS Chest Symptoms score: sum the raw scores of questions 1, 5-6 (ranging 0-12)
- E-RS Total Score: sum the raw scores of all questions 1-14 of the three domain scores. The E-RS total score ranges from 0 to 40, with higher scores indicating a higher symptom worsening



The following annotates the raw score values associated with each response category for the E-RS items:

1. Did your chest feel congested today?

0. Not at all
1. Slightly
2. Moderately
3. Severely
4. Extremely

2. How often did you cough today?

0. Not at all
1. Rarely
2. Occasionally
3. Frequently
4. Almost constantly

3. How much mucus (phlegm) did you bring up when coughing today?

0. None at all
1. A little
1. Some
2. A great deal
3. A very great deal
NOTE: Score "a little" and "some" the same.

4. How difficult was it to bring up mucus (phlegm) today?

0. Not at all
1. Slightly
2. Moderately
3. Quite a bit
4. Extremely

5. Did you have chest discomfort today?

0. Not at all
1. Slightly
2. Moderate
3. Severe
4. Extreme

6. Did your chest feel tight today?

0. Not at all
1. Slightly
2. Moderately
3. Severely
4. Extremely

7. Were you breathless today?

0. Not at all
1. Slightly
2. Moderately
3. Severely
4. Extremely

8. Describe how breathless you were today:

0. Unaware of breathlessness
1. Breathless during strenuous activity
2. Breathless during light activity
3. Breathless when washing or dressing
3. Present when resting
NOTE: Score "Breathless when washing or dressing" and "Present when resting" the same.

9. Were you short of breath today when performing your usual personal care activities like washing or dressing?

0. Not at all
1. Slightly
2. Moderately
3. Severely
3. Extremely
4. Too breathless to do these
NOTE: Score "severely" and "extremely" the same

10. Were you short of breath today when performing your usual indoor activities like cleaning or household work?

0. Not at all
1. Slightly
2. Moderately
3. Severely
3. Extremely
3. Too breathless to do these
NOTE: Score "severely", "extremely", and "too breathless to do these" the same

11. Were you short of breath today when performing your usual activities outside the home such as yard work or errands?

0. Not at all
1. Slightly
2. Moderately
3. Severely
3. Extremely
3. Too breathless to do these
NOTE: Score "severely", "extremely", and "Too breathless to do these" the same.

Importantly, this simple summation is an entirely different measurement scale from that used in the EXACT, which includes three additional items and focuses on measuring the frequency, duration and severity of acute exacerbations. Given that the domains contained with the E-RS are nearly identical to that of the EXACT, it is critical that these domains are clearly distinguished from one another in studies using both scoring algorithms.

8.9 Appendix 9: SAS code for subgroup analysis including contrasts of hypothesis

Subgroups:

- Sub-population (China and non-China)
- Sex (Male, Female)
- Age Group (< 65, ≥ 65 years old)
- Smoking Status (Current smoker, Former smoker)
- Screening Bronchodilator Reversibility (Reversible, Non-reversible)
- Baseline COPD Severity based on airflow limitation (mild-moderate, severe-very severe)
- Baseline ICS Use (Yes, No)

Note that all subgroups have 2 Levels, Level 1, and Level 2.

Note1: subgroup factor must be included in the class statement in SAS unless it is already in the "by default" stats model

Note2: TRTPN, AVISITN, and SUBGROUP must be in this order in the class statement

1. Differences between Level 1 and Level 2 in change from baseline in 1-h morning post-dose FEV_1 at week 24

We consider 4 levels for the treatment in this order (A): AB/FF 400/12, AB 400, FF 12, placebo; 2 levels for the <<SUBGROUP>> (B): *Level 1, Level 2*; and 6 levels for visits (C): day 1, week 1, week 4, week 12, week 18, and week 24.

To compare AB/FF 400/12 versus placebo:

```
proc mixed data = <<dataset>> method=reml;
  class usubjid trt01pn <<subgroup>> smokstat country avisitn;
  model chg = base trt01pn <<pre>> <<post>> age <<subgroup>> smokstat country avisitn
              trt01pn*avisitn trt01pn*<<subgroup>> avisitn*<<subgroup>>
              trt01pn*<<subgroup>>*avisitn
              / ddfm=kr;
  repeated avisitn / type=un subject=usubjid(trt01pn);
  lsmeans trt01pn*<<subgroup>>*avisitn / diff=all cl;
  lsmestimate trt01pn*<<subgroup>>*avisitn "Change from baseline in 1-h post-dose FEV1
              of AB/FF 400/12 vs. placebo between <<Level 1>> and <<Level 2>> at week 24"
```

```
              0 0 0 0 0 1 0 0 0 0 0 -1
              0 0 0 0 0 0 0 0 0 0 0 0
              0 0 0 0 0 0 0 0 0 0 0 0
              0 0 0 0 0 -1 0 0 0 0 0 1
              / cl;
run;
```

