- **Protocol number:** D6571C00001
- **Document title:** A 24 week treatment, multicenter, randomized, double blinded, double dummy, parallel-group, clinical trial evaluating the efficacy and safety of aclidinium bromide 400 µg/formoterol fumarate 12 µg fixed-dose combination BID compared with each monotherapy (aclidinium bromide 400 µg BID and formoterol fumarate 12 µg BID) and tiotropium 18 µg QD when administered to patients with stable chronic obstructive pulmonary disease
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Statistical Analysis Plan

Study Code	D6571C00001
Edition Number	2.0
Date	04/July/2017

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Prepared by:

PPD

PPD

04/July/2017
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Prepared by:

PPD

PPD

04/July/2017

Date

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
AB 400:	Aclidinium bromide 400
AB/FF 400/12:	Fixed dose combination of aclidinium bromide 400 µg and Formoterol 12
AE:	Adverse event
ALT:	Alanine aminotransferase
ALP:	Alkaline phosphatase
ANCOVA:	Analysis of covariance
AST:	Aspartate aminotransferase
ATC:	Anatomical therapeutic chemical
AUC:	Area under the curve
BID:	*Bis in Die* (twice a day)
BDRM:	Blind data review meeting
BMI:	Body mass index
BPM:	Beats per minute
BTR:	Best test review
CAT:	COPD Assessment Test
CI:	Confidence Interval
COPD:	Chronic obstructive pulmonary disease
CR:	Copy reference
CSR:	Clinical study report
CV:	Cardiovascular
CVAC:	Cardiovascular Adjudication Committee
DBP:	Diastolic blood pressure
DILI:	Drug-induced liver injury
ECG:	Electrocardiogram
EDC:	Electronic data capture
EMSCI:	Early morning symptoms
ENR:	Expanded normal ranges
EOT:	End of treatment
EOS:	End of study
E-RS:	EXACT-Respiratory symptoms
EU:	The European Union
EXACT:	Exacerbations of Chronic Pulmonary Disease Tool
FEV1:	Forced expiratory volume in one second
FF 12	Formoterol fumarate 12
FVC:	Forced vital capacity
HCRU:	Health Care Resources Utilization
HIV:	Human immunodeficiency virus
HL:	Hy's Law
HLT:	High Level Term
HR:	Heart rate
ICF:	Informed Consent Form
ICS:	Inhaled corticosteroids
IP:	Investigational product
ITT:	Intention to treat
IVRS:	Interactive Voice Response System
LABA:	Long-acting β_2-agonist
LAMA:	Long acting muscarinic agent
L:	Litter
LLN:	Lower limit of normality
LS Mean:	Least square mean
MACE:	Major adverse cardiac event
MAR:	Missing at random
MCID:	Minimal clinically important difference
MedDRA:	Medical dictionary for regulatory activities

MI:	Myocardial infarction / Multiple imputation
mL:	Millilitres
MMRM:	Mixed model for repeated measures
MNAR:	Missing not at random
msec	Milliseconds
MSSO:	Maintenance and Support Services Organization
N/A:	Not applicable
nAUC:	Normalised area under the curve
NiSCI:	Night-time symptoms
NNT:	Number needed to treat
PCS:	Potentially clinically significant
PDE:	Phosphodiesterases
PID:	Patient identifier
PFT:	Pulmonary function test
PHL:	Potential Hy's Law
PP:	Per protocol
PR interval:	Duration in milliseconds between two R peaks of two consecutive QRS complexes
PT:	Preferred term
PRO:	Patient reported outcome
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 interval:	QT interval corrected, Bazett formulae ($QT/RR^{1/2}$)
QTcF interval:	QT interval corrected, Fredericia formulae ($QT/RR^{1/3}$)
REML:	Restricted maximum likelihood
SABA:	Short-acting β_2-agonist agent
SAMA:	Short-acting inhaled anticholinergic agent
SAE:	Serious adverse event
SAP:	Statistical analysis plan
SBP:	Systolic blood pressure
SD:	Standard deviation
SE:	Standard error
SGRQ:	St. George's Respiratory Questionnaire
SMQ:	Standard MedDRA Query
SOC:	System organ class
TBL:	Total bilirubin
TEAE:	Treatment emergent adverse event
TESAE:	Treatment emergent serious adverse event
TIO 18:	Tiotropium 18
UK:	The United Kingdom
ULN:	Upper limit of normality
US:	The United States
WHO:	World health organization

AMENDMENT HISTORY

Date	Brief description of change
15/December/2016 (original doc.)	N/A
30/June/2017	The document was amended to include the following updates: • Added protocol deviation to exclude patients from the PP population without baseline FEV_1 values • Updated the compliance with the study medication using the drug accountability form (section 2.2, and 4.4.2) • Patients discontinuing the IP but continouning in the study only have spirometries at scheduled visits pre-drug administration. Therefore, analysis based on AUC cannot be done (including the sensitivity analysis specified in section 4.8.) • Updated calculation on exacerbations including the calculation of the offset and the imputation of stop date of HCRU and EXACT exacerbations (sections 4.10.3, 4.10.4, and 4.14.1.3) • Updated data handling for missing CAT questionnaire values (section 4.14.1.2) • Minor inconsistencies or mistakes have been fixed in this amendment • Updated “Changes of analysis from protocol” as appropiate

1. STUDY DETAILS

1.1 Study objectives

Primary objective for US:

To assess the bronchodilatory effect of AB/FF 400/12 µg compared to each individual component when administered twice daily via inhalation to COPD patients.

Primary objective for Market Access:

To assess the non-inferior bronchodilation of AB 400 µg BID as compared to tiotropium (TIO) 18 µg QD in COPD patients.

Secondary Objectives:

To further characterize the effect of AB/FF 400/12 µg on bronchodilation and health related quality of life compared to individual components when administered twice daily via inhalation to COPD patients.

Safety objectives:

To evaluate the safety and tolerability of AB/FF 400/12 µg as compared to individual components in COPD patients.

Exploratory objectives:

Treatment effects and comparisons in primary and secondary variables will be evaluated for the subgroup of patients which are more symptomatic at study entry (see Section 4.12.).

1.2 Study design

This is a 24 week treatment, multicenter, randomized, double blinded, double dummy, parallel-group study.

Target populations is based on current or former smokers, aged ≥ 40, symptomatic COPD patients (CAT score ≥10 at both, screening and randomization visit) with stable moderate to very severe airflow obstruction (post-bronchodilator test $FEV_1/FVC < 70\%$ and $FEV_1 < 80\%$ of the predicted normal value at Screening Visit).

Study design:

Figure 1 Study flow chart

<table>
<tr><td>Visit 1</td><td>Visit 2</td><td>Visit 3</td><td>Visit 4</td><td>Visit 5</td><td>Visit 6</td><td>Visit 7</td><td>Follow Up Contact</td></tr>
<tr><td>~ -2 weeks</td><td>Week 0</td><td>Week 1</td><td>Week 4</td><td>Week 12</td><td>Week 18</td><td>Week 24</td><td>Week 26</td></tr>
<tr><td rowspan="5">Screening (Run-in period) 14 ± 3 days</td><td colspan="6">Treatment Phase (24 weeks)</td><td rowspan="5">Follow Up 14 + 3 days</td></tr>
<tr><td colspan="6">AB/FF 400/12 µg (BID)</td></tr>
<tr><td colspan="6">AB 400 µg (BID)</td></tr>
<tr><td colspan="6">FF 12 µg (BID)</td></tr>
<tr><td colspan="6">TIO 18 µg</td></tr>
</table>

1.3 Flow chart of procedures

Period	Washout Period	Screening Period	Treatment							Follow-up call
Visit	**Visit 0 Registration[1]**	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**EOT/EOS Visit**	
Week	**Up to 4**	**Up to 2**	**0**	**1**	**4**	**12**	**18**	**24**		**26**
Day	**Up to -28**	**Up to -14**	**1**	**8**	**29**	**85**	**127**	**169**		**183**
Visit Window		**± 3 days**		**± 2 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**		**+ 3 days**
Informed consent form	X									
Medical, Smoking, COPD and Medication History	X	X								
Physical examination[2]		X[2]						X	X	
Blood pressure and 12-lead ECG [3]		X	X	X	X	X	X	X	X	
Bronchodilator test[4]		X								
Dispense wash-out medication	X	X								
Inclusion/exclusion criteria	X	X	X							
Clinical laboratory testing[5]		X						X	X	
Randomization			X							
SGRQ, CAT[6]		X (CAT)	X		X	X	X	X	X	
Device preference								X	X	
e-diary completion[7]		Daily since Screening Visit (Visit 1): EXACT in the evening and NiSCI and EMSCI in the morning							X	

Period	**Washout Period**	**Screening Period**	**Treatment**							**Follow-up call**
Visit	**Visit 0 Registration[1]**	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**EOT/EOS Visit**	
Week	**Up to 4**	**Up to 2**	**0**	**1**	**4**	**12**	**18**	**24**		**26**
Day	**Up to -28**	**Up to -14**	**1**	**8**	**29**	**85**	**127**	**169**		**183**
Visit Window		**± 3 days**		**± 2 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**		**+ 3 days**
Pre-dose PFT[8]			X	X	X	X	X	X	X	
Post-dose PFT			X[9]		X[10]	X[11]	X[10]	X[11]	X[12]	
Training on inhalers			X	As needed						
Dispense relief medication	X	As needed								
Assess study drug compliance				X	X	X	X	X		
Dispense study drug via IVRS			X			X				
Paper Diary[13]		X	X	X	X	X	X	X	X	X
Adverse Events/COPD exacerbations		X	X	X	X	X	X	X	X	X
Prohibited/concomitant medications	X	X	X	X	X	X	X	X	X	X[14]
SERIAL SPIROMETRY SUBSTUDY: Additional Assessments										
24-hour PFT[15]			X					X		

Time windows for all visits are related to visit 2.
[1] Patients requiring a washout of prohibited COPD medications will sign the ICF, be assigned a Patient Identification number (enrolment code) by the IWRS system, and receive Atrovent® and relief medication (albuterol/salbutamol) at Visit 0. Visit 0 may occur the same day as Visit 1 if the patient does not require a washout. In this case, only relief medication will be provided to the patient.

Period	Washout Period	Screening Period	Treatment							Follow-up call
Visit	Visit 0 Registration[1]	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	EOT/EOS Visit	
Week	Up to 4	Up to 2	0	1	4	12	18	24		26
Day	Up to -28	Up to -14	1	8	29	85	127	169		183
Visit Window		± 3 days		± 2 days	± 3 days	± 3 days	± 3 days	± 3 days		+ 3 days

EOT = End of Treatment; EOS = End of Study for patients who discontinue from the treatment and from the study at the same time. Patients who discontinue from the treatment post follow-up period should undergo a reduce EOS visit to collect the diaries.

[2] Height and weight only at Screening Visit
[3] Blood Pressure (after being seated for 5-10 minutes and before the ECG assessment) and ECG will be performed once at Screening Visit to determine patient eligibility and once in case of EOT visit. At other visits, ECG and Blood Pressure will be performed pre-morning dose (before the patient exerts any effort, including PFTs) and 2 hours post-morning dose at visits 2, 5 and 7.
[4] One pre-bronchodilator PFT, followed by one post-bronchodilator PFT 10-15 minutes after the inhalation of 4 puffs of albuterol/salbutamol through a spacer device. At the EOT, an optional PFT could be performed if required.
[5] Hematology and biochemistry. Serum pregnancy test only in female patients of child bearing potential.
[6] At Screening visit only the CAT questionnaire will be administered to assess the fulfillment of the inclusion criteria. At other visits, SGRQ and CAT questionnaires will be administered prior to study drug administration. St George's Respiratory Questionnaire (SGRQ) will be the first questionnaire to be administered.
[7] Patient will record number of doses taken of relief medication once daily (in the evening); IP intake will be recorded in the morning and evening; EXACT questionnaire will be completed every evening; and Night-time and Early Morning COPD symptoms questionnaire will be completed every morning.
[8] Two pre-PFTs (approximately 15 to 30 minutes apart) both to be completed within 60 minutes prior to the morning dose of study drug.
[9] At Visit 2: 5 minutes, 15 minutes, 30 minutes, 1 hour, 2 hours, and 3 hours post study drug administration.
[10] At Visits 4 and 6: 1 hour post study drug administration.
[11] At Visits 5 and 7: 30 minutes, 1 hour, 2 hours, and 3 hours post study drug administration.
[12] At EOT/EOS visit: 1 hour post COPD treatment administration.[13]Patient will record in the paper diary the AEs and new concomitant medication during the study.
[14] Only concomitant medication related to AEs must be recorded at follow-up contact.
[15] Additional PFTs at Visit 2 and 7 only for 35% of patients who will participate in the 24-hour serial spirometry sub-study: +4h, +6h, +9h, +10h, +12h (pre-evening dose), +12.5h, +13h, +14h, +22, +23.5h and +24h after the morning dose. Subjects participating in the sub-study who choose to discontinue from treatment will not complete the 24h spirometry assessments at the EOT visit.

Subjects who discontinue study IP treatment prior to week 24 (Visit 7) will be encouraged to remain in the study to undergo all study related remaining visits for the full 24 weeks' period. All patients who agree to continue study participation beyond the IP treatment discontinuation will complete an End of Treatment Visit (EOT). In this case, the IP and relief medication will be returned at the EOT visit but the paper diary and electronic diary will be re-dispensed to be used during the post-IP follow-up, and the prescription of a COPD medication will be done. From the EOT visit on, these patients will start a post-IP discontinuation follow-up period according to the planned visit schedule including spirometry assessments and SGRQ completion. Patients will be also followed up for COPD exacerbations, SAEs, and concomitant medication, and will be requested to record daily the EXACT questionnaire in the e-diary. Subjects participating in the sub-study who choose to discontinue from IP treatment will only complete regular scheduled visits and not complete any remaining sub-study assessments.

Smoking-status and country was used as a treatment allocation factor during the randomization process.

1.4 Number of subjects

Approximately, 2,200 patients will be screened in this trial (considering an estimated ineligibility rate of 30%) to have an overall sample size of 1,500 randomized patients to AB/FF 400/12 µg, AB 400 µg, FF 12 µg, and TIO 18 µg, based on a randomization ratio of 2:3:2:3, which corresponds to 300, 450, 300, and 450 patients per treatment arm, respectively.

Based on hypotheses derived from the evidence shown in previous Duaklir clinical trials, this sample size will provide at least 90% power to detect a statistically significant treatment difference of 100 mL between AB/FF 400/12 µg and AB 400 µg in change from baseline in 1-hour morning post-dose FEV_1 at week 24, and 65 mL between AB/FF 400/12 µg and FF 12 µg in change from baseline in morning pre-dose (trough) FEV_1 at week 24, assuming a standard deviation (SD) of 230 mL, using two-sided tests, and adjusting for multiple tests at 5% overall significance level. The expected minimum statistically significant effect is 37 mL in FEV_1. This sample size will provide enough power to detect a statistically significant treatment difference of 100 mL between AB/FF 400/12 µg and AB 400 µg and FF 12 µg in change from baseline in normalized AUC_{0-3} FEV_1 at week 24, assuming a SD of 220 mL.

The responder analysis of the St. George's Respiratory Questionnaire (SGRQ) total score based on a decrease of $\geq$ 4-units from baseline will be tested, comparing AB/FF 400/12 µg versus both monotherapies.

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

For the market access, this sample size will have 90% power to show that the lower bound of the two-sided 95% confidence interval for the difference between AB 400 µg and TIO 18 µg in change from baseline in morning pre-dose (trough) FEV_1 at week 24

is above -50 mL (non-inferiority limit), assuming that the expected difference is 0 mL, and a SD of 230 mL.

Primary and secondary efficacy variables to assess the effect of aclidnium/formoterol vs. each individual monocompoenent, and

	Step	Variable at week 24	Treatment Comparison
Primary Variables	1	Change from baseline in 1-hour post-dose FEV_1	AB/FF 400/12 µg vs. AB 400 µg
	2	Change from baseline in morning pre-dose FEV_1	AB/FF 400/12 µg vs. FF 12 µg
Secondary Variables	3	Change from baseline in $nAUC_{0-3}$ FEV_1	AB/FF 400/12 µg vs. AB 400 µg
	4	Change from baseline in $nAUC_{0-3}$ FEV_1	AB/FF 400/12 µg vs. FF 12 µg
	5	Responder analysis of SGRQ total score (MCID, a decrease of at least 4-units from baseline)	AB/FF 400/12 µg vs. AB 400 µg
	6	Responder analysis of SGRQ total score (MCID, a decrease of at least 4-units from baseline)	AB/FF 400/12 µg vs. FF 12 µg

Primary endpoint to assess the non-inferiority effect of aclidinium 400 µg vs, tiotropium 18 µg is as follow:

Change from baseline in morning pre-dose FEV_1 at week 24 is above -50 mL (non-inferiority limit)	AB 400 µg vs. TIO 18 µg

2. ANALYSIS SETS

2.1 Definition of analysis sets

Demographic and other baseline (screening) characteristics will be analysed using the Safety population. The analysis of all efficacy variables (except for exacerbations) will be performed on the ITT population. The analysis of exacerbations will be performed on the Safety population. The non-inferiority analysis will be performed on the Per Protocol population. All safety variables and other variables will be analysed using the Safety population.

Screening analysis set

The Screened population is defined as all subjects who attended screening visit and received a subject number.

Randomised analysis set

The randomised population is defined as all subjects in the screened population who were randomised to a treatment group in the study.

Safety analysis set

The safety population is defined as all randomised patients who took at least one dose of IP.

Efficacy analysis set

The Intention-to-Treat (ITT) population is defined as all randomised patients who take at least one dose of IP and have at least a baseline FEV_1, under the ITT principle and regardless the adherence to the randomised treatment.

The Per-Protocol (PP) population is defined as a subset of the ITT population consisting of patients who:

a. met all inclusion/exclusion criteria liable to affect the efficacy assessment

b. have sufficient treatment compliance (Section 2.2., item 39)

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).

PK analysis set

Not applicable

2.2 Violations and deviations

Patients will be assigned to the analysis populations during the Blind Data Review Meeting (BDRM), after the database lock; however, the conventions are agreed before the database lock in order to avoid potential bias when assigning the analysis populations at the end of the trial. This is the list of the important protocol deviations and those leading to exclude patients from the PP population:

	Protocol Deviation Coded Term	**IMPORTANT (Yes/No)**	**PP exclusion? (Yes/No)**
1	Positive pregnancy test	Yes	No
2	Post-BD FEV1/FVC ≥ 70 % at Screening (Visit 1) or missing value. Post-BD FEV1 ≥ 80% of predicted at Screening (Visit 1) or missing value.	Yes	Yes
3	Patient not able to perform acceptable and repeatable PFTs	Yes	Yes
4	Not signature of the ICF	Yes	No
5	Previous randomization in the present study (or simultaneous randomization)	Yes	Yes
6	Patients with predominant asthma	Yes	Yes
7	Respiratory Tract infection or COPD exacerbation within 6 weeks prior to Screening Visit or during the run-in period	Yes	Yes
8	Patients hospitalized for a COPD exacerbation within 3 months prior to Screening Visit	Yes	Yes
9	Clinically significant respiratory conditions other than COPD	Yes	Yes
10	Pulmonary rehabilitation program started/stopped within 3 months before Screening	Yes	Yes
11	Intake of another IMP within 30 days (or 6 half-lives, whichever is longer) before Screening Visit	Yes	Yes
12	Patients unable to give consent, or patients of consenting age but under guardianship, or vulnerable patients.	Yes	No
13	Insufficient wash-out for prohibited medications: Oral, intranasal or parenteral anticholinergics, LAMAs, SAMAs, LABAs, LABAs+ICS, SABAs+SAMA, LABA+LAMA, Methyl-xanthines, Leukotriene modifiers, PDE IV inhibitors, Continuous oral or parenteral corticosteroids (higher doses), Non-selective β-blocking agents.	No/Yes (case by case)	No/Yes (Case by case)

	Protocol Deviation Coded Term	**IMPORTANT (Yes/No)**	**PP exclusion? (Yes/No)**
14	Intake of prohibited medication except in case of a COPD exacerbation/Adverse Event (short course): Oral, intranasal or parenteral anticholinergics, LAMAs, SAMAs, LABAs, LABAs+ICS, SABAs+SAMA, LABA+LAMA, Methyl-xanthines, Leukotriene modifiers, PDE IV inhibitors, Continuous oral or parenteral corticosteroids (higher doses), Non-selective β-blocking agents.	No/Yes (case by case)	No/Yes (case by case)
15	Randomised patients who did not take IP / Randomised patients without baseline FEV_1 values	Yes	Yes
16	Kit dispensed not matching the kit assigned by IVRS	Yes	Yes
17	Treatment compliance < 70 % in any device (Genuair or Handihaler) according to the drug accountability	Yes	Yes
18	Last Visit performed not postponed despite of MODERATE exacerbation within 4 weeks of visit.	Yes	Yes
19	Patient with a SEVERE exacerbation not discontinued from the study affecting last visit	Yes	Yes
20	Screen failure administered with study drug	Yes	No
21	Critical Subjects rights breach or data integrity breach	Yes	No

*Those deviations would not be listed as important deviations in the CSR, as the patients will be excluded from the ITT.

3. SUMMARY OF VARIABLES AND COMPARISONS

3.1 Co-primary efficacy variables for US

The co-primary variables and comparisons are the following:

- Change from baseline in 1-hour morning post-dose dose FEV_1 of AB/FF 400/12 µg compared to AB 400 µg at week 24.
- Change from baseline in morning pre-dose (trough) FEV_1 of AB/FF 400/12 µg compared to FF 12 µg at week 24.

Trough FEV_1 will be computed as the average of the two pulmonary test readings just before 12 hours after post-evening dose, concretely as the average of the corresponding two values before the morning IP administration. If one value is missing, then the remaining one will be used as the trough value.

Baseline for both variables is defined as the average of the two FEV_1 values just prior to the administration of the first dose of IP at day 1 of treatment. If one of the two values is missing, then the available one will be used as baseline value. If both values are missing, the pre-bronchodilator value (at screening visit) will be used as the baseline value. Otherwise, the baseline value will not be calculated and will be considered missing.

3.2 Secondary efficacy variables

The secondary variables and comparisons are the following:

- Change from baseline in normalized $AUC_{0\text{-}3/3h}$ FEV_1 of AB/FF 400/12 µg compared to AB 400 µg at week 24.
- Change from baseline in normalized $AUC_{0\text{-}3/3h}$ FEV_1 of AB/FF 400/12 µg compared to FF 12 µg at week 24.
- Number (%) of patients achieving a clinically meaningful improvement (≥4-units reduction) from baseline of AB/FF 400/12 µg compared to AB 400 µg in SGRQ total score at week 24.
- Number (%) of patients achieving a clinically meaningful improvement (≥4-units reduction) from baseline of AB/FF 400/12 µg compared to FF 12 µg in SGRQ total score at week 24.

3.3 Primary efficacy variable for market access

The primary variable and comparison for market access is the following:

- Change from baseline in morning pre-dose (trough) FEV_1 at week 24 comparing AB 400 µg BID versus TIO 18 µg to demonstrate non-inferiority

3.4 Pre-specified Sequence of Testing for Multiplicity Adjustment

To control the family-wise type I error due to multiple objectives (multiplicity), the following pre-specified sequence of testing will be applied:

Testing Order in Hierarchy	Variable (at week 24)	Treatment Comparison
1	Change from baseline in 1-hour post-dose FEV_1	AB/FF 400/12 µg vs. AB 400 µg
2	Change from baseline in morning pre-dose FEV_1	AB/FF 400/12 µg vs. FF 12 µg
3	Change from baseline in $nAUC_{0-3}$ FEV_1	AB/FF 400/12 µg vs. AB 400 µg
4	Change from baseline in $nAUC_{0-3}$ FEV_1	AB/FF 400/12 µg vs. FF 12 µg
5	Responder analysis of SGRQ total score (a decrease of at least 4-units from baseline)	AB/FF 400/12 µg vs. AB 400 µg
6	Responder analysis of SGRQ total score (a decrease of at least 4-units from baseline)	AB/FF 400/12 µg vs. FF 12 µg

Note: Both co-primary variables (the first two testing hypothesis) should overcome the statistical hierarchy to meet the primary bronchodilator objective

For the Market Access, the non-inferiority between AB 400 µg and TIO 18 µg in change from baseline in morning pre-dose (trough) FEV_1 at week 24 will be tested at a significance level of 0.05.

3.5 Additional efficacy variables

Set of additional efficacy variables:

- Pulmonary Function Tests (section 4.10.1.)
- Signs and Symptoms and Health-related Quality of Life (section 4.10.2.)
- COPD Exacerbations (section 4.10.3.)
- Daily COPD Symptoms (E-RS) and use of relief medication (section 4.10.4.)
- Night-time and Early morning symptoms (section 4.10.5.)

3.6 Device preference and willingness to continue questionnaire

- Device preference and willingness to continue questionnaire (section 4.1.)

3.7 Safety Variables

- Adverse Events (AEs)/Serious Adverse Events (SAEs) (section 4.12.1., 4.12.2.)
- Cardiac & cerebrovascular disorders, MACE, anticholinergic & pneumonia events (section 4.12.3.)
- Clinical laboratory test (section 4.12.4.) and Hy's Law (section 4.12.5.)
- Blood pressure (section 4.12.6.)
- 12-lead ECG (section 4.12.7.)

4. ANALYSIS METHODS

4.1 General principles

The analysis of all efficacy variables (except for exacerbations) will be performed on the ITT population. The analysis of exacerbations will be performed on the Safety population.

Continuous variables will be summarized with descriptive statistics (the number of non-missing values, mean, standard deviation, median, minimum and maximum. Standard errors, and confidence intervals will be presented where specified in table, figures and listings shells) and all categorical variables will be summarized with frequency counts and percentages, by treatment. Missing data will not be presented with percentages (only with counts) and will not be included in the calculation of percentages of the non-missing categories. Efficacy data obtained during unscheduled visits will not be used.

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

Statistical analyses of demographic, baseline characteristics, efficacy and safety data will be performed by the sponsor. Tables, figures and listings will be compiled in the statistical report and appended to the CSR. Inferential efficacy analysis will go with descriptive values. In particular, those titled "change from baseline" will include descriptive values of the baseline prior the first IP intake, the absolute value at a particular time-point post first IP intake, and the change from baseline at that time-point.

Data processing, descriptive reporting and analysis of the efficacy and safety data will be performed using the SAS® software v. 9.4 or higher.

4.2 Patient disposition

A patient disposition table will show the total number of patients enrolled / screened, and the associated reasons for screen failure. Also, the number of patients randomised will be summarised treatment group and overall. The table will include the number of patients included in both, the Efficacy Estimand (as described in section 4.6.1.), and the Treatment Policy Estimand (as described in section 4.8.), including the following categories:

- Subjects who remain on study treatment and complete the study
- Subjects who remain on study treatment and complete the study, and attend to

the follow-up contact
- Subjects who discontinue study treatment and complete the study
- Subjects who discontinue study treatment and continue to be followed and then prematurely discontinue from the study
- Subjects who prematurely discontinue both treatment and study and provide no data after discontinuation

The number and percentage of patients included in each analysis set (randomised, safety, ITT, and PP) populations will be summarised by treatment group and overall, and along with all causes from exclusion from these populations.

Additionally, inclusion/exclusion screening criteria and the number and percentage of pateints fullfiling each exclusion criteria (by treatment and overall) will be tabulated.

To assess the adherence on IP treatment the analysis of time in days to withdrawal from IP will be analyzed based on a Cox-proportional hazard model adjusted by treatment group. When the discontinuation date is not available, then the last dose taken will be used instead.

4.3 Demographics and other baseline (screening) characteristics

The study population will be described using demographic and baseline characteristics and it will be summarised for the ITT and Safety population.

- Demographic characteristics to be summarised are age, sex, age group ≤65, 66-75, 76-85, >85], race, height, weight, and body mass index (BMI), and BMI category (underweight: <18.5 Kg/m^2; Normal weight: >=18.5 - <25 Kg/m^2; Overweight >=25 - <30 Kg/m^2; Obese: >=30 Kg/m^2).

Screening and baseline characteristics to be summarised include:

- COPD medical history
    - Smoking status (current smoker/former-smoker) and smoking duration in years
        - ❖ The smoking duration (in years) will be calculated for ex-smokers as the difference between the year they stopped smoking and the year they started to smoke +1, and for current smokers as the difference between the year of the screening visit and the year they started to smoke +1.
    - Smoking consumption (number of pack-years)
- Medical history by system organ class (SOC), and preferred term (PT)
- COPD history
    - COPD classification of airflow limitation based on the post-bronchodilator PFT at screening:
        - ❖ Stage I (mild): FEV_1/FVC <0.70 and FEV_1 >=80% predicted
        - ❖ Stage II (moderate): FEV_1/FVC < 0.70 and 50% ≤ FEV_1 < 80% predicted
        - ❖ Stage III (severe): FEV_1/FVC < 0.70 and 30% ≤ FEV_1 < 50% predicted
        - ❖ Stage IV (very severe): FEV_1/FVC <0.70 and FEV_1 <30% predicted

- COPD severity based on GOLD guidelines on symptoms, and risk of exacerbations at screening:
  - A category: CAT (COPD Assessment Test) <10, and exacerbation history in previous 12 months ≤ 1 (not requiring hospitalization)
  - B category: CAT≥10, and exacerbation history in previous 12 months ≤ 1 (not requiring hospitalization)
  - C category: CAT<10, and exacerbation history in previous 12 months ≥2 (or ≥1 if requiring hospitalization)
  - D category: CAT≥10, and exacerbation history in previous 12 months ≥2 (or ≥1 if requiring hospitalization)
- COPD duration (years):
  - Will be computed as the difference between the date of screening visit and the date of first diagnosis of COPD in the EDC.

    COPD duration = (year of screening visit - Year of diagnosis of COPD) + 1
- Number of patients with COPD exacerbations in the previous 12 months

- 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 change and Percentage reversibility in FEV_1:
    - The mean bronchodilator absolute reversibility will be computed as:

      FEV_1(post- albuterol/salbutamol)-FEV_1(pre- albuterol/salbutamol)
    - The percentage of bronchodilator reversibility will be computed as the percentage increase over pre-bronchodilator test value using the following formulae:

$$\frac{FEV_1(\text{post-albuterol/salbutamol}) - FEV_1(\text{pre-albuterol/salbutamol})}{FEV_1(\text{pre-albuterol/salbutamol})} \times 100$$

  - Percentage of patients 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:
  - Pulmonary function tests pre-IP at baseline 1)
    - Absolute values of FEV_1, and FVC
    - Percent of predicted FEV_1, and FVC
  - SGRQ
  - CAT

- Prior medication is discussed in Section 4.5.1.

4.4 Analysis of Study Medication

4.4.1 Exposure to study medication

Exposure to IP for the Safety population during the treatment duration will be summarized. It will be calculated as the number of days from the date of the first dose of IP taken to the date of the last dose taken, inclusive. For those subjects who discontinued and the date of last dose taken is not available, then the discontinuation date will be used instead. Descriptive statistics will be presented by treatment group and overall. Treatment exposure will also be summarized by the following categories: patients (number and percentage) with ≥ 1 day, ≥ 1 week, ≥ 4 weeks, ≥ 12 weeks, ≥ 18 weeks, ≥ 24 weeks of treatment exposure. Patient-years of exposure will be calculated as the sum of the treatment durations for all patients divided by 365.25.

4.4.2 Compliance with study medication

Patients are expected to take two inhalations of Pressair®/Genuair®, one in the morning and one in the evening, plus using one capsule of Handihaler® in the morning.

Schema of IP administration to ensure double-blind trial

Treatment arm	Morning administration	Evening administration
AB 400 µg/FF 12 µg BID	AB/FF 400/12 µg (Pressair®/Genuair®) + placebo to TIO 18 µg (Handihaler®)	AB/FF 400/12 µg (Pressair®/Genuair®)
AB 400 µg BID	AB 400 µg (Pressair®/Genuair®) + placebo to TIO 18 µg (Handihaler®)	AB 400 µg (Pressair®/Genuair®)
FF 12 µg BID	FF 12 µg (Pressair®/Genuair) + placebo to TIO 18 µg (Handihaler®)	FF 12 µg (Pressair®/Genuair®)
TIO 18 µg QD	placebo to AB/FF 400/12 µg, AB 400 µg and FF 12 µg (Pressair®/Genuair®) + TIO 18 µg (Handihaler®)	Placebo to AB/FF 400/12 µg, AB 400 µg and FF 12 µg (Pressair®/Genuair®)

Criterion for non-compliant patients leading to be excluded from the PP population is reported as a protocol deviation in section 2.2. (item 17).

The compliance for Pressair®/Genuair® will be based on the drug accountability form which is based on the dose indicator observed during IP treatment period, by checking the number of inhalations taken. The compliance will be reported overall from first IP dose to last IP dose, i.e. from the date of visit on day 1 to date of last dosing day at week 24 (or discontinuation EOT visit date). Since the Pressair®/Genuair® indicator only shows ranges of the doses remaining and this is the way it is collected in the EDC, the derived value shown in the next table will be used for computation of compliance:

Range specified in EDC: doses remaining (dose used)	Status	Value to derive compliance of doses used
	Empty	64
	In use	0
	Not used	0
65 to 61 (1 to 5)	In use	3 unless patient took only one dose at the clinic and discontinued, where 1 will be imputed.
60 to 56 (6 to 10)	In use	8
55 to 51 (11 to 15)	In use	13
50 to 46 (16 to 20)	In use	18
45 to 41 (21 to 25)	In use	23
40 to 36 (26 to 30)	In use	28
35 to 31 (31 to 35)	In use	33
30 to 26 (36 to 40)	In use	38
25 to 21 (41 to 45)	In use	43
20 to 16 (46 to 50)	In use	48
15 to 11 (51 to 55)	In use	53
10 to 6 (56 to 60)	In use	58
5 to 1 (61 to 65)	In use	63
NA	In use	Missing

The compliance will be calculated as follow:

• Compliance (%) for Pressair®/Genuair® (observed divided by expected number of puffs):

$$C_{\mathrm{P/G}} = \frac{\text{Total number of treatment inhalations of Pressair®/Genuair®}}{\text{Total number of inhalations expected to be taken}} * 100$$

• Compliance (%) for Handihaler® (observed divided by expected number of capsules):

$$C_{\mathrm{H}} = \frac{\text{Total number of capsules used of Handihaler®}}{\text{Total number of capsules expected}} * 100$$

Overall compliance will be calculated as:

$$\frac{C_{\mathrm{P/G}} + C_{\mathrm{H}}}{2}$$

In case of a patient missing entry, the number of puffs/capsules for that entry will be imputed to 0.

Descriptive statistics will be presented by treatment group and overall for the safety population. The table will show the compliance of Pressair®/Genuair®, the compliance of Handihaler®, and the overall compliance as the mean of both devices.

In addition, a subject will be considered treatment-compliant if the compliance rate is greater or equal to 70% in Pressair®/Genuair®, and greater or equal to 70% in

Handihaler®. Number and percentage of patient compliance (yes/no) will be presented by treatment group and overall for the safety population.

4.5 Analyses of prior and concomitant medication

4.5.1 Prior medication

Prior medication will be analysed for the Safety Population in two different ways:

1. Prior medication will be shown as the number of patients taking prior medication and tabulated by Anatomical Therapeutic Chemical 3 code, ATC3 text, (or ATC2 if the ATC3 is missing), preferred name (WHO DRUG Enhanced Extended Herbal March 2016), and by treatment group. Two time periods are defined:

   1.1. Within 15 days prior to the Informed Consent date (ICF)
   1.2. From the ICF date (not included) to the day before the first dose of double-blind investigational product

   If a patient uses more than 1 medication in a particular preferred name, that patient will be counted only once in this preferred name.

2. Prior medication indicated for COPD only will be any medication for COPD taken within 15 days prior to the Informed Consent date, expect for vaccines which refer the year previous the informed consent date. The number of patients taking prior medication for COPD will be grouped and tabulated by treatment group, and by the following therapeutic categories: short-acting β_2 agonists [SABAs]; short-acting muscarinic antagonists [SAMAs]; SABA and ICS combinations; SABA and SAMA combinations; long-acting β2 agonists [LABAs]; long-acting muscarinic antagonists [LAMAs]; LABA and ICS combinations (free and fixed); LABA and LAMA combinations (free and fixed); LAMA and ICS free; and triple combinations (LABA and LAMA and ICS in any kind of combination or free); inhaled corticosteroids [ICSs]; systemic corticosteroid; xanthines; leukotriene modifiers; oxygen; oral phosphodiesterase type 4 [PDE4]; influenza vaccine. Those patients included in fixed or free combinations will not appear in the monotherapies; e.g. if a patient is taking LABA and LAMA as free combination will not be counted in the LABA and LAMA categories alone.

4.5.2 Concomitant medication

Concomitant medication is defined as any medication taken during the double-blind treatment duration between the date of the first dose of study drug and the date of the last dose of study drug. Any medications started the date or after the date of the last dose of double-blind study drug will not be considered concomitant medications.

Concomitant medications will be analysed based on two periods: 1) medications that the patient started to take before the first IP intake and continued after the first study drug administration, and 2) medications that the patient started to take during the double-blind treatment duration.

Number and percentage of patients taking concomitant medication will be summarised overall, and by ATC3 text (or ATC2 if the ATC3 is missing), preferred name, and treatment group for each period. If a patient uses more than 1 medication in a particular preferred name, that patient will be counted only once in this preferred name.

Concomitant medication reported during the EOT or EOS visit date will not be taken into account.

Tables will be sorted in ATC3 alphabetical order and by preferred name within ATC3 in decreasing frequency in AB/FF 400/12 µg treatment group.

Concomitant medication will be summarised for the Safety Population.

4.5.3 Sensitivity analysis of concomitant medication

Following the treatment policy estimand (as defined in section 4.8.), cumulated concomitant medication data up to week 24 o EOS visit will be collected. The same analysis specified in the section 4.5.2. will be done.

4.6 Analysis of co-primary variables for US

Efficacy Estimand: The efficacy estimand quantifies the difference in outcomes for all subjects as if they continued on their initially randomized treatment. The efficacy estimand includes data collected up until the time of discontinuation from IP study treatment. It consists on spirometry data from scheduled visits obtained during the study period of 24 weeks of treatment, or up to the end of IP treatment visit for patients who withdrawn (data at EOT visit not included). Thus, the main analysis does not include spirometry data of the post-IP discontinuation follow-up period (but see the sensitivity analysis in section 4.8. including a new estimand based on treatment policy). This analysis will be carried out under the randomized treatment assignment, and missing data will be modelled using direct likelihood approaches under missing-at-random (MAR) assumptions. This estimand was already used to assess the contribution of each monotherapy to the aclidinium/formoterol combination in prior phase 3 clinical studies M/40464/30 and LAC-MD-31. Therefore keeping the same estimand is considered appropriate to be able to assess whether a closer difference (<10%) in aclidinium fine particle dose between the monotherapy and combination arm will have an influence on the contribution effect of formoterol to the aclidinium/formoterol combination.

4.6.1 Hypothesis testing

The co-primary variables and comparisons are:

- Change from baseline in 1-hour morning post-dose dose FEV_1 of AB/FF 400/12 µg compared to AB 400 µg at week 24.
- Change from baseline in morning pre-dose (trough) FEV_1 of AB/FF 400/12 µg compared to FF 12 µg at week 24.

For co-primary variables, the null (H_0) and alternative (H_a) hypotheses with µ representing the true mean are:

H_0: µ(AB/FF 400/12 µg) - µ(AB 400 µg) = 0 for change from baseline in 1h morning post-dose FEV_1 at week 24

H_a: µ(AB/FF 400/12 µg) - µ(AB 400 µg) ≠ 0;

H_0: µ(AB/FF 400/12 µg) - µ(FF12 µg) = 0 for change from baseline in morning pre-dose (trough) FEV_1 at week 24

H_a: µ(AB/FF 400/12 µg) - µ(FF12 µg) ≠ 0

The analyses of the co-primary variables will be performed using the efficacy estimand, and using the ITT population.

The co-primary efficacy variables, change from baseline in 1-hour morning post-dose FEV_1, and change from baseline in morning pre-dose (trough) FEV_1 at week 24 will be analyzed by means of mixed model for repeated measures (MMRM), adjusted for pre and post bronchodilator (albuterol/salbutamol) FEV_1 at screening visit, age, and baseline FEV_1 as covariates, and treatment group [AB FF 400/12/AB 400/FF 12/TIO 18], sex [male/female], smoking-status [current/ex-smokers], visit [Day 1, week 4, week 12, week 18 and week 24 for 1-h post-dose FEV_1; and week 1, week 4, week 12, week 18, and week 24 for trough FEV_1], and treatment group-by-visit interaction as fixed effect factors, and country [Bulgaria/Czech Republic/Germany/Hungary/Israel/Poland/Spain/Ukraine/UK/US] as random intercept (Appendix 1).

An unstructured covariance pattern will be used to estimate the variance-covariance of the within-subject repeated measures, i.e., R-side effects, and a G-side diagonal matrix for the random intercept. Parameters will be estimated using REML with Newton-Raphson algorithm and using the Kenward-Roger method for calculating the denominator degrees of freedom.

In case of the statistical model does not convergence, the compound symmetry covariance pattern will be used.

Each treatment effect and treatment differences between all treatments will be estimated by the Least Square means (LS Means) on the treatment-by-visit interaction at week 24, along with their standard errors (SE) and two-sided 95% confidence intervals (CI), and the p-value corresponding to the between-treatment group difference. Statistical comparisons will be two sided hypothesis tests, and the significance level will set at 0.05. P-values will be reported as two-sided.

All treatment effects and treatment differences will be performed on co-primary variables, although the most relevant ones are those described in the hypothesis testing, which in turn are included in the multiplicity adjustment strategy (and all other treatment differences will be exploratory only). Therefore, treatment comparisons are as follow:

- AB/FF 400/12 µg vs. AB 400 µg
- AB/FF 400/12 µg vs. FF 12 µg
- AB/FF 400/12 µg vs. TIO 18 µg
- AB 400 µg vs. TIO 18 µg

SAS outputs will be provided for co-primary efficacy variables.

4.7 Analysis of secondary variables

The efficacy estimand assumption will be also used for secondary variables.

4.7.1 Hypothesis testing

The secondary variables and comparisons are:

- Change from baseline in normalized $AUC_{0\text{-}3/3h}$ FEV_1 of AB/FF 400/12 µg compared to AB 400 µg at week 24.
- Change from baseline in normalized $AUC_{0\text{-}3/3h}$ FEV_1 of AB/FF 400/12 µg compared to FF 12 µg at week 24.
- Number (%) of patients achieving a clinically meaningful improvement (a decrease of at least 4 units from baseline) of AB/FF 400/12 µg compared to AB 400 µg in SGRQ total score at week 24 (Appendix 2).
- Number (%) of patients achieving a clinically meaningful improvement (a decrease of at least 4 units from baseline) of AB/FF 400/12 µg compared to FF 12 µg in SGRQ total score at week 24 (Appendix 2).