To compare AB 400 versus placebo:

```
proc mixed data = <<dataset>> method=reml;
  class usubjid trt01pn <<subgroup>> smokstat country avisitn;
  model chg = base trt01pn <<pre>> <<post>> age <<subgroup>> smokstat country avisitn
              trt01pn*avisitn trt01pn*<<subgroup>> avisitn*<<subgroup>>
              trt01pn*<<subgroup>>*avisitn
              / ddfm=kr;
  repeated avisitn / type=un subject=usubjid(trt01pn);
  lsmeans trt01pn*<<subgroup>>*avisitn / diff=all cl;
  lsmestimate trt01pn*<<subgroup>>*avisitn "Change from baseline in 1-h post-dose FEV1
              of AB 400 vs. placebo between <<Level 1>> and <<Level 2>> at week 24"
              0 0 0 0 0 0 0 0 0 0 0 0
              0 0 0 0 0 1 0 0 0 0 0 -1
              0 0 0 0 0 0 0 0 0 0 0 0
              0 0 0 0 0 -1 0 0 0 0 0 1
              / cl;
run;
```

2. Differences between Level 1 and Level 2 in change from baseline in trough FEV_1 at week 24

We consider 4 levels for the treatment in this order (A): AB/FF 400/12, AB 400, FF 12, placebo; 2 levels for the <<SUBGROUP>> (B): *Level 1, Level 2*; and 5 levels for visits (C): Week 1, Week 4, Week 12, Week 18, Week 24.

To compare AB/FF 400/12 versus placebo:

```
proc mixed data = <<dataset>> method=reml;
  class usubjid trt01pn <<subgroup>> smokstat country avisitn;
  model chg = base trt01pn <<pre>> <<post>> age <<subgroup>> smokstat country avisitn
              trt01pn*avisitn trt01pn*<<subgroup>> avisitn*<<subgroup>>
              trt01pn*<<subgroup>>*avisitn
```

```
              / ddfm=kr;
  repeated avisitn / type=un subject=usubjid(trt01pn);
  lsmeans trt01pn*<<subgroup>>*avisitn / diff=all cl;
  lsmestimate trt01pn*<<subgroup>>*avisitn "Change from baseline in trough FEV1 of AB/FF 400/12 vs. placebo between
              <<Level 1>> and <<Level 2>> at week 24"
              0 0 0 0 1 0 0 0 0 -1
              0 0 0 0 0 0 0 0 0 0
              0 0 0 0 0 0 0 0 0 0
              0 0 0 0 -1 0 0 0 0 1
              / cl;
run;
```

To compare AB 400 versus placebo:

```
proc mixed data = <<dataset>> method=reml;
  class usubjid trt01pn <<subgroup>> smokstat country avisitn;
  model chg = base trt01pn <<pre>> <<post>> age <<subgroup>> smokstat country avisitn
              trt01pn*avisitn trt01pn*<<subgroup>> avisitn*<<subgroup>>
              trt01pn*<<subgroup>>*avisitn
              / ddfm=kr;
  repeated avisitn / type=un subject=usubjid(trt01pn);
  lsmeans trt01pn*<<subgroup>>*avisitn / diff=all cl;
  lsmestimate trt01pn*<<subgroup>>*avisitn "Change from baseline in trough FEV1
              of AB 400 vs. placebo between <<Level 1>> and <<Level 2>> at week 24"
              0 0 0 0 0 0 0 0 0 0
              0 0 0 0 1 0 0 0 0 -1
              0 0 0 0 0 0 0 0 0 0
              0 0 0 0 -1 0 0 0 0 1
              / cl;
run;
```

3. Differences between Level 1 and Level 2 in change from baseline in peak FEV_1 at week 24

We consider 4 levels for the treatment in this order (A): AB/FF 400/12, AB 400, FF 12, placebo; 2 levels for the <<SUBGROUP>> (B): *Level 1, Level 2*; and 2 levels for visits (C): day 1, and week 24.

To compare AB/FF 400/12 versus placebo:

```
proc mixed data = <<dataset>> method=reml;
  class usubjid trt01pn <<subgroup>> smokstat country avisitn;
  model chg = base trt01pn <<pre>> <<post>> age <<subgroup>> smokstat country avisitn
              trt01pn*avisitn trt01pn*<<subgroup>> avisitn*<<subgroup>>
              trt01pn*<<subgroup>>*avisitn
              / ddfm=kr;
  repeated avisitn / type=un subject=usubjid(trt01pn);
  lsmeans trt01pn*<<subgroup>>*avisitn / diff=all cl;
  lsmestimate trt01pn*<<subgroup>>*avisitn "Change from baseline in peak FEV1 of AB/FF 400/12 vs. placebo between
              <<Level 1>> and <<Level 2>> at week 24"
              0 1 0 -1
              0 0 0 0
              0 0 0 0
              0 -1 0 1
              / cl;
run;
```