For secondary variables, the null (H_0) and alternative (H_a) hypotheses are:

H_0: µ(AB/FF 400/12 µg) - µ(AB 400 µg) = 0 for change from baseline in normalized $AUC_{0\text{-}3/3h}$ FEV_1 at week 24

H_a: µ(AB/FF 400/12 µg) - µ(AB 400 µg) ≠ 0;

H_0: µ(AB/FF 400/12 µg) - µ(FF12 µg) = 0 for change from baseline in normalized $AUC_{0\text{-}3/3h}$ FEV_1 at week 24

H_a: µ(AB/FF 400/12 µg) - µ(FF12 µg) ≠ 0

H_0: Odds ratio (AB/FF 400/12 µg vs. AB400 µg) = 1 for percentage of patients achieving a clinically meaningful improvement (>= 4 units) compared to baseline in the SGRQ total score at week 24

H_a: Odds ratio (AB/FF 400/12 µg vs. AB400 µg) ≠ 1;

H_0: Odds ratio (AB/FF 400/12 µg vs. FF12 µg) = 1 for percentage of patients achieving a clinically meaningful improvement (>= 4 units) compared to baseline in the SGRQ total score at week 24

H_a: Odds ratio (AB/FF 400/12 µg vs. FF12 µg) ≠ 1

The same MMRM model used for the co-primary variables will be used for the change from baseline in normalized $AUC_{0\text{-}3}$ FEV_1 at week 24.

The number (%) of patients achieving a clinically meaningful improvement (a decrease of at least 4-units from baseline) compared to monotherapies in the SGRQ total score will be analyzed based on a logistic random-effect model using GLIMMIX that includes a random intercept to account the variability between subjects, and treatment, sex, smoking-status, country, visit, and treatment group-by-visit interaction as fixed factors, and with age and baseline as covariate.

Odds ratios between treatments groups will be estimated on the treatment-by-visit interaction at week 24, along with their SE, 95% CI, and 2-sided p-values.

All treatment effects and treatment differences performed for co-primary variables will be also performed on secondary variables, although the most relevant ones are those described in the hypothesis testing, which in turn are included in the multiplicity adjustment strategy (and all other treatment differences will be exploratory only).

SAS outputs will be provided for secondary efficacy variables.

4.8 Sensitivity analysis for co-primary and secondary variables

Sensitivity analyses will be conducted to evaluate the robustness to variations of the missing data assumptions on the co-primary and secondary efficacy variables.

1. Sensitivity analysis based on the efficacy estimand:

1.1. Co-primary and secondary variables will descriptively analyzed by reason of withdrawal.

1.2. Copy Reference (CR) approach:
For co-primary (1-hour post-dose FEV_1, and trough FEV_1) and secondary variables ($nAUC_{0\text{-}3}$ FEV_1), a sensitivity analysis will be performed under Missing-Not-At-Random (MNAR) assumption. The analysis will be performed to compare AB/FF 400/12 µg versus AB 400 µg in the change from baseline in 1h morning post-dose FEV_1 at week 24, considering MNAR assumption that patients from the AB/FF 400/12 µg treatment arm behave as patients from the AB 400 µg after drop-out, so patients who withdraw from AB/FF 400/12 µg arm will be imputed as if they were a member of the AB 400 µg. The CR approach described by Michael O'Kelly and Ratitch Bohdana will be used. Using regression models, multiple datasets (N=20) will be created/imputed under a monotone missing approach for each treatment, and implemented via sequential modelling using SAS proc MI, where the imputation process will be done visit-by-visit (non-monotone "holes" are imputed based on MCMC). Then, for each imputed dataset, the same MMRM used in the main analysis (section 4.6.1.) will be adjusted so that the estimates/inference of this analysis can be compared with the original one. Finally, the results of the multiple datasets will be combined using the SAS proc MIANALYZE to obtain the estimation of the treatment effect and treatment comparison we are looking for. The same CR approach will be used to compare AB/FF 400/12 µg versus FF 12 µg in change from baseline in morning pre-dose (trough) FEV_1 at week 24; and to compare AB/FF 400/12 µg versus AB 400 µg and FF 12 µg in change from baseline in normalized $AUC_{0\text{-}3/3h}$ at week 24. Reference categories will be the monotherapies.

1.3. Responder analysis of SGRQ:
Sensitivity analysis for percentage of patients achieving a clinically meaningful improvement (>= 4-units reduction) compared to baseline in the SGRQ total score at week 24 when comparing AB/FF 400/12 µg versus AB 400 µg and FF

12, will be done using the same statistical models described in section 4.7.1., but considering all missing data as non-responder.

2. Sensitivity analysis based on a Treatment Policy Estimand:

The treatment policy estimand quantifies the difference in outcomes for subjects randomized to the IP study treatments, regardless of the treatments that subjects actually received. Includes data collected after discontinuation of IP study treatment. Thus, it consists on all data of entire study period (24-weeks) regardless if the patient was on study treatment or off study treatment, or until the end of study (EOS) visit, i.e., including all data regardless of whether study treatment was prematurely discontinued, or delayed, and/or irrespective of protocol adherence, unless the patient withdraws consent to study participation. Patients discontinuing the IP before week 24 and willing to continue in the study, will perform the EOT visit, and start a post-IP follow-up period according to the planned visit schedule, which include spirometry assessments. From the EOT visit until EOS visit patients will return to appropriate maintenance COPD medications as per the investigators discretion.

This analysis will be carried out under the randomized treatment assignment, and missing data will be modelled using direct likelihood approaches under missing-at-random (MAR) assumptions. The same statistical models used for both co-primary and secondary variables will be adjusted (except for AUC 0-3h, because, after discontinuation, at subsequent scheduled visits, we only collect spirometry data pre-treatment and and 1h post-treatment).

4.9 Primary efficacy variable for market access (non-inferiority)

The efficacy estimand assumption will be also used for market access.

4.9.1 Hypothesis testing

For market access, the null (H_0) and alternative (H_a) hypotheses are:

$$\begin{cases} H_0\text{: AB 400 µg - TIO 18 µg} \leq \text{-50 mL for change from baseline in morning pre-dose (trough) } FEV_1 \text{ at week 24} \\ H_a\text{: AB 400 µg - TIO 18 µg} > \text{-50 mL} \end{cases}$$

Non-inferiority will be established by showing that the lower bound of the two-sided 95% confidence interval for change from baseline in morning pre-dose (trough) FEV_1 at week 24 when comparing AB 400 µg vs. TIO 18 µg is higher than -50 mL (non-inferiority limit).

The comparison between AB 400 µg and TIO 18 µg in change from baseline in morning pre-dose (trough) FEV_1 at week 24 will be analysed by means of mixed model for repeated measures (MMRM). The model will adjust for pre and post bronchodilator (albuterol/salbutamol) FEV_1 at screening visit, age, and baseline FEV_1 as covariates, and treatment group, sex, smoking-status, visit, and treatment group-by-visit interaction as fixed effect factors, and country as random effect.

An unstructured covariance pattern will be used to estimate the variance-covariance of the within-subject repeated measures. Parameters will be estimated using REML with

Newton-Raphson algorithm and using the Kenward-Roger method for calculating the denominator degrees of freedom.

In case of the statistical model does not convergence, the compound symmetry covariance pattern will be used.

All treatment effects and treatment differences performed for co-primary variables will be shown, though we are interested in the treatment difference between AB 400 µg and TIO 18 µg at week 24, estimated by the Least Square means (LS Means) on the treatment-by-visit interaction at week 24, along with its standard error (SE), and two-sided 95% CI.

4.10 Analysis of additional efficacy variables

The efficacy estimand assumption will be also used for all additional variables.

In this case, no multiplicity adjustment for the control of family-wise type I error will be applied for the analysis of additional efficacy variables. All treatment differences will be reported as shown for the co-primary variables.

4.10.1 Pulmonary Function Tests

Onset of action will be analysed using ANCOVA models adjusting by pre and post-bronchodilator (salbutamol) FEV_1 at screening visit, age, and baseline FEV_1 as covariates, and treatment group, sex, smoking-status as fixed effect factors, and country as random intercept.

- Change from baseline in FEV_1 5 minutes after the first dose on day 1 (onset of action).
- Change from baseline in FEV_1 15 minutes after the first dose on day 1 (onset of action).

Additional pulmonary function tests, either change from baseline or absolute values will be analysed by using the same MMRM as applied to co-primary variables. Each treatment effect and treatment differences will be estimated by the Least Square means (LS Means) on the correspondent treatment-by-visit interaction. In addition, one MMRM model by time-point will be applied to change from baseline and absolute values. The additional pulmonary function tests are:

- Change from baseline in FEV_1 and FVC by visit and time-point at all visits.
- FEV_1 and FVC by visit and time-point at all visits.
- Change from baseline in morning pre-dose FEV_1 and FVC at all visits (weeks 1, 4, 12, 18, 24).
- Morning pre-dose FEV_1 and FVC at all visits (weeks 1, 4, 12, 18, and 24).
- Change from baseline in peak FEV_1 and FVC at day 1 and weeks, 12 and 24 (defined as the highest value observed in the 3-h period immediately after the morning IP administration).
- Change from baseline in normalised area under curve from time 0 to 3 hours ($AUC_{0-3/3h}$) FEV_1 and FVC at day 1 and weeks 12, and 24.

- Subset of patients: Change from baseline in FEV_1 and FVC by time-point at all visits.
- Subset of patients: Change from baseline in normalised area under curve from time 0 to 12 hours ($AUC_{0\text{-}12h}$) FEV_1 and FVC at day 1 and week 24.
- Subset of patients: Change from baseline in normalised area under curve from time 12 to 24 hours ($AUC_{12\text{-}24h}$) FEV_1 and FVC at day 1 and week 24.
- Subset of patients: Change from baseline in normalised area under curve from time 0 to 24 hours ($AUC_{0\text{-}24h}$) FEV_1 and FVC at day 1 and week 24.

The normalised $AUC_{0\text{-}3h}$, $AUC_{0\text{-}12h}$, $AUC_{12\text{-}24h}$, and $AUC_{0\text{-}24h}$ of FEV_1, and FVC will be calculated by means of the trapezoidal method.

Spirometric baseline values for FEV_1 and FVC will be calculated as the average of the two spirometric values just prior to the administration of the first dose of IP at day 1 of treatment. If one of the two values is missing, then the available one will be used as baseline value. If both values are missing, the pre-bronchodilator value (at screening visit) will be used as the baseline value. Otherwise, the baseline value will not be calculated and will be considered missing.

Normalized $AUC_{0\text{-}3}$:

For $AUC_{0\text{-}3h}$ assessment, the following criteria are required: 1) at least one available pre-IP PFT value (on Day 1, the pre-bronchodilator value if both pre-IP PFT values are missing); 2) at least one PFT value between 2h and 3h post-dose (inclusive);

$$\frac{1}{t_{6\ or\ 4} - t_0} \sum_{i=1}^{6\ or\ 4} \frac{(t_i - t_{i-1})(d_i + d_{i-1})}{2}$$

Where d_i is the spirometric value (i.e., FEV_1 or FVC) obtained at time t_i; t_i is the time (in hours) for which d_i is measured; d_0 is calculated as the average of both pre-IP time-points (or the pre-bronchodilator value if both pre-IP are missing);

At day 1, $t_0 = 0$, $t_1 = 0.083$, $t_2 = 0.25$, $t_3 = 0.5$, $t_4 = 1$, $t_5 = 2$, $t_6 = 3$.

For the rest of the visits, $t_0 = 0$, $t_1 = 0.5$, $t_2 = 1$, $t_3 = 2$, $t_4 = 3$.

Normalized $AUC_{0\text{-}12}$:

For $AUC_{0\text{-}12h}$ assessment, in addition to the two criteria specified for the $AUC_{0\text{-}3h}$, 3) at least one PFT value after 6h (not inclusive) post-dose should be available;

$$\frac{1}{t_{11\ or\ 9} - t_0} \sum_{i=1}^{11\ or\ 9} \frac{(t_i - t_{i-1})(d_i + d_{i-1})}{2}$$

Where d_i is the spirometric value (i.e., FEV_1 or FVC) obtained at time t_i; t_i is the time (in hours) for which d_i is measured; d_0 is calculated as the average of both pre-IP time-points (or the pre-bronchodilator value if both pre-IP are missing); and,

At day 1, $t_0 = 0$, $t_1 = 0.083$, $t_2 = 0.25$, $t_3 = 0.5$, $t_4 = 1$, $t_5 = 2$, $t_6 = 3$, $t_7 = 4$, $t_8 = 6$, $t_9 = 9$, $t_{10} = 12$.

For the rest of the visits, $t_0 = 0$, $t_1 = 0.5$, $t_2 = 1$, $t_3 = 2$, $t_4 = 3$, $t_5 = 4$, $t_6 = 6$, $t_7 = 9$, $t_{10} = 12$

Normalized $AUC_{12\text{-}24}$:

For $AUC_{12\text{-}24h}$ assessment, the following criteria are required: 1) the PFT value between 10 and 12h pre-evening dose; 2) at least one PFT value between 12.5 and 14h; 3) at least one PFT value between 22h and 24h (inclusive);

$$\frac{1}{t_6 - t_0} \sum_{i=1}^{6} \frac{(t_i - t_{i-1})(d_i + d_{i-1})}{2}$$

Where D_i is the spirometric value (i.e., FEV_1 or FVC) obtained at time t_i. t_i is the time (in hours) for which d_i is measured; And, $t_0 = 12$, $t_1 = 12.5$, $t_2 = 13$, $t_3 = 14$, $t_4 = 22$, $t_5 = 23.5$, $t_6 = 24$.

Normalized $AUC_{0\text{-}24}$:

For $AUC_{0\text{-}24h}$ assessment, it is required to fulfil all criteria specified in the previous AUCs calculations;

$$\frac{1}{t_{17\ or\ 15} - t_0} \sum_{i=1}^{17\ or\ 15} \frac{(t_i - t_{i-1})(d_i + d_{i-1})}{2}$$

Where d_i is the spirometric value (i.e., FEV_1 or FVC) obtained at time t_i; t_i is the time (in hours) for which d_i is measured; d_0 is calculated as the average of both pre-IP time-points (or the pre-bronchodilator value if both pre-IP are missing);

At day 1, $t_0 = 0$, $t_1 = 0.083$, $t_2 = 0.25$, $t_3 = 0.5$, $t_4 = 1$, $t_5 = 2$, $t_6 = 3$, $t_7 = 4$, $t_8 = 6$, $t_9 = 9$, $t_{10} = 12$, $t_{11} = 12.5$, $t_{12} = 13$, $t_{13} = 14$, $t_{14} = 22$, $t_{15} = 23.5$, $t_{16} = 24$

For the rest of the visits, $t_0 = 0$, $t_1 = 0.5$, $t_2 = 1$, $t_3 = 2$, $t_4 = 3$, $t_5 = 4$, $t_6 = 6$, $t_7 = 9$, $t_8 = 10$, $t_9 = 12$, $t_{10} = 12.5$, $t_{11} = 13$, $t_{12} = 14$, $t_{13} = 22$, $t_{14} = 23.5$, $t_{15} = 24$

All treatment effects and treatment difference combinations will be shown, as specified for co-primary variables.

4.10.2 Symptoms and Health-related Quality of Life

Change from baseline in SGRQ (Appendix 2) and CAT (Appendix 3) will be analysed by using the same mixed models as applied for co-primary variables, but using the appropriate baselines but removing pre and post bronchodilator covariates. Each treatment effect and treatment differences will be estimated by the Least Square means (LS Means) on the correspondent treatment-by-visit interaction.

- Change from baseline in SGRQ total score and three dimension scores at weeks 4, 12, 18 and 24.
- Change from baseline in the CAT score at weeks 4, 12, 18 and 24.

The number (%) of patients achieving a clinically meaningful improvement in SGRQ and CAT will be analysed using the same logistic random-effect model as applied for secondary responder variables, using the corresponding baselines. Odds ratios will be estimated on the correspondent treatment-by-visit interaction.

- Number (%) of patients achieving a clinically meaningful improvement (a decrease of at least 4 units from baseline) in SGRQ total score at Weeks 4, 12, 18 and 24. [Note that total score at week 24 is already defined as a secondary variable]
- Number (%) of patients achieving a clinically meaningful improvement (MCID, ≥2 units decrease) in CAT total score at weeks 4, 12, 18 and 24.

All treatment effects and treatment difference combinations will be shown.

4.10.3 COPD Exacerbations

We will consider on-treatment IP COPD exacerbation events which start during the period from the first IP dose to the last IP dose.

The following variables will be analysed based on Health Resource Utilization (HCRU) definition (worsening of symptoms requiring a change in COPD treatment and/or hospitalization and/or emergency room treatment):

- Frequency distribution of COPD exacerbations (any, mild, moderate, severe, and moderate to severe)
- Number (%) of patients with at least one COPD exacerbation (any, mild, moderate, severe, and moderate to severe)
- Number of COPD exacerbations (any, mild, moderate, severe, and moderate to severe)
- Rate of COPD exacerbations per patient/year (any, mild, moderate, severe, and moderate to severe). The descriptive rate of COPD exacerbations per patient/year will be calculated by dividing the total number of exacerbations for a patient by time on study (in years). For patients having no exacerbations, the exacerbations will be assigned to 0.
- Duration (days) of the COPD exacerbations (any, and moderate to severe). The duration (days) of COPD exacerbations is computed as the interval in days from the stop date to the start date of a COPD exacerbation, plus 1 day. Totally or partially missing start and stop dates will be imputed as per rules of Section 4.14.1.3.

See Section 14.4.2.3. for the definition of a relapse of an exacerbation.

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

The time (days) to first COPD exacerbation is computed as the time elapsed from the first IP intake date to the exacerbation starting date (non-censored data) or date of last IP administration whatever occurs first (censored data). If date of last IP administration is missing (the patient drops-out from the trial) then the discontinuation date will be used, however if the patient completes the study, week 24 date will be used.

Derived from the EXACT questionnaire (Appendix 4):

- Frequency distribution of COPD exacerbations
- Number (%) of patients with at least one COPD exacerbation

- Number of COPD Exacerbations
- Rate of COPD exacerbations per patient/year
- Duration (days) of the COPD exacerbations
- Time (days) to first COPD exacerbation

The frequency distribution of COPD exacerbations will be analysed descriptively.

The number of patients with at least one COPD exacerbation will be analysed descriptively, and by means of a logistic regression model including age as a covariate, and sex, 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/ex-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.

The mean number of COPD exacerbations will be analysed descriptively.

The rate of COPD exacerbations per years of exposure will be analysed and by means of negative binomial (NB) regression models including age as a covariate, and sex, 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/ex-smokers), country, prior history of exacerbation over 12 months before randomization (yes/no), treatment group as factors, and the offset.

The offset will be calculated as the IP exposure time (as defined in Section 4.4.1) minus the sum of the duration (in days) of all COPD exacerbation episodes, plus 1 day, and then transformed to years and expressed on the logarithmic scale. The duration of a COPD exacerbation episode will be calculated as the stop minus the start date, plus 1 day. If the start date of an event is partially missing, then the rules specified in the section 4.14.1.6. will be applied; however, if the stop date of an episode is "unknown/ongoing" or totally missing, or if it is known but beyond the last IP dose (e.g. a patient who discontinues the IP but remains in the study), then the date of the last IP dose will be used to calculate the offset. Specific rules about how to impute stop dates which are totally missing are detailed in Section 4.14.1.3.

If the NB regression model does not converge, the Poisson regression model with robust variance estimate using sandwich method will be applied. A scale parameter will be included to take overdispersion into account in fitting Poisson regression model. This would be a similar SAS GENMOD model to the one used for the Negative Binomial, but will specify Poisson as the distribution and include a scale parameter (DSCALE).

Rate ratios will be calculated with the corresponding 95% CI and p-values. In addition, rate differences and number needed to treat (NNT) to avoid one exacerbation per patient per year will be calculated with the corresponding 95% CI. To calculate the confidence interval for NNT, first, the variance-covariance matrix (Ω) for the log-scaled rates is calculated from standard errors for least-squares means and the difference estimated from regression model; next, the variance-covariance matrix (Σ) for the exacerbation rates of two treatment groups is derived from Ω using the Delta-method; finally, the variance for difference of exacerbation rates between two treatment groups is calculated using variance-covariance matrix Σ for rates, and the 95% confidence interval for rate

difference is constructed based on Σ, assuming estimated exacerbation rates are normally distributed. The confidence interval for NNT is the reciprocal of the confidence interval for rate difference. When the upper bound of the confidence interval of NNT is negative it will be left missing.

The duration (days) of the COPD exacerbations (any, and moderate-to-severe) will be descriptively analysed.

Time (days) to first COPD exacerbation will be analysed through Cox Proportional Hazard model including age as a covariate, and sex, 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/ex-smokers), country, prior history of exacerbation over 12 months before randomization (yes/no), and treatment group as factors. Kaplan-Meier survival curves for moderate-to-severe exacerbations will be displayed for each treatment.

All treatment effects and exacerbation rate (or treatment differences) combinations between treatment groups will be shown, as specified for co-primary variables.

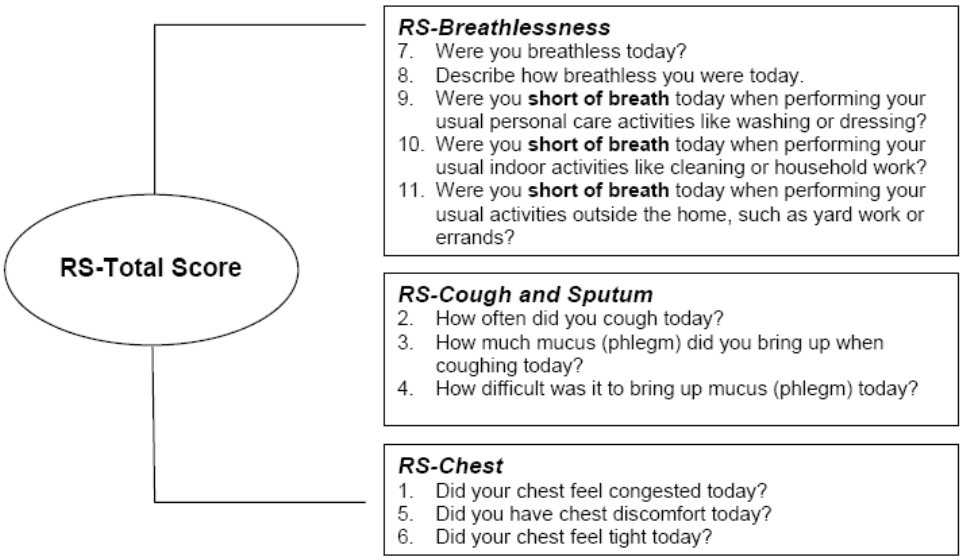
4.10.4 Sensitivity analysis of COPD exacerbations (HCRU & EXACT)

The treatment policy estimand assumption will be used for analysing cumulated exacerbations events up to week 24 (regardless if the patient was on IP or not) or EOS visit. Same analyses specified in the previous section will be done. We will consider on-study COPD exacerbation events starting during the period from the first IP dose to EOS/Week 24 date (the first on occurring).

For the inferential analysis of the rate of COPD exacerbations, the offset will be calculated as the exposure time (number of days from Day 1 to Week 24 or EOS visit) minus the sum of the duration of all COPD exacerbation episodes, plus 1 day, and then transformed to years and expressed on the logarithmic scale. The duration of a COPD exacerbation episode will be calculated as stop minus start exacerbation dates, plus 1 day. If the start and/or stop date of an event is partially missing, then the rules specified in section 4.14.1.6. will be applied; however, if the stop date of an episode is "unknown/ongoing" or totally missing, or if it is known but beyond the EOS/Week 24, then the date of the EOS/Week 24 will be used to calculate the offset. Specific rules about how to impute totally missing stop dates are detailed in Section 4.14.1.3.

4.10.5 Daily COPD Symptoms (E-RS)

The EXACT-Respiratory Symptoms (E-RS) scale was designed to address the need for a daily diary for evaluating the effect of treatment on the severity of respiratory symptoms in stable COPD. Patient's COPD symptoms (Patient Reported Ouctomes, PRO) can be obtained through 3 domain scores embedded within the EXACT: E-RS Breathlessness, E-RS Cough and Sputum, and E-RS Chest Symptoms. An E-RS Total score is computed for each day of diary collection.



A daily E-RS total score can be obtained by first recoding the item responses (completed by patients each evening, prior to bedtime) using the raw score assignments found below in Appendix 5 and taking the sum of the 11 items (range from 0 to 40).

In addition to this single total score, the domain scores based on the factor structure of the tool can be derived by summing each of the items in the respective domain: E-RS breathlessness is the sum of items 7, 8, 9, 10, and 11 (score range 0-17); E-RS cough & sputum is the sum of items 2, 3, 4 (score range 0-11), and E-RS chest is the sum of items 1, 5, 6 (score range 0-12).

The following variables (based on daily e-diary evening answers) will be analysed:

- Change from baseline in E-RS total score and breathlessness, cough & sputum and chest domains at all visits and over 24 weeks.
- Responder analysis: Number (%) of patients with a clinically meaningful improvement in E-RS total score, and by domain at all visits.

Descriptive statistics will be presented by treatment group at baseline and at scheduled visits at weeks 4, 12, 18, and 24, and overall over the study period.

For each patient, all non-missing data comprised between two consecutive (non-skipped) scheduled visits (ending the night before the scheduled visit) will be included (or between a visit and the last IP date, if a patient withdrawn). Overall period is defined as a period between first dose and last IP dose.

E-RS daily COPD symptoms for each period (visit or overall) will be derived as the average scores reported during this period per number of days with non-missing responses in e-diary. 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 divided by the total number of days with non-missing values reported that week. Baseline values will be computed only for those patients recording at least 4 diary entries during this period.

Change from baseline in E-RS daily COPD symptoms will be analysed by means of MMRM models (at the same scheduled visits) adjusting by baseline (E-RS) and age as covariates, and treatment group, sex, smoking-status, visit, and treatment-by-visit

interaction as fixed effect factors, and country as random intercept. An unstructured covariance pattern will be used to estimate the variance-covariance of the within-subject repeated measures, In case of the statistical model does not convergence, the compound symmetry covariance pattern will be used.

A figure showing change from baseline in E-RS total score will be drawn by week, using the same MMRM model but substituting the factors visit, and treatment-by-visit interaction by week and treatment-by-week interaction.

Responder analyses of change from baseline in daily total E-RS scores (breathlessness, cough and sputum, chest, and total) will be analysed using logistic random-effect models using GLIMMIX (all treatment visits are included in the statistical model) based on the following MCIDs:

- E-RS-Total ≤ -2.0 (scale range: 0-40) [this is a reduction from baseline of at least 2-units]
- E-RS-Breathlessness ≤ -1.0 (scale range: 0-17)
- E-RS-Cough and Sputum ≤ -0.70 (scale range 0-11)
- E-RS-Chest Symptoms ≤ -0.70 (scale range: 0-12)

The same statistical model used for the secondary variables based on responder analysis will be adjusted (with the corresponding E-RS baselines).

Treatment effect and treatment differences of all these analysis will be estimated by the LS Means, odds ratios for responder analysis, on the correspondent treatment-by-visit interaction. All treatment effects and treatment difference combinations will be shown, as specified for co-primary variables.

4.10.6 Use of relief medication

For the number of puffs of relief medication, the following question is answered daily by patients (based also on daily e-diary evening answers): *How many puffs of relief medication (albuterol/salbutamol) have you inhaled in the last 24 hours (from yesterday when you went to bed until now)?*

Therefore, the following variable will be analysed:

- Change from baseline in the use of relief medication at all visits and over 24 weeks.

The same descriptive analysis and MMRM inferential model specified for daily COPD symptoms (E-RS) will adjusted for the use of relief medication (using the same covariates and factors, but with the corresponding number of puffs as baseline). Same baseline definition described for E-RS will be used.

4.10.7 Night-time and Early Morning Symptoms (NiSCI & EMSCI)

A daily PRO diary questionnaire of night-time and early morning symptoms of COPD will be recorded by patients in the e-diary (Appendix 6). This questionnaire is answered every morning, and is about the presence and severity of cough, wheezing, shortness of breath (breathlessness), tightness, chest congestion, and phlegm (expectoration) at night and early morning; nocturnal awakenings; and activities limitation in the early morning.

The following variables will be analysed:

NiSCI:

- Change from baseline in the average number of times a patient woke up during a night because of COPD Symptoms
- Change from baseline in the average rating of the night cough severity
- Change from baseline in the average rating of the night wheezing severity
- Change from baseline in the average rating of the night shortness of breath severity
- Change from baseline in the average rating of the night tightness chest severity
- Change from baseline in the average rating of the night chest congestion severity
- Change from baseline in the average rating of the night difficulty bringing up phlegm severity
- Change from baseline in the average rating of overall night-time COPD symptom severity

EMSCI:

- Change from baseline in the average rating rating of the early mornings cough severity
- Change from baseline in the average rating of the early mornings wheezing severity
- Change from baseline in the average rating of the early mornings shortness of breath severity
- Change from baseline in the average rating of the early mornings tightness chest severity
- Change from baseline in the average rating of the early mornings chest congestion severity
- Change from baseline in the average rating of the early mornings difficulty bringing up phlegm severity
- Change from baseline in the average rating of overall early mornings COPD symptom severity
- Change from baseline in the average rating of COPD symptoms limiting early morning activities

For each patient, all non-missing data comprised between two consecutive (non-skipped) visits will be used for analysis (or between a visit and the date of discontinuation, if a patient withdrawn). Overall period is defined as a period between first dose and last IP dose.

Baseline is defined as the 7-day interval ending the day of the first dose of double-blind IP dose. Baseline values will be computed only for those patients recording at least 4 diary entries during this period. The denominator will be based on the number of days with available data.

These are the data conventions which will apply to both night-time and early morning symptoms:

- ✓ The change from baseline in the average number of times a patient woke up because of COPD symptoms for each period (visit or overall) will be derived as the average scores reported during this period per number of days with non-missing responses in e-diary.
- ✓ The change from baseline in the average ratings of the cough, wheezing, shortness of breath, tightness, chest congestion, difficulty bringing up phlegm, and overall COPD symptom severity will be calculated as the mean scores for each period (visit or overall) per number of days with non-missing responses in e-diary, and having into account the following categorization:
  - o I did not experience any symptom = 0
  - o Mild = 1
  - o Moderate = 2
  - o Severe = 3
  - o Very Severe = 4
- ✓ The change from baseline in the average rating of COPD symptoms limiting early morning activities which is categorized as Not at all, A little, Moderately, A good deal, and A very great deal, will be calculated having into account the following transformation:
  - o Not at all = 0
  - o A little = 1
  - o Moderately = 2
  - o A good deal = 3
  - o A very great deal = 4

Descriptive statistics will be presented by treatment group at baseline and at scheduled visits at weeks 4, 12, 18, and 24, and overall over the study period.

Daily diary questionnaires will be analyzed by means of MMRM models (at the same scheduled visits) adjusted for age, and baseline as covariates, and treatment group, sex, smoking-status, visit, and treatment group-by-visit interaction as fixed effect factors, and country as random intercept. An unstructured covariance pattern will be used to estimate the variance-covariance of the within-subject repeated measures, In case of the statistical model does not convergence, the compound symmetry covariance pattern will be used.

Treatment effect and treatment differences of all these analysis will be estimated by the LS Means, odds ratios for responder analysis, on the correspondent treatment-by-visit interaction. All treatment effects and treatment difference combinations will be shown.

Change from baseline in the average rating of overall night-time COPD symptom severity, and change from baseline in the average rating of overall early mornings COPD symptom severity will be drawn by week, using the same MMRM model but substituting the factors visit, and treatment-by-visit interaction by week and treatment-by-week interaction.

4.11 Device preference and willingness to continue questionnaire

At the end of the treatment period (or upon early discontinuation) patients will be requested to assess their impression of the ease of use of the Pressair®/Genuair® and HandiHaler® inhalers (device preference and willingness to continue questionnaire).

At the end of the treatment period (at week 24 or EOT/EOS), patients will be requested to evaluate the convenience of the device by means of the questionnaires included in Appendix 7. Data will be recorded by the patient in the e-diary.

The number (%) of patients fulfilling each category at each specific question/attribute will be analysed overall using descriptive statistics (with their 95% CI), by treatment group and overall. The percentage of patients who prefer Genuair will be also compared to 50% by means of an exact binomial test (data from patients who have a preference will be used); the test will be performed overall.

In addition, the extent to which patients prefer continuing using each device (0-100) will be descriptively analysed (number of non-missing values, mean, standard deviation, median, minimum and maximum, and 95% CI), and using a paired t-test.

4.12 Subgroup analysis

Subgroup analysis of CAT total score categories at baseline: between ≥10 and <15, between ≥15 and <20, and ≥20 will be done. Co-primary and secondary efficacy variables will be analysed for each category, using the same statistical models.

4.13 Analysis of safety and tolerability variables

The efficacy estimand assumption will be also used for all additional variables. However, safety variables will be analysed on the Safety population.

4.13.1 Adverse events (AEs)

Adverse events (including HCRU COPD exacerbations) will be coded using the Medical Dictionary for Regulatory Activities, MedDRA, version 19.0. An AE will be considered a treatment emergent adverse event (TEAE) if it starts at the time of or after the first IP administration. Otherwise, it will be considered as a non-TEAE. An AE that occurs more than 15-days after the last IP intake will not be considered a TEAE.

All tables will be sorted by alphabetical order of system organ class (SOC), high-level term (HLT) (when applicable) and by decreasing frequency patients of preferred term (PT) within SOC and HLT (when applicable) for the AB/FF 400/12 µg arm.

A comprehensive summary of TEAEs will be presented with the number and percentage of patients with non-TEAE, TEAE, TEAE leading to discontinuation, serious adverse events (SAE), major adverse cardiac events (MACE), and adverse events with fatal outcome will be presented by treatment and overall using descriptive statistics.

In case of a subject has more than one episode of the same preferred term with different levels of intensity, causality, or seriousness, then the subject will be counted once in each combination of this preferred term and intensity, causality, or seriousness level, respectively.

The number of TEAE and the number and percentage of patients with at least one TEAE will be tabulated by treatment and overall; 1) by SOC, HLT, PT; 2) by SOC,

HLT, PT, and intensity; 3) by SOC, HLT, PT, and causality; 4) by SOC, HLT, PT, and seriousness; 5) by SOC, HLT, PT, and outcome.

The number of TEAEs and the number and percentage of patients with TEAEs reported by > 1% of patients in any treatment group will be tabulated by treatment and overall by PT.

The number of treatment emergent SAEs (TESAE) and the number and percentage of patients with at least one TESAE will be tabulated by treatment and overall; 1) by SOC, HLT and PT; 2) by SOC, PT, and intensity; 3) by SOC, PT, and causality.

The number and percentage of patients with TEAEs leading to discontinuation (reported as the main cause of discontinuation) will be tabulated by treatment and overall; 1) by SOC, and PT; 2) by SOC, PT, and intensity; 3) by SOC, PT, and causality.

The number and percentage of patients with fatal TESAEs will be tabulated by treatment and overall: 1) by SOC, and PT; 2) by SOC, PT, and causality.

A listing of TESAEs, TEAEs leading to discontinuation, and fatal SAEs (both treatment emergent and non-treatment emergent) will also be provided.

4.13.2 Sensitivity analysis of SAEs

The treatment policy estimand assumption will be used for analysing cumulated SAE after the first IP intake and up the final time point (plus 15 follow up days for those patients who complete the 24-week treatment period). Same analyses specified in the previous section will be done.

4.13.3 Cardiac & cerebrovascular disorders, MACE, anticholinergic & pneumonia events

Summary of TEAEs of special interest includes: cardiac, cerebrovascular, anticholinergic, pneumonia, and β_2-adrenergic events. SOC terms, along with Standard MedDRA Query (SMQs) and PTs used are included in the table below.

TEAEs in the cardiac disorders and the cerebrovascular disorders will be reported including the number, percentage, and incidence of patients with the TEAEs by SMQ category and PT, and by treatment and overall. A list of patients with cardiac and cerebrovascular TEAE under SMQ category will be provided, including medical history (PT), concomitant medication (preferred name), ECG abnormal findings, and lab PCS findings.

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). Adjudicated MACEs will be tabulated with the number, percentage, and incidence of patients with adjudicated MACEs, and by treatment and overall. A listing of patients with all terms that were reviewed by the adjudication committee with the PT and the adjudicated term will be presented.

The incidence of treatment emergent adverse potential anticholinergic events will be tabulated by SOC and PT, and will be summarized by treatment and overall. β_2 adrenergic events will be tabulated by SMQ and PT, and by treatment and overall. Pneumonias (both TEAE and TESAE) will be tabulated by PT and overall, and by treatment and overall.

Incidence of patients with TEAEs per 1000 patient-years of exposure is calculated as the number of patients with TEAEs × 1000/total patient-year exposure to investigational product. It is expressed as number of patients with an event per 1,000 patient-year.

Definition of Treatment-Emergent Adverse Events of Interest		
Events of interest	Standard MedDRA Query Category plus additional High Level Terms or Preferred Term, if applicable	
Cardiac events	Ischemic Heart Disease:	
	• Myocardial infarction	Narrow search SMQ
	• Other Ischemic Heart Disease	Narrow search SMQ
	Tachyarrhythmias	Tachyarrhythmias (incl supraventricular and ventricular tachyarrhythmias) (SMQ) (narrow and broad search SMQ) plus additional PTs: tachycardia, heart rate increase and palpitation
	Cardiac failure	Narrow search SMQ
	Bradycardia	Bradyarrhythmia terms, non-specific (narrow search SMQ) plus 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) plus Ischaemic central nervous system vascular conditions (narrow search SMQ)
Major adverse cardiovascular events (MACEs)	All Adjudicated MACE by CVAC: cardiac death, non-fatal myocardial infarction and non-fatal stroke	
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, ileus 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	
B_2 adrenergic events	Hypertension	Hypertension (narrow search SMQ)
	Hyperglycemia	Hyperglycemia / new onset diabetes mellitus (narrow search SMQ)
	Tachyarrhythmias	Tachyarrhythmias (incl supraventricular and ventricular tachyarrhythmias) (SMQ) (narrow and broad search SMQ) plus Additional PTs: tachycardia, heart rate increase, and palpitation
	Tremor (excluding congenital)	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.	

CVAC = Cardiovascular Adjudication Committee; MACE = Major Adverse Cardiovascular Event; MedDRA = Medical Dictionary for Regulatory Activities; PT = prefered term; HLT = high level term
SMQ = Standard MedDRA Query; SOC = system organ class; TEAE = treatment-emergent adverse event.
SMQ = Standard MedDRA Query; SOC = system organ class; TEAE = treatment-emergent adverse event.
MSSO = Maintenance and Support Services Organization; The MSSO SMQ based on the MedDRA version 19.0 will be used.

4.13.4 Clinical laboratory parameters: haematology, biochemistry, and pregnancy test

Laboratory assessments include standard haematology, biochemistry, and serum pregnancy test (only in female patients of child bearing potential). Laboratory parameters are measured at screening visit (baseline), after 24 weeks on treatment, or at EOT/EOS in case of early termination. All clinical laboratory results will be presented in International System units.

Descriptive statistics (n, mean, SD, median, minimum, maximum, Q1, and Q3) will be reported for clinical laboratory values at baseline and change from baseline at week 24 and end of study, by treatment arm and overall. Baseline value is defined as the last value before first IP intake at screening visit. End of study is defined as the last post-baseline value following the first IP dose, either at week 24 or early termination at EOT/EOS visit.

A clinical laboratory value will be considered potentially clinically significant (PCS) if it is outside either the lower or upper limit of the expanded normal range (ENR) listed in the table below. Laboratory PCS abnormalities will be classified as *new, worsened, or notable abnormalities,* and will be reported at week 24, and end of study:

- A clinical laboratory test value will be defined as a *new abnormality* if the observed laboratory value is within the ENR at baseline but not at week 24 (or end of study), or if it is outside the ENR at baseline and outside the ENR at week 24 (or end of study) at the opposite extreme (i.e., it changed from outside the lower limit of normal to outside the upper limit of normal or vice versa)
- A clinical laboratory test value will be defined as a *worsened abnormality* if the baseline value is above the upper limit of the corresponding ENR, and the ratio of the value at week 24 (or end of study) to the baseline is also greater than the corresponding coefficient specified in the upper limit of the ENR column in the table; or, conversely, if the baseline value is below the lower limit of the corresponding ENR, and the ratio of the value at week 24 (or end of study) to the baseline value is also lower than the corresponding coefficient specified in the lower limit of the ENR column in the table
- A clinical laboratory test value will be defined as a *notable abnormality* if it falls below the lower limit or above the upper limit in the notable abnormalities columns.

The number and percentage of new, worsened, or notable PCS abnormalities will be summarized by means of shift contingency tables comparing the values at screening visit (lower, normal, upper) with the post-baseline values (newly, worsening and/or notable) as follow: new / increase; new / decrease; worsening / increase; worsening / decrease; notable > upper limit; notable < lower limit.

A table with number and percentages of patients with PCS will be calculated relative to the number of patients with available baseline and at least one post-baseline value. The table will show: 1) An overall summary including any PCS value determined at any scheduled visit, including re-tests, early termination visits, or unscheduled visits; 2) PCS at week 24; 3) PCS at end of study (following the definition of end of study). Results will be reported by treatment group and overall.

A supportive listing of patients with potentially clinically significant post-baseline values will be provided. A listing of all TEAEs for patients with potentially clinically significant laboratory values, and classified as abnormal clinicaclly relevant by the investigator, will also be provided.

The number and percentage of patients with a result of any laboratory parameter classified as abnormal clinically relevant by the investigator will be tabulated at week 24 and end of study, and by treatment group and overall. In addition, a listing of TEAEs for patients with abnormal clinically relevant parameters will be provided.

The results of pregnancy tests performed at screening and at the end of the trial will be reported by means of listings.

Expanded Normal Ranges and Notable Abnormalities for Laboratory Parameters

Laboratory parameter	Expanded normal ranges		Notable abnormalities	
	*xLLN***	*xULN**	*Lower Limit*	*Upper Limit*
HEMATOLOGY				
Hemoglobin	0.85	1.15	< 60 g/L	> 230 g/L
Hematocrit	0.85	1.15	< 24%	N.A.
Erythrocytes	0.85	1.15	N.A.	N.A.
MCV	0.85	1.15	N.A.	N.A.
Platelets	0.85	1.15	< 100 x 10^9/L	N.A.
Leukocytes				
Total	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				
ASAT	N.A.	1.15	N.A.	> 3xULN
ALAT	N.A.	1.15	N.A.	> 3xULN
Alkaline phosphatase	N.A.	1.15	N.A.	> 3xULN
γGT	N.A.	1.15	N.A.	> 3xULN
Bilirubin	N.A.	1.15	N.A.	> 51.3 µmol/L
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
LDH	N.A.	1.15	N.A.	> 3xULN
BUN	N.A.	1.15	N.A.	> 17.9 mmol/L
Creatinine	N.A.	1.15	N.A.	> 265 µmol/L
Uric acid	N.A.	1.15	N.A.	> 714 µmol/L
Cholesterol	N.A.	1.15	N.A.	N.A.
Triglycerides	N.A.	1.15	N.A.	N.A.
Glucose	0.85	1.15	< 2.22 mmol/L	> 22.2 mmol/L
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.

Protein	0.85	1.15	< 20 g/L	> 90 g/L
Albumin	0.85	1.15	N.A.	N.A.

xLLN = Multiplying factor for the lower limit of the expanded normal range*
*xULN**= Multiplying factor for the upper limit of the expanded normal range*
N.A.= Not Applicable

4.13.5 Hy's Law

Hy's law is a rule of thumb that a drug is at high risk of causing a fatal drug-induced liver injury (DILI) when given to a large population.