To compare AB 400 versus placebo:

```
proc mixed data = <<dataset>> method=reml;
  class usubjid trt01pn <<subgroup>> smokstat country avisitn;
  model chg = base trt01pn <<pre>> <<post>> age <<subgroup>> smokstat country avisitn
              trt01pn*avisitn trt01pn*<<subgroup>> avisitn*<<subgroup>>
              trt01pn*<<subgroup>>*avisitn
              / ddfm=kr;
  repeated avisitn / type=un subject=usubjid(trt01pn);
  lsmeans trt01pn*<<subgroup>>*avisitn / diff=all cl;
  lsmestimate trt01pn*<<subgroup>>*avisitn "Change from baseline in peak FEV1
              of AB 400 vs. placebo between <<Level 1>> and <<Level 2>> at week 24"
              0 0 0 0
              0 1 0 -1
              0 0 0 0
              0 -1 0 1
              / cl;
run;
```

4. Differences between Level 1 and Level 2 in TDI focal score at week 24

TDI and SGRQ main analyses are change from baseline. Therefore, the same MMRM model will be used. Except for that the baseline to use is the BDI and that pre and post bronchodilator covariates must not be included as covariates of adjustment

We consider 4 levels for the treatment in this order (A): AB/FF 400/12, AB 400, FF 12, placebo; 2 levels for the <<SUBGROUP>> (B): *Level 1, Level 2*; and 3 levels for visits (C): Week 4, Week 12, Week 24.

To compare AB/FF 400/12 versus placebo:

```
proc mixed data = <<dataset>> method=reml;
  class usubjid trt01pn <<subgroup>> smokstat country avisitn;
  model aval = bdi trt01pn age <<subgroup>> smokstat country avisitn
              trt01pn*avisitn trt01pn*<<subgroup>> avisitn*<<subgroup>>
              trt01pn*<<subgroup>>*avisitn
              / ddfm=kr;
  repeated avisitn / type=un subject=usubjid(trt01pn);
  lsmeans trt01pn*<<subgroup>>*avisitn / diff=all cl;
  lsmestimate trt01pn*<<subgroup>>*avisitn "TDI focal score of AB/FF 400/12 vs. placebo between
              <<Level 1>> and <<Level 2>> at week 24"
              0 0 1 0 0 -1
              0 0 0 0 0 0
              0 0 0 0 0 0
              0 0 -1 0 0 1
              / cl;
run;
```

To compare AB 400 versus placebo:

```
proc mixed data = <<dataset>> method=reml;
  class usubjid trt01pn <<subgroup>> smokstat country avisitn;
  model aval = bdi trt01pn age <<subgroup>> smokstat country avisitn
              trt01pn*avisitn trt01pn*<<subgroup>> avisitn*<<subgroup>>
              trt01pn*<<subgroup>>*avisitn
              / ddfm=kr;
  repeated avisitn / type=un subject=usubjid(trt01pn);
  lsmeans trt01pn*<<subgroup>>*avisitn / diff=all cl;
```

```
  lsmestimate trt01pn*<<subgroup>>*avisitn "TDI focal score of AB 400 vs. placebo between
              <<Level 1>> and <<Level 2>> at week 24"
              0 0 0 0 0 0
              0 0 1 0 0 -1
              0 0 0 0 0 0
              0 0 -1 0 0 1
              / cl;
run;
```

5. Differences between Level 1 and Level 2 in change from baseline SGRQ total score at week 24

We consider 4 levels for the treatment in this order (A): AB/FF 400/12, AB 400, FF 12, placebo; 2 levels for the <<SUBGROUP>> (B): *Level 1, Level 2*; and 3 levels for visits (C): Week 4, Week 12, Week 24.

To compare AB/FF 400/12 versus placebo:

```
proc mixed data = <<dataset>> method=reml;
  class usubjid trt01pn <<subgroup>> smokstat country avisitn;
  model chg = base trt01pn age <<subgroup>> smokstat country avisitn
              trt01pn*avisitn trt01pn*<<subgroup>> avisitn*<<subgroup>>
              trt01pn*<<subgroup>>*avisitn
              / ddfm=kr;
  repeated avisitn / type=un subject=usubjid(trt01pn);
  lsmeans trt01pn*<<subgroup>>*avisitn / diff=all cl;
  lsmestimate trt01pn*<<subgroup>>*avisitn "Change from baseline in SGRQ total score of AB/FF 400/12 vs. placebo
              between <<Level 1>> and <<Level 2>> at week 24"
              0 0 1 0 0 -1
              0 0 0 0 0 0
              0 0 0 0 0 0
              0 0 -1 0 0 1
              / cl;
run;
```

To compare AB 400 versus placebo:

```
proc mixed data = <<dataset>> method=reml;
  class usubjid trt01pn <<subgroup>> smokstat country avisitn;
  model chg = base trt01pn age <<subgroup>> smokstat country avisitn
              trt01pn*avisitn trt01pn*<<subgroup>> avisitn*<<subgroup>>
              trt01pn*<<subgroup>>*avisitn
              / ddfm=kr;
  repeated avisitn / type=un subject=usubjid(trt01pn);
  lsmeans trt01pn*<<subgroup>>*avisitn / diff=all cl;
  lsmestimate trt01pn*<<subgroup>>*avisitn "Change from baseline in SGRQ total score of AB 400 vs. placebo
              between <<Level 1>> and <<Level 2>> at week 24"
              0 0 0 0 0 0
              0 0 1 0 0 -1
              0 0 0 0 0 0
              0 0 -1 0 0 1
              / cl;
run;
```

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