During the course of the study the investigator remains vigilant for increases in liver biochemistry and is responsible for determining whether a patient meets Potential Hy's Law (PHL) criteria at any point during the study.

A review and assessment of cases to determine whether PHL cases agree with Hy's Law (HL) criteria is performed. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than DILI caused by the IP.

Potential Hy's Law (PHL):

At least one event of aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥ 3x upper limit of normal (ULN) and with total bilirubin (TBL) ≥ 2xULN at any point during the study following the start of study medication irrespective of an increase in Alkaline Phosphatase (ALP).

Hy's Law (HL):

AST or ALT ≥ 3x ULN and with TBL ≥ 2xULN, where no other reason, other than the IP, can be found to explain the combination of increases, e.g., elevated ALP indicating cholestasis, viral hepatitis, another drug.

For PHL and HL the elevation in transaminases must precede or be coincident with (i.e. on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

A listing of all Hy's Law including PHL and/or HL will be provided along with medical histoy, concomitant medication, and TEAE reported by treatment arm.

4.13.6 Blood pressure

Systolic blood pressure (SBP) and diastolic blood pressure (DBP) values are measured at screening, baseline (last value measured pre-morning before IP at Day 1), and at all scheduled post-baseline visits (both pre-morning dose, and 2h post-dose), or at EOT/EOS visit in case of early termination.

Absolute values and change from baseline by time-point (including end of study) in SBP and DBP will be reported by treatment and overall. End of study is defined as the last post-baseline value following the first IP dose, either at any scheduled visit, or at EOT/EOS visit in case of early termination.

Blood pressure values are considered to be PCS if they meet either the high or low criteria in the table below.

A table with number and percentages of patients with PCS in SBP and DBP will be calculated relative to the number of patients with available baseline and at least one post-baseline value. The table will show: 1) An overall summary including any PCS value determined at any scheduled visit, including re-tests, early termination visits, or

unscheduled visits; 2) PCS at all scheduled visits; 3) PCS at end of study. Results will be reported by treatment and overall.

Criteria for Potentially Clinically Significant Blood Pressure

SBP notable increase	≥180 and increase from baseline ≥20
SBP notable decrease	≤90 and decrease from baseline ≥20
DBP notable increase	≥105 and increase from baseline ≥15
DBP notable decrease	≤50 and decrease from baseline ≥15

A supportive listing of non-abnormal/abnormal post-baseline values will be provided. A listing of all TEAEs for patients with abnormal blood pressure post-baseline values will also be provided. PCS listings will include all data, i.e., scheduled and unscheduled visits.

4.13.7 12-lead ECG

12-lead ECGs are performed at screening (baseline, the last values performed prior to IP administration), pre-morning IP at all post-baseline visits, and 2h post-dose at day 1, and weeks 12 and 24, or at EOT/EOS visit in case of early termination.

ECG intervals will be summarized by time-point and end of study by summary statistics of absolute and change from baseline values, by treatment group and overall. The following parameters will be reported: Heart rate (beats/min.), PR interval (msec.), QRS interval (msec.), QT interval (msec.), QTcB interval (msec.), QTcF interval (msec.), and RR interval (msec.). End of study is defined as the last post-baseline value following the first IP dose, either at any scheduled visit, or at EOT/EOS visit in case of early termination.

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 by reported by finding, parameter, type of finding, time-point (including end of study), and by treatment group and overall.

The number and percentage of patients with at least one clinically significant (PCS) ECG value within each of heart rate, PR, QRS, QTcB, and QTcF parameters, and will be reported based on both criteria showed in the table below. Two criteria were defined based on severity level, thus criteria 1 is less severe than criteria 2.

A table with number and percentages of patients with PCS will be calculated relative to the number of patients with available baseline and at least one post-baseline value. The table will show: 1) An overall summary including any PCS value determined at any scheduled visit, including re-tests, early termination visits, or unscheduled visits); 2) PCS at all scheduled visits; 3) PCS at end of study. Results will be reported by treatment and overall.

Definition of potentially clinically significant (PCS) values in 12-lead ECG parameters

	Criteria 1	Criteria 2
QTcB, and QTcF intervals		
Absolute values	> 480 milliseconds (msec)	> 500 msec
Absolute change from baseline	> 30 msec	> 60 msec
QRS interval	≥ 100 msec and an increase of ≥ 25% over baseline value	≥ 150 msec if baseline is < 150 msec
PR interval	≥ 200 msec and an increase of ≥ 25% over baseline value	≥ 250 msec if baseline is < 250 msec
Heart Rate		
Tachycardia event	≥ 110 beats per minute (bpm) and an increase of ≥ 15% over baseline value	≥ 120 bpm if baseline is < 120 bpm
Bradycardia event	≤ 50 bpm and a decrease of ≥ 15% over baseline value	≤ 40 bpm if baseline is > 40 bmp

bpm = beats per minute; ECG = electrocardiogram; QTcB = QT interval corrected for heart rate using the Bazett formula ($QTcB = QT/(RR)^{½}$); QTcF = QT interval corrected for heart rate using the Fridericia formula ($QTcF = QT/(RR)^{⅓}$).

The number and percentage of patients with ECGs classified as abnormal clinically relevant will be tabulated by time-point and end of study, by treatment group. In addition, a listing of TEAEs for patients with ECGs classified as abnormal clinically relevant will be provided.

A listing of TEAE for patients with at least one PCS ECG value will be done.

4.14 Data Handling

If not specified, efficacy and safety data will be analyzed based on the protocol-defined visits.

4.14.1 Imputation of missing data

4.14.1.1 Pulmonary function tests

For FEV_1 and FVC imputation of pre and post-bronchodilator (albuterol/salbutamol) intake will be performed in two steps:

- 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 patients (whole sample).

Missing data for pulmonary variables (FEV1, and FVC), will be dealt with direct likelihood approach (Beunckens et al., 2005).

4.14.1.2 Signs and Symptoms and Health-related Quality of Life

If missing, the CAT value at visit 2 (baseline) will be imputed with the screeing value.

For SGRQ, the way of dealing with missing items and multiple responses are described in the SGRQ manual.

SGRQ and CAT missing data will be dealt with direct likelihood approach.

4.14.1.3 Imputation for COPD exacerbations (HCRU and EXACT) dates

The way to impute partially start missing dates of a COPD exacerbation episode is described in section 4.14.1.6.

In case of the stop date of a COPD exacerbation is unknown/ongoing or totally missing, then the EOS/W24 date (the first on occurring) will be used to impute such date.

Additionally, if the stop date of a COPD exacerbation is imputed, and a new exacerbation episode starts afterwards, and concomitantly to the previous one, both exacerbations will be considered “relapsed” (the same exacerbation), and the duration and severity of this exacerbation established following the rules specified in section 4.14.2.4.

4.14.1.4 Daily COPD symptoms (E-RS) and use of relief medication

No imputation will be done. Missing data for relief medication use will be dealt with direct likelihood approach (Beunckens et al., 2005).

4.14.1.5 Night-time and Early Morning Symptoms (NiSCI & EMSCI)

No imputation will be done. Missing data for relief medication use will be dealt with direct likelihood approach (Beunckens et al., 2005).

4.14.1.6 Imputation for Safety and tolerability variables and dates

If intensity is missing for an AE started before the first dose of double-blind investigational product, then an intensity of mild will be assigned. If the intensity is missing for an AE that started on or after the first day of double-blind investigational product dosing, then an intensity of severe will be assigned. The imputed values for

intensity assessment will be used for the incidence summary; the actual values will be presented in the data listings.

If the causality to the investigational product is missing for an AE started on or after the date of the first dose of double-blind investigational product, a relationship of related will be assigned. The imputed values for relationship to double-blind investigational product will be used for incidence summary, while the actual values will be presented in data listings.

The following imputation rules apply to cases in which the start date is incomplete (i.e., partial missing) for adverse events.

Missing day and month:

- If the year is the same as the year of the date of the first dose of double-blind study drug, then the day and month of the date of the first dose of double-blind study drug will be assigned to the missing fields.
- If the year is prior to the year of the date of the first dose of double-blind study drug, then December 31 will be assigned to the missing fields.
- If the year is after the year of the date of the first dose of double-blind study drug, then January 1 will be assigned to the missing fields.

Missing month only:

- The day will be treated as missing and both month and day will be replaced according to the above procedure.

Missing day only:

- If the month and year are the same as the year and month of the date of the first dose of double-blind study drug, then the date of the first dose of double-blind study drug will be assigned to the missing day.
- If either the year is before the year of the date of the first dose of double-blind study drug or if both years are the same but the month is before the month of the date of the first dose of double-blind study drug, then the last day of the month will be assigned to the missing day.
- If either the year is after the year of the date of the first dose of double-blind study drug or if both years are the same but the month is after the month of the date of the first dose of double-blind study drug, then the first day of the month will be assigned to the missing day.
- If the stop date is complete and the imputed start date as above is after the stop date, the start date will be imputed by the stop date.
- If the start date is completely missing and the stop date is complete, then using the following algorithm to impute the start date:
    - If the stop date is after the date of the first dose of double-blind study drug, the date of the first dose of double-blind study drug will be assigned to the missing start date.
    - If the stop date is before the date of the first dose of double-blind study drug, the stop date will be assigned to the missing start date.

4.14.1.7 Imputation for dates for prior and concomitant medication

For prior or concomitant medications, including relief medications, incomplete (i.e., partial missing) start date and/or stop date will be imputed. When the start date and the stop date are both incomplete for a patient, impute the start date first.

Incomplete Start Date

The following rules will be applied to impute the missing numerical fields. If the stop date is complete and the imputed start date is after the stop date, then the start date will be imputed using the stop date. Particularly, for the concomitant medication, if stop date is present, but the start date is totally missing, then the start date of concomitant medication will be calculated as a first dose in-take date.

Missing day and month

- If the year of the incomplete start date is the same as the year of the date of the first dose of double-blind study drug, then the day and month of the date of the first dose will be assigned to the missing fields.
- If the year of the incomplete start date is prior to the year of the date of the first dose of double-blind study drug, then December 31 will be assigned to the missing fields.
- If the year of the incomplete start date is after the year of the date of the first dose of double-blind study drug, then January 1 will be assigned to the missing fields.

Missing month only

- The day will be treated as missing and both month and day will be replaced according to the above procedure.

Missing day only

- If the month and year of the incomplete start date are the same as the month and year of the date of the first dose of double-blind study drug, then the day of the date of the first dose will be assigned to the missing day.
- If either the year is before the year of the date of the first dose of double-blind study drug or if both years are the same but the month is before the month of the date of the first dose of double-blind study drug, then the last day of the month will be assigned to the missing day.
- If either the year is after the year of the date of the first dose of double-blind study drug or if both years are the same but the month is after the month of the date of the first dose of double-blind study drug, then the first day of the month will be assigned to the missing day.

Incomplete Stop Date

The following rules will be applied to impute the missing numerical fields. If the date of the stop date is missing, replace it with the last dose of double-blind study drug. If the imputed stop date is before the start date (imputed or non-imputed start date), then the imputed stop date will be equal to the start date.

Missing day and month

- If the year of the incomplete stop date is the same as the year of the date of the last dose of double-blind study drug, then the day and month of the date of the last dose will be assigned to the missing fields.

- If the year of the incomplete stop date is prior to the year of the date of the last dose of double-blind study drug, then December 31 will be assigned to the missing fields.
- If the year of the incomplete stop date is after the year of the date of the last dose of double-blind study drug, then January 1 will be assigned to the missing fields.

Missing month only

- The day will be treated as missing and both month and day will be replaced according to the above procedure.

Missing day only

- If the month and year of the incomplete stop date are the same as the month and year of the date of the last dose of double-blind study drug, then the day of the date of the last dose will be assigned to the missing day.
- If either the year is before the year of the date of the last dose of double-blind study drug or if both years are the same but the month is before the month of the date of the last dose of double-blind study drug, then the last day of the month will be assigned to the missing day.
- If either the year is after the year of the date of the last dose of double-blind study drug or if both years are the same but the month is after the month of the date of the last dose of double-blind study drug, then the first day of the month will be assigned to the missing day.

4.14.2 Computation of derived variables

4.14.2.1 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.

4.14.2.2 Patients randomized in more than one site

- For patients randomized in more than one site, investigator will be instructed to discontinue the patient from all treatments/sites, and analysed under the first randomization IP, and until completation/discontinuation. Additionally, a listing with safety values for all IP intake will be reported.

4.14.2.3 Repeated and unscheduled assessments for efficacy

- For repeated visits, the spirometry observation from the last repeated visit will be used in statistical analyses both pre and post IP intake.
- Spirometry data, SGRQ, and CAT data from 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, this data will be listed.

4.14.2.4 COPD Exacerbations based on Health Care Resource Utilisation (HCRU) definition

COPD exacerbation according to the health care utilisation definition will be evaluated by the investigator at each visit on the basis of the information registered by the patient (and subsequently checked by the investigator at each visit) into the electronic Patient Diary and paper Patient Diary. COPD exacerbation episodes will not be recorded in the

AE form of the EDC, but in a devoted COPD Exacerbation form of the EDC.

Any subject who suffers a severe exacerbation (requiring hospitalization) or more than two moderate exacerbations will be discontinued from the study. Information to be recorded in the COPD Exacerbation includes start and stop date, treatment received (antibiotics, systemic corticosteroids, increase in relief medication), outcome, need of hospitalisation, etc. The onset of an exacerbation will be defined by the onset of symptoms worsening. The end of the exacerbation will be defined by the investigator based on symptoms recovery or stabilization and end of treatment received for the episode.

A new COPD exacerbation episode is defined as the patient being off oral steroids and antibiotics for ≥ 7 days since prior exacerbation. If the patient is off oral steroids and antibiotics for less than 7 days, then it will be considered as a "relapse" of the previous exacerbation, and it will be treated as the same COPD exacerbation episode within the COPD exacerbation form of the EDC.

For this study purposes, a COPD exacerbation using the HCRU definition is defined according to the following severity categories:

Severity of COPD exacerbation

Severity	**Definition**
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 bronchodilator and/or inhaled corticosteroid use)
Moderate	Increase of COPD symptoms during at least 2 consecutive days, which does not lead to hospitalisation 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 hospitalisation (overnight stay at hospital or emergency room) or death

In case of relapse:

- The duration of the COPD exacerbation should be calculated from the start date of the first episode to the stop date of the last episode.

- The severity should be chosen as the more severe condition of all episodes.

- To classify the causality with the study drug we should select the most adverse result, i.e., related with the study drug if applies.

4.14.2.5 Repeated or unscheduled assessments of safety parameters

For laboratory tests, blood pressure and ECG parameters, the following strategy will be used for re-tests in order to produce the tables:

- 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

Regarding listings, all values including scheduled visits (including re-test value), unscheduled visits, an early termination visits (EOT or EOS) will be shown.

4.14.2.6 Selection of repeated questionnaires

In case of duplicities in the questionnaires and in the questionnaires per patient-day, the answers from the first repeated questionnaire will be used in statistical analyses both pre and post IP intake.

5. INTERIM ANALYSIS

N/A

6. CHANGES OF ANALYSIS FROM PROTOCOL

The endpoints and statistical models described in the Protocol have not changed in this amendment, except for the rate of COPD exacerbations where the offset assessment for the rate of COPD exacerbations have been updated according to a new FDA requirement.

7. REFERENCES

1. Snedecor GW, Cochran WG. Statistical methods (8th edition). Ames, Iowa: Iowa State University Press, 1989
2. Winer BJ, Brown DR, Kenneth KM. Statistical principles in experimental design (third edition). New York: McGraw-Hill, 1991
3. Beunckens C, Molenberghs G and Kenward MG. Direct likelihood analysis versus simple forms of imputation for missing data in randomized clinical trials. Clinical Trials 2005; 2: 379–86.
4. Stokes ME, Davis CS, and Koch GG. 2000. Categorical Data Analysis Using the SAS® System, 2nd Edition. Cary, NC: SAS® Institute Inc.
5. Hosmer DW, Lemeshow S. Applied logistic regression. New York: John Wiley and Sons, 1989
6. Collett D. Modelling binary data. London: Chapman and Hall, 1991
7. Everitt BS, Dunn G. Applied Multivariate Data Analysis. London: Edward Arnold,1991; pp.: 191-4
8. Aitkin M, Anderson D, Francis B, Hinde J. Statistical Modelling in GLIM. Oxford: Clarendon Press, 1989; pp.: 223-5
9. Rothman KJ, Greeenland S. Modern Epidemiology, 2nd ed. Philadelphia: Lippincott-Raven Publishers,1998; pp.: 29-46
10. Jones PW., Quirk FH., Baveystock CM. The St George's Respiratory Questionnaire. Respir Med 1991;85(Suppl B):25-31
11. Kenward MG, Molenberghs G, Thijs H. Pattern-mixture models with proper time dependence. Biometrika 2003; 90: 53-71.
12. O'Kelly Michael, Ratitch Bohdana. Clinical Trials With Missing Data. A guide for Practitioners. Statistics in Practice. John Wiley & Sons, Ltd, 2014.

8. APPENDIXES

8.1 Appendix 1: Statistical model for trough FEV_1

Level 1 (occasion level):

$$tFEV1_{it} = \beta_{0i} + \beta_{1i} + \gamma_{21}week_{it} + \gamma_{22}(trt_i * week_{it}) + \varepsilon_{it}$$

[i: patient (1…1,500); t: Week (1, 4, 12, 18, 24)]

And β_{0i} and β_{1i} are random coefficients

Level 2:

$$\beta_{0i} = \gamma_{00} + \gamma_{01}pre_i + \gamma_{02}post_i + \gamma_{03}age_i + \gamma_{04}bas_i + \gamma_{05}trt_i + \gamma_{06}sex_i + \gamma_{07}smoke_i + U_{0i}$$ (patient level)

$$\beta_{1i} = \gamma_{10} + \gamma_{11}country_i + U_{1i}$$ (country level- 10 countries)

Overall model:

$$tFEV1_{it} = \gamma_{00} + \gamma_{10} + \gamma_{01}pre_i + \gamma_{02}post_i + \gamma_{03}age_i + \gamma_{04}bas_i + \gamma_{05}trt_i + \gamma_{06}sex_i + \gamma_{07}smoke_i + \gamma_{11}country_i + \gamma_{21}week_{it} + \gamma_{22}(trt_i * week_{it}) + U_{0i} + U_{1i} + \varepsilon_{it}$$

$$\varepsilon_{it} \sim N(0, R_i)$$

$$\begin{pmatrix} U_{0i} \\ U_{1i} \end{pmatrix} = U_i \sim N(0, G)$$

H_0: $G = 0$ => There are no differences between countries

Matrix notation:

$$\begin{pmatrix} tFEV1_1 \\ \dots \\ tFEV1_{1,500} \end{pmatrix} = X_i\Gamma + Z_iU_i + \varepsilon_{it} =$$

$$= \begin{pmatrix} 1 & pre_1 & post_1 & age_1 & bas_1 & trt_1 & sex_1 & smoke_1 & country_1 & week_1 & trt*week_1 \\ \vdots & \vdots & & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\ 1 & pre_{ni} & post_{ni} & age_{ni} & bas_{ni} & trt_{ni} & sex_{ni} & smoke_{ni} & country_{ni} & week_{ni} & trt*week_{ni} \end{pmatrix} \begin{pmatrix} \gamma_0 \\ \gamma_{01} \\ \gamma_{02} \\ \gamma_{03} \\ \gamma_{04} \\ \gamma_{05} \\ \gamma_{06} \\ \gamma_{07} \\ \gamma_{11} \\ \gamma_{21} \\ \gamma_{22} \end{pmatrix} + \begin{pmatrix} 11 \\ \vdots \\ 11 \end{pmatrix} \begin{pmatrix} U_{0i} \\ U_{1i} \end{pmatrix}$$

$$+ \begin{pmatrix} \varepsilon_{i1} \\ \vdots \\ \varepsilon_{i1500} \end{pmatrix}$$

Where,

$$\mathrm{tFEV1_{it}} \sim \mathrm{N}(\mathrm{X_i}\Gamma, (\mathrm{Z_i}\mathrm{G}\mathrm{Z_i'} + \mathrm{R_i}\mathrm{I}))$$

[Cov(ε,U)=0]

As $\varepsilon_{\mathrm{it}} \sim N(0, \mathrm{R}_i)$, $\mathrm{R_i}$ (might not be $\sigma^2\mathrm{I}$) could be unstructured:

$$R_i = \begin{pmatrix} \sigma_1^2 & \sigma_{12} & \sigma_{13} & \sigma_{14} & \sigma_{15} \\ & \sigma_2^2 & \sigma_{23} & \sigma_{34} & \sigma_{25} \\ & & \sigma_3^2 & \sigma_{34} & \sigma_{35} \\ & & & \sigma_4^2 & \sigma_{45} \\ & & & & \sigma_5^2 \end{pmatrix}$$ (covariance matrix of patient *i* from visit 1 to visit 5)

This structure would be placed repeatedly in the diagonal of a matrix for each patient, and 0 outside the diagonal. Needs to estimate t(t+1)/2 parameters.

σ_u^2 is a constant and it is the same in each country.

V=ZGZ' + R = σ_u^2 + $\mathrm{R_i}$

(Note that, when R = σ^2I and Z = 0, the mixed model reduces to the standard linear model.)

SAS differentiates between *G-side* and *R-side* effects in the model. *G-side* are random effects that enter through the *G* matrix above and *R-side* effects enter through the *R* matrix above.

SAS CODE:

```
proc mixed data=dataset;
    class TRT01PN AVISITN COUNTRY SEX SMOKST USUBJID;
    model CHG=TRT01PN AVISITN TRT01PN*AVISITN FEV1PR FEV1PO AGE BASE SEX
                SMOKST / s cl ddfm=kr;
    repeated AVISITN / subject=usubjid(TRT01PN) type=un r rcorr;
    random COUNTRY / g;
    lsmeans TRT01PN*AVISITN / diff cl pdiff;
run;
```

8.2 Appendix 2: St. George's respiratory questionnaire (SGRQ)

The SGRQ contains 50 items divided into three dimensions (symptoms, activity, and impact scores). Three dimension scores are calculated for the SGRQ using empirically derived weights:

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

A Total score is calculated to summarise the impact of the disease on overall health status.

These dimension and Total scores range from 0 to 100, where each result is expressed as a percentage of the weights summed up by a patient on the maximum possible sum of weights that corresponds to the worst possible state of the patient ("100" indicates the worst health status).

The algorithms to be used for score calculations and the way of dealing with missing items and multiple responses are described in the SGRQ manual (Jones and Forde, 2008).

The algorithms have been modified to treat the skip items (number 5 and 14 of the questionnaire). Thus, if a patient has not experienced a severe attack (item 5 = no attacks) then item 6 is not applicable and then "less than a day" should be assigned to question 5; if a patient has not reported any medication in 4 questions of item 14 (i.e., they are missing), then the responses will be imputed as 'false'.

Item Scoring

Question	***Answer***	***Score***
Symptom Component (Questions 1-8)		
1) Over the past 3 months, I have coughed:	Almost every day Several days a week A few days a month Only with respiratory infections Not at all	80.6 63.2 29.3 28.1 0.0
2) Over the past 3 months, I have brought up phlegm (sputum):	Almost every day Several days a week A few days a month Only with respiratory infections Not at all	76.8 60.0 34.0 30.2 0.0
3) Over the past 3 months, I have had shortness of breath:	Almost every day Several days a week A few days a month Only with respiratory infections Not at all	87.2 71.4 43.7 35.7 0.0
4) Over the past 3 months, I have had wheezing attacks:	Almost every day Several days a week A few days a month Only with respiratory infections Not at all	86.2 71.0 45.6 36.4 0.0

Item Scoring

Question	***Answer***	***Score***
5) How many times during the past 3 months have you suffered from severe or very unpleasant respiratory attacks?	more than 3 times 3 times 2 times 1 time none of the time	86.7 73.5 60.3 44.2 0.0
6) How long did the worst respiratory attack last? (Go to Question 7 if you did not have a severe attack)	a week or more 3 or more days 1 or 2 days less than a day	89.7 73.5 58.8 41.9
7) Over the past 3 months, in a typical week, how many good days (with few respiratory problems) have you had?	No good days 1 or 2 good days 3 or 4 good days nearly every day was good every day was good	93.3 76.6 61.5 15.4 0.0
8) If you wheeze, is it worse when you get up in the morning?	No Yes	0.0 62.0
Activity Component (Questions 11 and 15)		
11) These are questions about what activities usually make you feel short of breath these days.		
Sitting or lying still	True False	90.6 0.0
Washing or dressing yourself	True False	82.8 0.0
Walking around the house	True False	80.2 0.0
Walking outside on level ground	True False	81.4 0.0
Walking up a flight of stairs	True False	76.1 0.0
Walking up hills	True False	75.1 0.0
Playing sports or other physical activities	True False	72.1 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 False	74.2 0.0
I cannot take a bath or shower, or I take a long time to do it	True False	81.0 0.0
I walk slower than other people my age, or I stop to rest	True False	71.7 0.0
Jobs such as household chores take a long time, or I have to stop to rest	True False	70.6 0.0
If I walk up one flight of stairs, I have to go slowly or stop	True False	71.6 0.0
If I hurry or walk fast, I have to stop or slow down	True False	72.3 0.0
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	True False	74.5 0.0

Item Scoring

Question	***Answer***	***Score***
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 False	71.4 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 False	63.5 0.0
Impact Component (Questions 9, 10, 12, 13, 14, 16, and 17)		
9) How would you describe your respiratory condition?	The most important problem I have Causes me quite a lot of problems Causes me a few problems Causes no problem	83.2 82.5 34.6 0.0
10) If you have ever held a job, my respiratory problems	made me stop working altogether interfere with or made me change my job do not affect my job	88.9 77.6 0.0
12) These are more questions about your cough and shortness of breath these days.		
Coughing hurts	True False	81.1 0.0
Coughing makes me tired	True False	79.1 0.0
I am short of breath when I talk	True False	84.5 0.0
I am short of breath when I bend over	True False	76.8 0.0
My coughing or breathing disturbs my sleep	True False	87.9 0.0
I get exhausted easily	True False	84.0 0.0
13) These are questions about other effects that your respiratory problems may have in you these days.		
My coughing or breathing is embarrassing in public	True False	74.1 0.0
My respiratory problem are a nuisance to my family, friends, or neighbors	True False	79.1 0.0
I get afraid or panic when I cannot catch my breath	True False	87.7 0.0
I feel that I am not in control of my respiratory problems	True False	90.1 0.0
I do not expect my respiratory problem to get any better	True False	82.3 0.0
I have become frail or an invalid because of my respiratory problem	True False	89.9 0.0
Exercise is not safe for me	True False	75.7 0.0
Everything seems too much of an effort	True False	84.5 0.0

Item Scoring

Question	*Answer*	*Score*
14) These are questions about your respiratory treatment.		
My treatment does not help me very much	True False	88.2 0.0
I get embarrassed using my medication in public	True False	53.9 0.0
I have unpleasant side effects from my medication	True False	81.1 0.0
My treatment interferes with my life a lot	True False	70.3 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 False	64.8 0.0
I cannot go out for entertainment or recreation	True False	79.8 0.0
I cannot go out of the house to do the shopping	True False	81.0 0.0
I cannot do household chores	True False	79.1 0.0
I cannot move far from my bed or chair	True False	94.0 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 Stops me from doing one or two things Stops me from doing most of the things Stops me from doing everything	0.0 42.0 84.2 96.7

Each component of the questionnaire is scored separately in 3 steps:

a. The weights in the table correspond to the actual positive responses for all items in the component are summed. The component score is calculated by dividing the summed weights by the adjusted maximum possible weight for that component and expressing the result as a percentage:

$$\frac{100 \times \text{summed weights from positive items in that component}}{\text{Sum of weights for all items in that component}}$$

The total score is calculated in similar way:

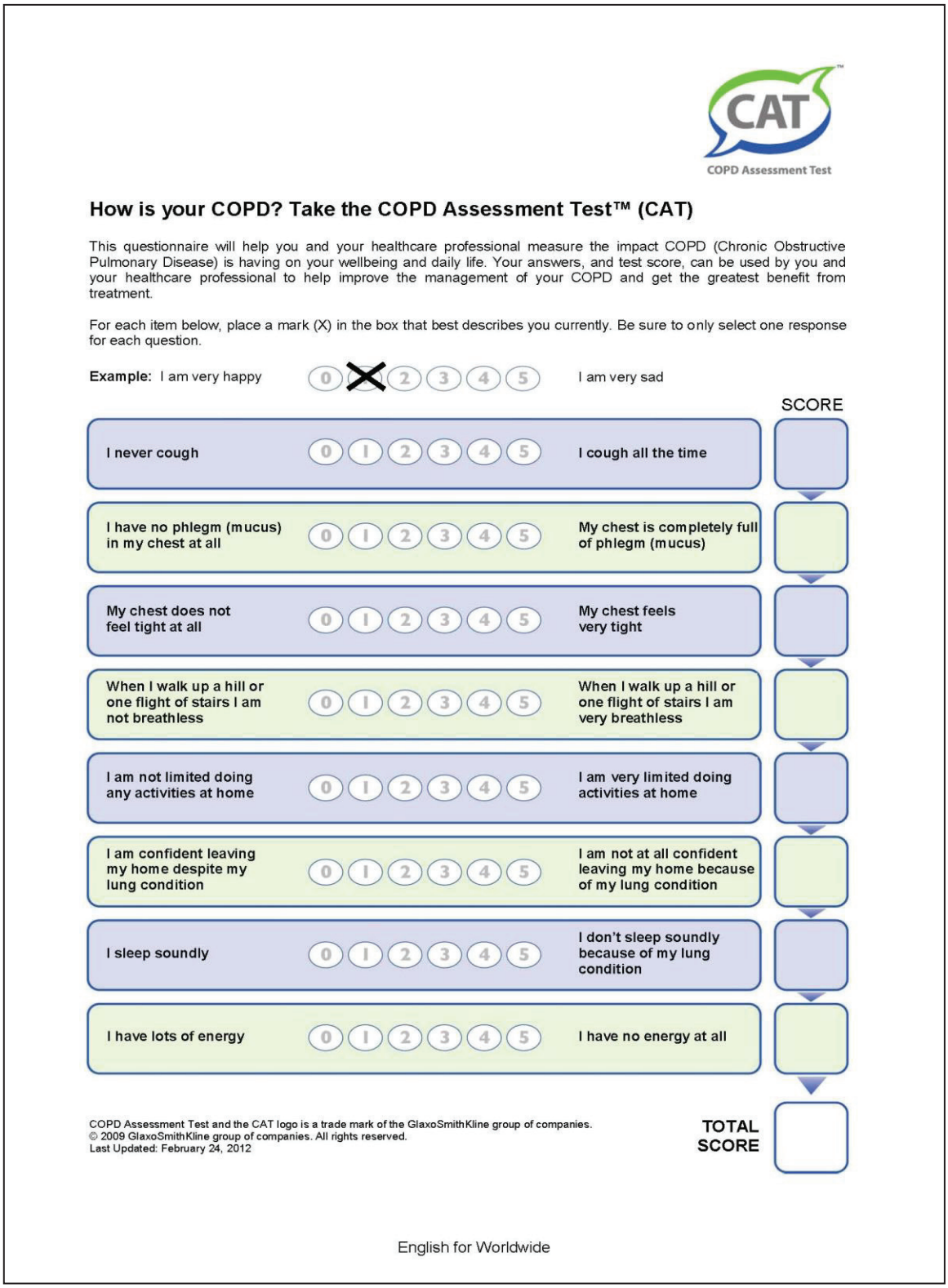
$$\frac{100 \times \text{summed weights from positive items in the questionnaire}}{\text{Sum of weights for all items in the questionnaire}}$$

Adjusted sum of maximum possible weights for each component and total:

Symptoms	662.5
Activity	1209.1
Impacts	2117.8
Total	3989.4

b. The weights for any missed items are deducted from the maximum possible weight for each dimension. The weights for all missed items are deducted from the maximum possible weight for the total score.

8.3 Appendix 3: COPD Assessment Test (CAT)



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

AstraZeneca

8.4 Appendix 4: EXACT and raw score assignment

The Exacerbations of Chronic Pulmonary Disease Tool is a patient-reported outcome (PRO) measure designed to provide researchers with a single, standardized, reliable, and valid method for assessing frequency (counts), severity (score), and duration (days) of exacerbations of chronic obstructive pulmonary disease.

The EXACT is a 14-item daily diary designed for electronic administration. Patients are instructed to complete the diary each evening just prior to bedtime, reflecting back on their experiences "today". Daily administration is essential in order to capture change in the patient's condition consistent with exacerbation, including worsening, improvement, and stabilization indicative of recovery.

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. 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, 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.

Baseline is defined as a 7-day interval ending the date before the first dose of double blind investigational product. Baseline EXACT score is the mean within patient score over 7 days, with data present for a minimum of 4 of 7 days. If fewer than 4 days of data are available, the EXACT Baseline score should not be calculated.

For those trial participants who experience one or more exacerbations during the study, the EXACT baseline value is re-established following each exacerbation. To reset Baseline values following an exacerbation, the patient's mean EXACT score during the 4th week following Recovery (Days 22-28 post-Recovery) is computed, with a minimum of 4 days of data required and in the absence of a new exacerbation. If the patient experiences a new event during this 4 week period, a new Baseline is not calculated until the 4th week following Recovery from that subsequent event. A new Baseline established following Recovery from the first exacerbation will be denoted as BaselineR1, with subsequent new Baselines established labelled accordingly as BaselineR2 and so on, as appropriate.

Onset is defined as the first day in which the patient experiences an acute, sustained worsening of their baseline condition. Onset is identified in one of two ways: Either (1) an increase in EXACT score $\geq$ 12 points above the patient's mean Baseline for 2 consecutive days, with Day 1 of the 2 days serving as Day1 (Onset) of the event OR (2) an increase $\geq$ 9 points above the patient's mean Baseline for 3 consecutive days, with Day 1 of the 3 days serving as Day1 (Onset) of the event. The presence of either constitutes Onset of an event.

Event Duration requires identification of the following parameters: (1) Onset, (2) Three-day Rolling Average; (3) Maximum Observed Value; (4) Threshold for Improvement;

and (5) Recovery. It is possible that Improvement may occur at multiple time points during an event and that this Improvement may or may not reflect full Recovery.

- ✓ Three-day Rolling Average: A Three-day Rolling Average is used to account for day-to-day variability in EXACT scores that can occur during an exacerbation. This is operationalized as a 3-day rolling of the mean EXACT score [Dayx-1, Dayx, Dayx+1], with the first computation based on Days 1 (Onset), 2, and 3 of the event and continuing forward sequentially (Days 2, 3, 4; Days 3, 4, 5, etc.). Only one of the 3 data points need to be present for this computation.
- ✓ Maximum Observed Value (MOV): Highest EXACT score observed during a given time period, using a 3-day Rolling Average.
- ✓ The Threshold for Improvement is a decrease in EXACT score ≥ 9 points from the previous day's score during an event.
- ✓ Recovery is defined as the first day in which a patient experiences a persistent, sustained improvement in their condition. For scoring purposes, Recovery is a reduction in EXACT score ≥ 9 points benchmarked against the MOV during the first 14 days of the event, with this improvement maintained for 7 consecutive days using a 3-day Rolling Average. If the MOV occurs more than once during the 14-day period, the first day on which the value occurs is used as the benchmark for computation of Recovery. The first day of the 7-day period is designated the day of Recovery (DayR).
- ✓ Score increases consistent with Onset and occurring any time after the 7th day of the Recovery period are counted as a new event. To identify a new exacerbation, use the last available Baseline value. The reset Baseline value (BaselineRX) is used if a participant's Baseline was re-established otherwise the original Baseline value is used.

The total number of COPD exacerbations is either equal to 0 (If no onset is present), 1 (if onset is present and no new event is identified), or is equal to 1+ the number of new event(s) identified.

Duration is the length of time in days from Onset to Recovery. Duration is calculated as the difference, in days, between the day of Onset (Day1) and the day of Recovery (DayR). The day of Recovery (DayR) is not included in calculating Duration days.

Severity is the EXACT score on the worst day of the event from Onset (Day1) to Recovery (DayR).

The following annotates the raw score values associated with each response category for the EXACT 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. Slight
	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.
12. Were you tired or weak today?	0. Not at all
	1. Slightly
	2. Moderately
	3. Severely
	4. Extremely
13. Last night, was your sleep disturbed?	0. Not at all
	1. Slightly
	2. Moderately
	3. Severely
	4. Extremely
14. How scared or worried were you about your lung problems today?	0. Not at all
	1. Slightly
	2. Moderately
	3. Severely
	3. Extremely
	NOTE: Score "severely" and "extremely" the same.

Raw summed score to scale score conversion table for EXACT Total Score:

Raw Summed Score	EXACT Total Score	Raw Summed Score	EXACT Total Score
0	0	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

This conversion table converts raw summed scores to a 0 to 100 scale via logit scores, for ease of interpretation.

8.5 Appendix 5: Annotated E-RS for Raw Score Assignment

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.

8.6 Appendix 6: Night-time and Early Morning Symptoms (NiSCI and EMSCI)

CCI

Nighttime Symptoms of COPD Instrument (NiSCI) and Early Morning Symptoms of COPD Instrument (EMSCI): Post psychometric validation version :
-Universal English Version: 15 May 2014-

Instructions

- We would like you to complete this diary every day, in the morning, anytime between 7 AM and 11 AM.
- The diary asks you questions about the symptoms of your chronic obstructive pulmonary disease, also called COPD.
- COPD is a lung disease that makes breathing difficult.

The diary is made up of two parts:

1. The first part of the diary asks you a few questions about your COPD symptoms LAST NIGHT.
   - » When you think about LAST NIGHT, we would like you to think about the time from when you went to bed last night until you woke up and got out of bed this morning to start your day.
2. The second part of the diary asks you a few questions about your COPD symptoms after you woke up this morning.
   - » When you think about THIS MORNING, please think about the time since you got out of bed to start your day.

CCI

CCI

Nighttime Symptoms of COPD Instrument (NiSCI) and Early Morning Symptoms of COPD Instrument (EMSCI): Post psychometric validation version :
-Universal English Version: 15 May 2014-

NiSCI

This is the first part of the diary that asks you about your COPD symptoms LAST NIGHT.

When you think about LAST NIGHT, we would like you to think about the time from when you went to bed last night until you woke up and got out of bed this morning to start your day.

Please complete the NIGHTTIME SYMPTOM diary now.

---

1. Last night, did you wake up because of your COPD symptoms?
☐ No
☐ Yes

1a. How many times did you wake up because of your COPD symptoms?
_____times

---

2. Did you experience any of the following last night?

2a. Cough	☐ No	☐ Yes
2b. Wheezing	☐ No	☐ Yes
2c. Shortness of breath	☐ No	☐ Yes
2d. Tightness in your chest	☐ No	☐ Yes
2e. Chest congestion	☐ No	☐ Yes
2f. Difficulty bringing up phlegm	☐ No	☐ Yes

You indicated that you experienced a cough last night…

2a.i. How severe was your cough?
☐ Mild
☐ Moderate
☐ Severe
☐ Very Severe

You indicated that you experienced wheezing last night…

2b.i. How severe was your wheezing?
☐ Mild
☐ Moderate
☐ Severe
☐ Very Severe

You indicated that you experienced shortness of breath last night…

2c.i. How severe was your shortness of breath?
☐ Mild
☐ Moderate
☐ Severe
☐ Very Severe

CCI

CCI

Nighttime Symptoms of COPD Instrument (NiSCI) and Early Morning Symptoms of COPD Instrument (EMSCI): Post psychometric validation version :
-Universal English Version: 15 May 2014-

You indicated that you experienced tightness in your chest last night…

2d.i. How severe was the tightness in your chest?
- ☐ Mild
- ☐ Moderate
- ☐ Severe
- ☐ Very Severe

You indicated that you experienced chest congestion last night…

2e.i. How severe was your chest congestion?
- ☐ Mild
- ☐ Moderate
- ☐ Severe
- ☐ Very Severe

You indicated that you experienced difficulty bringing up phlegm last night…

2f.i. How severe was the difficulty with bringing up phlegm?
- ☐ Mild
- ☐ Moderate
- ☐ Severe
- ☐ Very Severe

---

3. Overall, how severe were your COPD symptoms last night?
- ☐ I did not experience any symptoms
- ☐ Mild
- ☐ Moderate
- ☐ Severe
- ☐ Very Severe

CCI

CCI

Nighttime Symptoms of COPD Instrument (NiSCI) and Early Morning Symptoms of COPD Instrument (EMSCI): Post psychometric validation version :
-Universal English Version: 15 May 2014-

EMSCI

This is the second part of the diary.

This part asks you about your COPD symptoms THIS MORNING.

When you think about THIS MORNING, please think about the time since you got out of bed to start your day.

---

1. Did you experience any of the following this morning?

1a. Cough	☐ No	☐ Yes
1b. Wheezing	☐ No	☐ Yes
1c. Shortness of breath	☐ No	☐ Yes
1d. Tightness in your chest	☐ No	☐ Yes
1e. Chest congestion	☐ No	☐ Yes
1f. Difficulty bringing up phlegm	☐ No	☐ Yes

You indicated that you experienced a cough this morning…

1a.i. How severe was your cough?
- ☐ Mild
- ☐ Moderate
- ☐ Severe
- ☐ Very Severe

You indicated that you experienced wheezing this morning…

1b.i. How severe was your wheezing?
- ☐ Mild
- ☐ Moderate
- ☐ Severe
- ☐ Very Severe

You indicated that you experienced shortness of breath this morning…

1c.i. How severe was your shortness of breath?
- ☐ Mild
- ☐ Moderate
- ☐ Severe
- ☐ Very Severe

You indicated that you experienced tightness in your chest this morning…

1d.i. How severe was the tightness in your chest?
- ☐ Mild
- ☐ Moderate
- ☐ Severe
- ☐ Very Severe

CCI

CCI

Nighttime Symptoms of COPD Instrument (NiSCI) and Early Morning Symptoms of COPD Instrument (EMSCI): Post psychometric validation version :
-Universal English Version: 15 May 2014-

You indicated that you experienced chest congestion this morning…

1e.i. How severe was your chest congestion?
- ☐ Mild
- ☐ Moderate
- ☐ Severe
- ☐ Very Severe

You indicated that you experienced difficulty bringing up phlegm this morning…

1f.i. How severe was the difficulty with bringing up phlegm?
- ☐ Mild
- ☐ Moderate
- ☐ Severe
- ☐ Very Severe

---

2. Overall, how severe were your COPD symptoms this morning?
- ☐ I did not experience any symptoms
- ☐ Mild
- ☐ Moderate
- ☐ Severe
- ☐ Very Severe

---

3. How much have you limited your activities this morning because of your COPD symptoms?
- ☐ Not at all
- ☐ A little
- ☐ Moderately
- ☐ A good deal
- ☐ A very great deal

CCI

8.7 Appendix 7: Device Preference and willingness to continue questionnaire

Device Preference

Which device do you prefer?:
(Please, tick one box only)

☐ Genuair/Pressair®

☐ HandiHaler®

☐ No preference

Which device do you prefer in term of the following attributes?
(Please, tick one box only)

Attribute	Which do you prefer ... ?
Ease of use	☐ Genuair/Pressair® ☐ HandiHaler® ☐ No preference
Convenience	☐ Genuair/Pressair® ☐ HandiHaler® ☐ No preference
Ease of learning to use	☐ Genuair/Pressair® ☐ HandiHaler® ☐ No preference
Ease of holding	☐ Genuair/Pressair® ☐ HandiHaler® ☐ No preference
Ease of operating	☐ Genuair/Pressair® ☐ HandiHaler® ☐ No preference
Ease of preparation of the dose	☐ Genuair/Pressair® ☐ HandiHaler® ☐ No preference
Feedback to indicate correct inhalation	☐ Genuair/Pressair® ☐ HandiHaler® ☐ No preference

Willingness to continue

Please rate the extend to which you would be willing to continue using each of the devices:
(Please, write a number between "0 = not willing" and "100 = definitely willing" in the space provided below)

- Genuair/Pressair® |_|_|_|
- HandiHaler® |_|_|_|

8.8 INDEX OF TABLEs, FIGUREs AND LISTINGs

This is an amended TFL index from the *D6571C00001_TFL index_Final Version* signed off on May the 10th, 2017.

DEMOGRAPHIC DATA

Study population and inclusion/exclusion criteria

Table	Description
Table 11.1.1.	Patient disposition. All Patients.
Table 11.1.2.	Analysis sets. Randomized patients.
Table 11.1.3.1.	Inclusion criteria at screening visit.
Table 11.1.3.2.	Inclusion criteria not met at screening visit. Descriptive statistics. Safety population.
Table 11.1.4.1.	Exclusion criteria at screening visit.
Table 11.1.4.2.	Exclusion criteria met at screening visit. Descriptive statistics. Safety population.

Patients' time to withdrawal

Table	Description
Table 11.1.5.	Time (days) to withdrawal from IP. Descriptive statistics, and analysis based on the Cox Proportional Hazard model. Safety population.

PATIENTS' CHARACTERISTICS AT SCREENING VISIT

Table	Description
11.1.6.1.	Demographic characteristics at screening visit. Safety population.

11.1.6.2.	Demographic characteristics at screening visit. Intention-to-Treat population.
11.1.7.1.	Cigarette smoking status, smoking duration and smoking consumption. Safety population.
11.1.7.2.	Cigarette smoking status, smoking duration and smoking consumption. Intention-to-Treat population.
11.1.8.	Medical history at screening visit. Description by system organ class and preferred term. Safety population.
11.1.9.1.	COPD severity (based on airflow limitation and GOLD guidelines) and duration. Safety population.
11.1.9.2.	COPD severity (based on airflow limitation and GOLD guidelines) and duration. Intention-to-Treat population.
11.1.10.1.	Number of patients with COPD exacerbations in the previous 12 months. Safety population.
11.1.10.2.	Number of patients with COPD exacerbations in the previous 12 months. Intention-to-Treat population.
11.1.11.1.	Pulmonary function test at screening visit. Pre-bronchodilator test: Absolute values and percent of predicted of the FEV1 and FVC. Safety population.
11.1.11.2.	Pulmonary function test at screening visit. Pre-bronchodilator test: Absolute values and percent of predicted of the FEV1 and FVC. Intention-to-Treat population.

11.1.12.1.	Pulmonary function test at screening visit. Post-bronchodilator test: Absolute values and percent of predicted of the FEV1, FVC, and Ratio FEV1 / FVC. Safety population.
11.1.12.2.	Pulmonary function test at screening visit. Post-bronchodilator test: Absolute values and percent of predicted of the FEV1, FVC, and Ratio FEV1 / FVC. Intention-to-Treat population.
11.1.13.1.	Pulmonary function test at screening visit. Bronchodilator test reversibility: Mean absolute reversibility (change from pre-test) and bronchial (%) reversibility (percentage increase over pre-test) and number and percentage of patients reversible (meet the reversibility criteria). Safety population.
11.1.13.2.	Pulmonary function test at screening visit. Bronchodilator test reversibility: Mean absolute reversibility (change from pre-test) and bronchial (%) reversibility (percentage increase over pre-test) and number and percentage of patients reversible (meet the reversibility criteria). Intention-to-Treat population.
11.1.14.	Pulmonary function test parameters (absolute values and percent predicted FEV1 and FVC). Pre-Investigational medicinal Product at baseline (visit 2-day 1). Safety population.
11.1.15.	Pulmonary function test parameters (absolute values and percent predicted FEV1 and FVC). Pre-Investigational medicinal Product at baseline (visit 2-day 1). Intention-to-Treat population.
11.1.16.	St. George's Respiratory Questionnaire (SGRQ) total and three dimension scores at baseline (visit 2-day 1). Safety population.
11.1.17.	St. George's Respiratory Questionnaire (SGRQ) total and three dimension scores at baseline (visit 2-day 1). Intention-to-Treat population.
11.1.18.	COPD Assessment Test (CAT) at baseline (visit 2-day 1).

	Safety population.
11.1.19.	COPD Assessment Test (CAT) at baseline (visit 2-day 1). Intention-to-Treat population.

TREATMENT COMPLIANCE

Table	Description
11.1.20.	Treatment compliance. Descriptive analysis by treatment. Safety population.

Prior medication and concomitant medication

Table	Description
11.1.21.	Prior medication by ATC3 text and preferred name. Safety population.
11.1.22.	COPD related prior medication by therapeutic categories. Safety population.
11.1.23.	Number (%) of patients with concomitant medication by ATC3 text, and preferred name. Medications started to be taken before the first IP intake and continued after the first IP intake. Safety population.
11.1.24.	Number (%) of patients with concomitant medication by ATC3 text, and preferred name. Medications started to be taken after the first IP intake. Safety population.
11.1.25.	Sensitivity analysis for patients continuing study participation beyond the IP treatment discontinuation. Number (%) of patients with concomitant medication by ATC3 text, and preferred name. Medications started to be taken before the first IP intake and continued after the first IP intake. Safety population.

11.1.26.	Sensitivity analysis for patients continuing study participation beyond the IP treatment discontinuation. Number (%) of patients with concomitant medication by ATC3 text, and preferred name. Medications started to be taken after the first IP intake. Safety population.

EFFICACY DATA

1-h post dose FEV1 over 24 weeks on treatment

Table	Description
11.2.1.1.	Change from baseline in 1-hour morning post-dose FEV1 (L) over 24 weeks on treatment (day 1, weeks 4, 12, 18, and 24). Summary statistics. Intention-to-Treat population.
11.2.1.2.	Change from baseline in 1-hour morning post-dose FEV1 (L) over 24 weeks on treatment (day 1, weeks 4, 12, 18, and 24). Treatment comparisons. Intention-to-Treat population.
11.2.1.3.	Sensitivity analysis for missing data (MNAR) in change from baseline in 1-hour morning post-dose FEV1(L) over 24 weeks on treatment (day 1, weeks 4, 12, 18, and 24). Treatment comparisons. Intention-to-Treat population.
11.2.1.4.	Sensitivity analysis by reason of withdrawl for change from baseline in 1-hour morning post-dose FEV1 (L) over 24 weeks on treatment (day 1, weeks 4, 12, 18, and 24). Summary statistics. Intention-to-Treat population.
11.2.2.1.	Change from baseline in 1-hour morning post-dose FEV1 (L) over 24 weeks on treatment (day 1, weeks 4, 12, 18, and 24) for patients continuing study participation beyond the IP treatment discontinuation. Summary statistics. Safety population.

11.2.2.2.	Change from baseline in 1-hour morning post-dose FEV1 (L) over 24 weeks on treatment (day 1, weeks 4, 12, 18, and 24) for patients continuing study participation beyond the IP treatment discontinuation. Treatment comparisons. Safety population.
11.2.3.1.	Absolute values in 1-hour morning post-dose FEV1 (L) over 24 weeks on treatment (day 1, weeks 4, 12, 18, and 24). Summary statistics. Intention-to-Treat population.
11.2.3.2.	Absolute values in 1-hour morning post-dose FEV1 (L) over 24 weeks on treatment (day 1, weeks 4, 12, 18, and 24). Treatment comparisons. Intention-to-Treat population.

Morning pre-dose (trough) FEV1 and FVC over 24 weeks on treatment

Table	**Description**
11.2.4.1.	Change from baseline in morning pre-dose (trough) FEV1 (L) over 24 weeks on treatment (weeks 1, 4, 12, 18, and 24). Summary statistics. Intention-to-Treat population.
11.2.4.2.	Change from baseline in morning pre-dose (trough) FEV1 (L) over 24 weeks on treatment (weeks 1, 4, 12, 18, and 24). Treatment comparisons. Intention-to-Treat population.
11.2.4.3.	Sensitivity analysis for missing data (MNAR) in change from baseline morning pre-dose (trough) FEV1 (L) over 24 weeks on treatment (weeks 1, 4, 12, 18, and 24). Treatment comparisons. Intention-to-Treat population.
11.2.4.4.	Sensitivity analysis by reason of withdrawl for change from baseline in morning pre-dose (trough) FEV1 (L) over 24 weeks on treatment (weeks 1, 4, 12, 18, and 24). Summary statistics. Intention-to-Treat population.

11.2.5.1.	Change from baseline in morning pre-dose (trough) FEV1 (L) over 24 weeks on treatment for patients continuing study participation beyond the IP treatment discontinuation. Summary statistics. Safety population.
11.2.5.2.	Change from baseline in morning pre-dose (trough) FEV1 (L) over 24 weeks on treatment (weeks 1, 4, 12, 18, and 24) for patients continuing study participation beyond the IP treatment discontinuation. Treatment comparisons. Safety population.
11.2.6.1.	Non-inferiority assessment: Change from baseline in morning pre-dose (trough) FEV1 (L) over 24 weeks on treatment (weeks 1, 4, 12, 18, and 24). Summary statistics. Per protocol population.
11.2.6.2.	Non-inferiority assessment: Change from baseline in morning pre-dose (trough) FEV1 (L) over 24 weeks on treatment (weeks 1, 4, 12, 18, and 24). Treatment comparisons. Per protocol population.
11.2.7.1.	Absolute values in morning pre-dose (trough) FEV1 (L) over 24 weeks on treatment (weeks 1, 4, 12, 18, and 24). Summary statistics. Intention-to-Treat population.
11.2.7.2.	Absolute values in morning pre-dose (trough) FEV1 (L) over 24 weeks on treatment (weeks 1, 4, 12, 18, and 24). Treatment comparisons. Intention-to-Treat population.
11.2.8.1.	Change from baseline in morning pre-dose (trough) FVC (L) over 24 weeks on treatment (weeks 1, 4, 12, 18, and 24). Summary statistics. Intention-to-Treat population.

11.2.8.2.	Change from baseline in morning pre-dose (trough) FVC (L) over 24 weeks on treatment (weeks 1, 4, 12, 18, and 24). Treatment comparisons. Intention-to-Treat population.
11.2.9.1.	Absolute values in morning pre-dose (trough) FVC (L) over 24 weeks on treatment (weeks 1, 4, 12, 18, and 24). Summary statistics. Intention-to-Treat population.
11.2.9.2.	Absolute values in morning pre-dose (trough) FVC (L) over 24 weeks on treatment (weeks 1, 4, 12, 18, and 24). Treatment comparisons. Intention-to-Treat population.

Normalized AUC FEV1 over 24 weeks on treatment

Table	**Description**
11.2.10.1.	Change from baseline in normalized AUC 0-3/3h FEV1 (L) over 24 weeks on treatment (day 1, and weeks 12, and 24). Summary statistics. Intention-to-Treat population.
11.2.10.2.	Change from baseline in normalized AUC 0-3/3h FEV1 (L) over 24 weeks on treatment (day 1, and weeks 12, and 24). Treatment comparisons. Intention-to-Treat population.
11.2.11.1.	Sensitivity analysis for missing data (MNAR) in change from baseline in normalized AUC 0-3/3h FEV1 (L) over 24 weeks on treatment (day 1, and weeks 12, and 24). Treatment comparisons. Intention-to-Treat population.
11.2.11.2.	Sensitivity analysis by reason of withdrawl for change from baseline in in normalized AUC 0-3/3h FEV1 (L) over 24 weeks on treatment (day 1, and weeks 12, and 24). Summary statistics. Intention-to-Treat population.

11.2.12.1.	Substudy patients: Change from baseline in normalized AUC 0-12/12h FEV1 (L) over 24 weeks on treatment (day 1, and week 24). Summary statistics. Intention-to-Treat population.
11.2.12.2.	Substudy patients: Change from baseline in normalized AUC 0-12/12h FEV1 (L) over 24 weeks on treatment (day 1, and week 24). Treatment comparisons. Intention-to-Treat population.
11.2.13.1.	Substudy patients: Change from baseline in normalized AUC 12-24/12h FEV1 (L) over 24 weeks on treatment (day 1, and week 24). Summary statistics. Intention-to-Treat population.
11.2.13.2.	Substudy patients: Change from baseline in normalized AUC 12-24/12h FEV1 (L) over 24 weeks on treatment (day 1, and week 24). Treatment comparisons. Intention-to-Treat population.
11.2.14.1.	Substudy patients: Change from baseline in normalized AUC 0-24/24h FEV1 (L) over 24 weeks on treatment (day 1, and week 24). Summary statistics. Intention-to-Treat population.
11.2.14.2.	Substudy patients: Change from baseline in normalized AUC 0-24/24h FEV1 (L) over 24 weeks on treatment (day 1, and week 24). Treatment comparisons. Intention-to-Treat population.
11.2.15.1.	Change from baseline in normalized AUC 0-3/3h FVC (L) over 24 weeks on treatment (day 1, and weeks 12, and 24). Summary statistics. Intention-to-Treat population.
11.2.15.2.	Change from baseline in normalized AUC 0-3/3h FVC (L) over 24 weeks on treatment (day 1, and weeks 12, and 24). Treatment comparisons. Intention-to-Treat population.
11.2.16.1.	Substudy patients: Change from baseline in normalized AUC 0-12/12h FVC (L) over 24 weeks on treatment (day 1, and week 24).

	Summary statistics. Intention-to-Treat population.
11.2.16.2.	Substudy patients: Change from baseline in normalized AUC 0-12/12h FVC (L) over 24 weeks on treatment (day 1, and week 24). Treatment comparisons. Intention-to-Treat population.
11.2.17.1.	Substudy patients: Change from baseline in normalized AUC 12-24/12h FVC (L) over 24 weeks on treatment (day 1, and week 24). Summary statistics. Intention-to-Treat population.
11.2.17.2.	Substudy patients: Change from baseline in normalized AUC 12-24/12h FVC (L) over 24 weeks on treatment (day 1, and week 24). Treatment comparisons. Intention-to-Treat population.
11.2.18.1.	Substudy patients: Change from baseline in normalized AUC 0-24/24h FVC (L) over 24 weeks on treatment (day 1, and week 24). Summary statistics. Intention-to-Treat population.
11.2.18.2.	Substudy patients: Change from baseline in normalized AUC 0-24/24h FVC (L) over 24 weeks on treatment (day 1, and week 24). Treatment comparisons. Intention-to-Treat population.

Symptoms and health-related QoL: SGRQ and CAT over 24 weeks of treatment

Table	**Description**
11.2.19.1.	Number (%) of patients achieving a clinically meaningful improvement (a decrease of at least 4-units) from baseline in the SGRQ total score over 24 weeks on treatment (weeks 4, 12, 18, and 24). Summary statistics. Intention-to-Treat population.
11.2.19.2.	Number (%) of patients achieving a clinically meaningful improvement (a decrease of at least 4-units) from baseline in the SGRQ total score over 24 weeks on treatment (weeks 4, 12, 18, and 24).

	Treatment comparisons. Intention-to-Treat population.
11.2.19.3.	Sensitivity analysis considering patient's missing data as non-responders in number (%) of patients achieving a clinically meaningful improvement (a decrease of at least 4-units) from baseline in the SGRQ total score over 24 weeks on treatment (weeks 4, 12, 18, and 24). Treatment comparisons. Intention-to-Treat population.
11.2.19.4.	Sensitivity analysis by reason of withdrawl for number (%) of patients achieving a clinically meaningful improvement (a decrease of at least 4-units) from baseline in the SGRQ total score over 24 weeks on treatment (weeks 4, 12, 18, and 24). Summary statistics. Intention-to-Treat population.
11.2.20.1.	Number (%) of patients achieving a clinically meaningful improvement (a decrease of at least 4-units) from baseline in the SGRQ total score at week 24, for patients continuing study participation beyond the IP treatment discontinuation. Summary statistics. Intention-to-Treat population.
11.2.20.2.	Number (%) of patients achieving a clinically meaningful improvement (a decrease of at least 4-units) from baseline in the SGRQ total score at week 24, for patients continuing study participation beyond the IP treatment discontinuation. Treatment comparisons. Intention-to-Treat population.
11.2.21.1.	Change from baseline in SGRQ total score and three dimension scores over 24 weeks on treatment (weeks 4, 12, 18, and 24). Summary statistics. Intention-to-Treat population.
11.2.21.2.	Change from baseline in SGRQ total score and three dimension scores over 24 weeks on treatment (weeks 4, 12, 18, and 24). Treatment comparisons. Intention-to-Treat population.

11.2.22.1.	Change from baseline in COPD Assessment Test (CAT) score over 24 weeks on treatment (weeks 4, 12, 18, and 24). Summary statistics. Intention-to-Treat population.
11.2.22.2.	Change from baseline in COPD Assessment Test (CAT) score over 24 weeks on treatment (weeks 4, 12, 18, and 24). Treatment comparisons. Intention-to-Treat population.
11.2.23.1.	Number (%) of patients achieving a clinically meaningful improvement (a decrease of at least 2-units) from baseline in COPD Assessment Test (CAT) score over 24 weeks on treatment (weeks 4, 12, 18, and 24). Summary statistics. Intention-to-Treat population.
11.2.23.2.	Number (%) of patients achieving a clinically meaningful improvement (a decrease of at least 2-units) from baseline in COPD Assessment Test (CAT) score over 24 weeks on treatment (weeks 4, 12, 18, and 24). Treatment comparisons. Intention-to-Treat population.

FEV1 and FVC by visit and time-point

Table	**Description**
11.2.24.1.	Change from baseline FEV1 (L) by visit and time-point (day 1, weeks 1, 4, 12, 18, and 24). Summary statistics. Intention-to-Treat population.
11.2.24.2.	Change from baseline FEV1 (L) by visit and time-point (day 1, weeks 1, 4, 12, 18, and 24). Treatment comparisons. Intention-to-Treat population.
11.2.25.1.	FEV1 (L) by visit and time-point (day 1, weeks 1, 4, 12, 18, and 24). Summary statistics. Intention-to-Treat population.

11.2.25.2.	FEV1 (L) by visit and time-point (day 1, weeks 1, 4, 12, 18, and 24). Treatment comparisons. Intention-to-Treat population.
11.2.26.1.	Substudy patients: Change from baseline FEV1 (L) by visit and time-point (day 1, weeks 1, 4, 12, 18, and 24). Summary statistics. Intention-to-Treat population.
11.2.26.2.	Substudy patients: Change from baseline FEV1 (L) by visit and time-point (day 1, weeks 1, 4, 12, 18, and 24). Treatment comparisons. Intention-to-Treat population.
11.2.27.1.	Change from baseline FVC (L) by visit and time-point (day 1, weeks 1, 4, 12, 18, and 24). Summary statistics. Intention-to-Treat population.
11.2.27.2.	Change from baseline FVC (L) by visit and time-point (day 1, weeks 1, 4, 12, 18, and 24). Treatment comparisons. Intention-to-Treat population.
11.2.28.1.	FVC (L) by visit and time-point (day 1, weeks 1, 4, 12, 18, and 24). Summary statistics. Intention-to-Treat population.
11.2.28.2.	FVC (L) by visit and time-point (day 1, weeks 1, 4, 12, 18, and 24). Treatment comparisons. Intention-to-Treat population.
11.2.29.1.	Substudy patients: Change from baseline FVC (L) by visit and time-point (day 1, weeks 1, 4, 12, 18, and 24). Summary statistics. Intention-to-Treat population.
11.2.29.2.	Substudy patients: Change from baseline FVC (L) by visit and time-point (day 1, weeks 1, 4, 12, 18, and 24). Treatment comparisons. Intention-to-Treat population.

Onset of action of bronchodilation FEV1

Table	Description
11.2.30.1.	Onset of action: Change from baseline in FEV1 5 minutes after the fisrt dose on day 1. Summary statisitics. Intention-to-Treat population.
11.2.30.2.	Onset of action: Change from baseline in FEV1 5 minutes after the fisrt dose on day 1. Treatment comparisons. Intention-to-Treat population.
11.2.31.1.	Onset of action: Change from baseline in FEV1 15 minutes after the fisrt dose on day 1. Summary statisitics. Intention-to-Treat population.
11.2.31.2.	Onset of action: Change from baseline in FEV1 15 minutes after the fisrt dose on day 1. Treatment comparisons. Intention-to-Treat population.

Peak FEV1 and FVC (highest value observed within the 3h after the morning IP intake)

Table	Description
11.2.32.1.	Change from baseline in peak FEV1 over 24 weeks on treatment (day 1, weeks 12, and 24). Summary statisitics. Intention-to-Treat population.
11.2.32.2.	Change from baseline in peak FEV1 over 24 weeks on treatment (day 1, weeks 12, and 24). Treatment comparisons. Intention-to-Treat population.
11.2.33.1.	Change from baseline in peak FVC over 24 weeks on treatment (day 1, weeks 12, and 24). Summary statisitics.

	Intention-to-Treat population.
11.2.33.2.	Change from baseline in peak FVC over 24 weeks on treatment (day 1, weeks 12, and 24). Treatment comparisons. Intention-to-Treat population.

COPD exacerbations (Health Care resource utilisation HCRU, and derived from EXACT)

Table	**Description**
11.2.34.	Frequency distribution of HCRU COPD exacerbations (any, mild, moderate, severe, and moderate-to-severe), and EXACT exacerbations. Summary statistics. Safety population.
11.2.35.1.	Number (%) of patients with at least one HCRU COPD exacerbations (any, mild, moderate, severe, and moderate or severe), and EXACT exacerbations. Summary statistics. Safety population.
11.2.35.2.	Number (%) of patients with at least one HCRU COPD exacerbations (any, mild, moderate, severe, and moderate or severe), and EXACT exacerbations. Treatment comparisons. Safety population.
11.2.36.	Mean number of HCRU COPD exacerbations (any, mild, moderate, severe, and moderate or severe), and EXACT exacerbations. Summary statistics. Safety population.
11.2.37.1.	Rate of HCRU COPD exacerbations per patient/year (any, mild, moderate, severe, and moderate or severe), and EXACT exacerbations. Summary statistics. Safety population.

11.2.37.2.	Rate of HCRU COPD exacerbations per patient/year (any, mild, moderate, severe, and moderate or severe), and EXACT exacerbations. Log-linear model. Safety population.
11.2.38.	Duration (days) of the HCRU COPD exacerbations (any, and moderate-to-severe), and EXACT exacerbations. Summary statistics. Safety population.
11.2.39.	Time (days) to first HCRU COPD exacerbation (any, and moderate-to-severe), and EXACT exacerbations. Summary statistics, and Cox Proportional Hazard model. Safety population.
11.2.40.	Frequency distribution of HCRU COPD exacerbations (any, mild, moderate, severe, and moderate-to-severe), and EXACT exacerbations for patients continuing study participation beyond the IP treatment discontinuation. Summary statistics. Safety population.
11.2.41.1.	Number (%) of patients with at least one HCRU COPD exacerbations (any, mild, moderate, severe, and moderate or severe), and EXACT exacerbations for patients continuing study participation beyond the IP treatment discontinuation. Summary statistics. Safety population.
11.2.41.2.	Number (%) of patients with at least one HCRU COPD exacerbations (any, mild, moderate, severe, and moderate or severe), and EXACT exacerbations for patients continuing study participation beyond the IP treatment discontinuation. Treatment comparisons. Safety population.
11.2.42.	Mean number of HCRU COPD exacerbations (any, mild, moderate, severe, and moderate or severe), and EXACT exacerbations for patients continuing study participation beyond the IP treatment discontinuation. Summary statistics. Safety population.

11.2.43.1.	Rate of HCRU COPD exacerbations per patient/year (any, mild, moderate, severe, and moderate or severe), and EXACT exacerbations for patients continuing study participation beyond the IP treatment discontinuation. Summary statistics. Safety population.
11.2.43.2.	Rate of HCRU COPD exacerbations per patient/year (any, mild, moderate, severe, and moderate or severe), and EXACT exacerbations for patients continuing study participation beyond the IP treatment discontinuation. Log-linear model. Safety population.
11.2.44.	Duration (days) of the HCRU COPD exacerbations (any, and moderate-to-severe), and EXACT exacerbations for patients continuing study participation beyond the IP treatment discontinuation. Summary statistics. Safety population.
11.2.45.	Time (days) to first HCRU COPD exacerbation (any, and moderate-to-severe), and EXACT exacerbations for patients continuing study participation beyond the IP treatment discontinuation. Summary statistics, and Cox Proportional Hazard model. Safety population.

E-RS Total score, Breathlessness, Cough & Sputum, and Chest domains socres

Table	**Description**
11.2.46.1.	Change from baseline in the E-RS total score, breathlessness, cough and sputum, and chest domain scores over 24 weeks on treatment (baseline, weeks 4, 12, 18, 24, and overall). Summary statistics. Intention-to-Treat population.
11.2.46.2.	Change from baseline in the E-RS total score, breathlessness, cough and sputum, and chest domain scores over 24 weeks on treatment (weeks 4, 12, 18, 24, and overall). Treatment comparisons. Intention-to-Treat population.

11.2.47.1.	Number (%) of patients achieving a clinically meaningful improvement (a decrease of at least 2-units) from baseline in the E-RS total score over 24 weeks on treatment (weeks 4, 12, 18, 24, and overall). Summary statistics. Intention-to-Treat population.
11.2.47.2.	Number (%) of patients achieving a clinically meaningful improvement (a decrease of at least 2-units) from baseline in the E-RS total score over 24 weeks on treatment (weeks 4, 12, 18, 24, and overall). Treatment comparisons. Intention-to-Treat population.
11.2.48.1.	Number (%) of patients achieving a clinically meaningful improvement (a decrease of at least 1-units) from baseline in the E-RS breathlessness score over 24 weeks on treatment (weeks 4, 12, 18, 24, and overall). Summary statistics. Intention-to-Treat population.
11.2.48.2.	Number (%) of patients achieving a clinically meaningful improvement (a decrease of at least 1-units) from baseline in the E-RS breathlessness score over 24 weeks on treatment (weeks 4, 12, 18, 24, and overall). Treatment comparisons. Intention-to-Treat population.
11.2.49.1.	Number (%) of patients achieving a clinically meaningful improvement (a decrease of at least 0.7-units) from baseline in the E-RS cough and sputum score over 24 weeks on treatment (weeks 4, 12, 18, 24, and overall). Summary statistics. Intention-to-Treat population.
11.2.49.2.	Number (%) of patients achieving a clinically meaningful improvement (a decrease of at least 0.7-units) from baseline in the E-RS cough and sputum score over 24 weeks on treatment (weeks 4, 12, 18, 24, and overall). Treatment comparisons. Intention-to-Treat population.

11.2.50.1.	Number (%) of patients achieving a clinically meaningful improvement (a decrease of at least 0.7-units) from baseline in the E-RS chest score over 24 weeks on treatment (weeks 4, 12, 18, 24, and overall). Summary statistics. Intention-to-Treat population.
11.2.50.2.	Number (%) of patients achieving a clinically meaningful improvement (a decrease of at least 0.7-units) from baseline in the E-RS chest score over 24 weeks on treatment (weeks 4, 12, 18, 24, and overall). Treatment comparisons. Intention-to-Treat population.

Relief medication

Table	**Description**
11.2.51.1.	Change from baseline in the use of relief medication over 24 weeks on treatment (baseline, weeks 4, 12, 18, 24, and overall). Summary statistics. Intent-to-Treat Population.
11.2.51.2.	Change from baseline in the use of relief medication over 24 weeks on treatment (weeks 4, 12, 18, 24, and overall). Intent-to-Treat Population.

Night-time and Early morning symptoms (NiSCI & EMSCI)

Table	**Description**
11.2.52.1.	NiSCI: Change from baseline in the average number of times a patient woke up during a night because of COPD symptoms over 24 weeks on treatment (baseline, weeks 4, 12, 18, 24, and overall). Summary statistics. Intention-to-Treat population.
11.2.52.2.	NiSCI: Change from baseline in the average number of times a patient woke up during a night because of COPD symptoms over 24 weeks on treatment (weeks 4, 12, 18, 24, and overall). Treatment comparisons. Intention-to-Treat population.

11.2.53.1.	NiSCI: Change from baseline in the average rating of night severity (cough, wheezing, shortness of breath, tightness chest congestion, difficulty bringing up phlegm, and overall night-time COPD symptom) over 24 weeks on treatment (baseline, weeks 4, 12, 18, 24, and overall). Summary statistics. Intention-to-Treat population.
11.2.53.2.	NiSCI: Change from baseline in the average rating of night severity (cough, wheezing, shortness of breath, tightness chest congestion, difficulty bringing up phlegm, and overall night-time COPD symptom) over 24 weeks on treatment (weeks 4, 12, 18, 24, and overall). Treatment comparisons. Intention-to-Treat population.
11.2.54.1.	EMSCI: Change from baseline in the average rating of night severity (cough, wheezing, shortness of breath, tightness chest congestion, difficulty bringing up phlegm, and overall night-time COPD symptom) over 24 weeks on treatment (baseline, weeks 4, 12, 18, 24, and overall). Summary statistics. Intention-to-Treat population.
11.2.54.2.	EMSCI: Change from baseline in the average rating of night severity (cough, wheezing, shortness of breath, tightness chest, congestion, difficulty bringing up phlegm, and overall night-time COPD symptom) over 24 weeks on treatment (weeks 4, 12, 18, 24, and overall). Treatment comparisons. Intention-to-Treat population.
11.2.55.1.	EMSCI: Change from baseline in the average rating of COPD symptoms limiting early morning activities over 24 weeks on treatment (baseline, weeks 4, 12, 18, 24, and overall). Summary statistics. Intention-to-Treat population.
11.2.55.2.	EMSCI: Change from baseline in the average rating of COPD symptoms limiting early morning activities over 24 weeks on treatment (weeks 4, 12, 18, 24, and overall). Treatment comparisons. Intention-to-Treat population.

Device preference and willingness to continue questionnaire

Table	Description
11.2.56.1.	Number (%) of patients at the end of treatment period by device preference inhaler (Genuair/Pressair®, HandiHaler®, No preference) and attribute (ease of use, convenience, ease of learning to use, ease of holding, ease of operating, ease of preparation of the dose, feedback to indicate correct inhalation). Summary statistics. Intention-to-Treat population.
11.2.56.2.	Number (%) of patients at the end of treatment period by device preference inhaler (Genuair/Pressair®, HandiHaler®, No preference) and attribute (ease of use, convenience, ease of learning to use, ease of holding, ease of operating, ease of preparation of the dose, feedback to indicate correct inhalation). Binomial test. Intention-to-Treat population.
11.2.57.1.	Preference willing to continue using each of the devices (Genuair/Pressair®, HandiHaler®). Summary statistics. Intention-to-Treat population.
11.2.57.2.	Preference willing to continue using each of the devices (Genuair/Pressair®, HandiHaler®). Paired t-test. Intention-to-Treat population.

Subgroup analysis for co-primary and secondary efficacy variables

Table	Description
11.2.58.1.	Change from baseline in 1-hour morning post-dose FEV1 (L) at week 24 by COPD Assessment Test (CAT) category. Summary statistics. Intention-to-Treat population.
11.2.58.2.	Change from baseline in 1-hour morning post-dose FEV1 (L) at week 24 by COPD Assessment Test (CAT) category. Treatment comparisons. Intention-to-Treat population.

11.2.59.1.	Change from baseline in morning pre-dose (trough) FEV1 (L) at week 24 by COPD Assessment Test (CAT) category. Summary statistics. Intention-to-Treat population.
11.2.59.2.	Change from baseline in morning pre-dose (trough) FEV1 (L) at week 24 by COPD Assessment Test (CAT) category. Treatment comparisons. Intention-to-Treat population.
11.2.60.1.	Change from baseline in normalized AUC 0-3/3h FEV1 (L) at week 24 by COPD Assessment Test (CAT) category. Summary statistics. Intention-to-Treat population.
11.2.60.2.	Change from baseline in normalized AUC 0-3/3h FEV1 (L) at week 24 by COPD Assessment Test (CAT) category. Treatment comparisons. Intention-to-Treat population.
11.2.61.1.	Number (%) of patients achieving a clinically meaningful improvement (a decrease of at least 4-units) from baseline in the SGRQ total at week 24 by COPD Assessment Test (CAT) category. Summary statistics. Intention-to-Treat population.
11.2.61.2.	Number (%) of patients achieving a clinically meaningful improvement (a decrease of at least 4-units) from baseline in the SGRQ total score at week 24 by COPD Assessment Test (CAT) category. Treatment comparisons. Intention-to-Treat population.

FIGURES

Figure	**Description**
11.2.62.	Time (days) to withdrawal from IP - Kaplan-Meier Plot. Intention-to-Treat Population.
11.2.63.	Change from Baseline in 1-hour Morning Postdose FEV1 by Visit over 24 Weeks: LSMean (+/- SE).

	Intention-to-Treat Population.
11.2.64.	Change From Baseline in Morning Predose Trough FEV1 (L) By Visit over 24 Weeks. LSMeans (± SE). Intention-to-Treat Population.
11.2.65	Change From Baseline in normalized AUC 0-3/3h FEV1 (L) By Visit over 24 Weeks. LSMeans (± SE). Intention-to-Treat Population.
11.2.66.	Change from baseline FEV_1 by time at Week 24. LSMeans (± SE). Intent-to-Treat Population.
11.2.67.	Change from baseline FEV_1 by time at Week 24 (12-h serial spirometry sub-study). LSMeans (± SE). Intent-to-Treat Population.
11.2.68.	Change From Baseline in SGRQ total score at Weeks 4, 12, and 24 LSMeans (± SE). Intent-to-Treat Population.
11.2.69.	Percentage of patients achieving a clinically meaningful improvement (≥4-units) compared to baseline in the SGRQ Total score at Week 24. Intent-to-Treat Population.
11.2.70.	Time to first moderate-to-severe COPD exacerbation (Days) (eCRF)- Kaplan-Meier Plot. ITT-Exacerbations population.
11.2.71.	Time to first COPD exacerbation (Days) (EXACT)- Kaplan-Meier Plot. ITT-Exacerbations population.
11.2.72.	Change from Baseline in 1-hour Morning Postdose FEV1 by reason of withdrawal and treatment arm. Intention-to-Treat Population.

11.2.73.	Change from Baseline in trough FEV1 by reason of withdrawal and treatment arm. Intention-to-Treat Population.
11.2.74.	Change from Baseline in nAUC0-3 FEV1 by reason of withdrawal and treatment arm. Intention-to-Treat Population.

SAS output of statistical analysis

Table	**Description**
11.2.75.	Change from baseline in 1-hour morning post-dose FEV1 (L) over 24 weeks on treatment. Intention-to-Treat population.
11.2.76.	Change from baseline in morning pre-dose (trough) FEV1 (L) over 24 weeks on treatment. Intention-to-Treat population.
11.2.77.	Change from baseline in in normalized AUC 0-3/3h FEV1 (L) over 24 weeks on treatment. Intention-to-Treat population.
11.2.78.	Number (%) of patients achieving a clinically meaningful improvement (≥4-units) compared to baseline in the SGRQ Total score at Week 24. Intent-to-Treat Population.

11.3 SAFETY DATA

Table	**Description**
11.3.1.	Patient exposure. Descriptive analysis by treatment. Safety population.

Summary of adverse events

Table	**Description**
11.3.2.	Summary of Adverse Events. Safety population.

Adverse events

Table	Description
11.3.3.	Number (%) of patients with any treatment emergent adverse event (TEAE) and number of TEAE episodes by system organ class, high level term, and preferred term. Safety population.
11.3.4.	Number (%) of patients with any treatment emergent adverse event (TEAE) and number of TEAE episodes by system organ class, high level term, preferred term, and severity. Safety population.
11.3.5.	Number (%) of patients with any treatment emergent adverse event (TEAE) and number of TEAE episodes by system organ class, high level term, preferred term, and causality. Safety population.
11.3.6.	Number (%) of patients with any treatment emergent adverse event (TEAE) and number of TEAE episodes by system organ class, high level term, preferred term, and seriousness. Safety population.
11.3.7.	Number (%) of patients with any treatment emergent adverse event (TEAE) and number of TEAE episodes by system organ class, high level term, preferred term, and outcome. Safety population.
11.3.8.	Number (%) of patients with TEAEs and number of TEAE episodes reported by > 1% of patients in any treatment group by preferred term. Safety population.

Serious and significant adverse events

Table	Description
11.3.9.	Number (%) of patients with any treatment emergent serious adverse event (TESAE), and number of TESAE episodes by system organ class, high level term, and preferred term. Safety population.
11.3.10.	Number (%) of patients with any treatment emergent serious adverse event (TESAE), and number of TESAE episodes by system organ

	class, preferred term, and intensity. Safety population.
11.3.11.	Number (%) of patients with any treatment emergent serious adverse event (TESAE) and number of TESAE episodes by system organ class, preferred term, and causality. Safety population.
11.3.12.	Number (%) of patients with any treatment emergent serious adverse event (TESAE), and number of TESAE episodes by system organ class, high level term, and preferred term. Sensitivity analysis including patients continuing study participation beyond the IP treatment discontinuation. Safety population.
11.3.13.	Number (%) of patients with any treatment emergent serious adverse event (TESAE), and number of TESAE episodes by system organ class, high level term, preferred term, and intensity. Sensitivity analysis including patients continuing study participation beyond the IP treatment discontinuation. Safety population.
11.3.14.	Number (%) of patients with any treatment emergent serious adverse event (TESAE), and number of TESAE episodes by system organ class, high level term, preferred term, and causality. Sensitivity analysis including patients continuing study participation beyond the IP treatment discontinuation. Safety population.

Adverse events leading to discontinution

Table	**Description**
11.3.15.	Number (%) of patients with any treatment emergent adverse event (TEAE) leading to discontinuation by system organ class, and preferred term. Safety population.
11.3.16.	Number (%) of patients with any treatment emergent adverse event (TEAE) leading to discontinuation by system organ class, preferred term, and intensity. Safety population.
11.3.17.	Number (%) of patients with any treatment emergent adverse event (TEAE) leading to discontinuation by system organ class, preferred

	term, and causality. Safety population.
11.3.18.	Number (%) of patients with any treatment emergent adverse event (TEAE) leading to discontinuation by system organ class, and preferred term. Sensitivity analysis including patients continuing study participation beyond the IP treatment discontinuation. Safety population.
11.3.19.	Number (%) of patients with any treatment emergent adverse event (TEAE) leading to discontinuation by system organ class, preferred term, and intensity. Sensitivity analysis including patients continuing study participation beyond the IP treatment discontinuation. Safety population.
11.3.20.	Number (%) of patients with any treatment emergent adverse event (TEAE) leading to discontinuation by system organ class, preferred term, and causality. Sensitivity analysis including patients continuing study participation beyond the IP treatment discontinuation. Safety population.

Deaths

Table	**Description**
11.3.21.	Number and percentage of patients with a treatment emergent fatal TESAE by system organ class and preferred term. Safety population.
11.3.22.	Number and percentage of patients with a treatment emergent fatal TESAE by system organ class, preferred term, and causality. Safety population.
11.3.23.	Number and percentage of patients with a treatment emergent fatal TESAE by system organ class and preferred term. Sensitivity analysis including patients continuing study participation beyond the IP treatment discontinuation. Safety population.
11.3.24.	Number and percentage of patients with a treatment emergent fatal TESAE by system organ class, preferred term, and causality. Sensitivity analysis including patients continuing study participation beyond the IP treatment discontinuation. Safety population.

Listings of serious, fatal, or leading to discontinuation AEs

Table	Description
11.3.25.	Listing of treatment emergent serious adverse events (TESAEs). Safety population.
11.3.26.	Listing of treatment-emergent adverse events (TEAE) leading to discontinuation. Safety population.
11.3.27.	Listing of fatal serious adverse events (SAEs). All patients.
11.3.28.	Listing of treatment emergent serious adverse events (TESAEs). Sensitivity analysis including patients continuing study participation beyond the IP treatment discontinuation. Safety population.
11.3.29.	Listing of treatment-emergent adverse events (TEAE) leading to discontinuation. Sensitivity analysis including patients continuing study participation beyond the IP treatment discontinuation. Safety population.
11.3.30.	Listing of fatal serious adverse events (SAEs). Sensitivity analysis including patients continuing study participation beyond the IP treatment discontinuation. All patients.

Cardiac & cerebrovascular disorders, MACE, anticholinergic & prneumonia events

Table	Description
11.3.31.	Incidence of treatment emergent cardiac and cerebrovascular adverse events by specific SMQ category and preferred term. Safety Population.
11.3.32.	List of patients with treatment emergent cardiac and cerebrovascular disorders by specific SMQ category. Safety Population.
11.3.33.	Incidence of adjudicated major adverse cardiovascular events by preferred term. Safety Population.

11.3.34.	List of patients with treatment emergent major adverse cardiovascular events by preferred term. Safety Population.
11.3.35.	Incidence of treatment emergent adverse events of anticholinergic syndrome by system organ class, and preferred term. Safety Population.
11.3.36.	Incidence of treatment emergent adverse events of β2 adrenergic events by SMQ category, and preferred term. Safety Population.
11.3.37.	Incidence of treatment emergent adverse events of pneumonia by preferred term. Safety Population.

Laboratory assessments

Table	**Description**
11.3.38.	Haematology. Absolute values and changes from baseline. Safety population.
11.3.39.	Haematology. Shift table of potentially clinically significant values in laboratory parameters. Safety population.
11.3.40.	Haematology. List of patients with potentially clinically significant post-baseline clinical Laboratory values. Safety population.
11.3.41.	Haematology. Listing of TEAEs for patients with potentially clinically significant postbaseline clinical laboratory values. Safety population.
11.3.42.	Haematology. Number (%) of patients with abnormal clinically relevant parameters. Safety population.
11.3.43.	Haematology. Listing of TEAE for patients with abnormal clinically relevant parameters. Safety population.
11.3.44.	Biochemistry. Absolute values and changes from baseline.

	Safety population.
11.3.45.	Biochemistry. Shift table of potentially clinically significant values in laboratory parameters. Safety population.
11.3.46.	Biochemistry. List of patients with potentially clinically significant post-baseline clinical Laboratory values. Safety population.
11.3.47.	Biochemistry. Listing of TEAEs for patients with potentially clinically significant postbaseline clinical laboratory values. Safety population.
11.3.48.	Biochemistry. Number (%) of patients with abnormal clinically relevant parameters. Safety population.
11.3.49.	Biochemistry. Listing of TEAE for patients with abnormal clinically relevant parameters. Safety population.
11.3.50.	Biochemistry. Listing of potential Hy's Law (PHL), and Hy's Law (HL) Safety population.
11.3.51.	Listing of positive pregnancy test results at screening and at the end of the trial. Safety population.

Blood Pressure

Table	**Description**
11.3.52.	Blood Pressure: Absolute values and changes from baseline by time point in systolic blood pressure (SBP) and diastolic blood pressure (DBP). Safety population.
11.3.53.	Blood Pressure: Number (%) of patients with potentially clinically significant values in systolic blood pressure (SBP) and diastolic blood pressure (DBP). Safety population.

11.3.54.	Blood Pressure: List of patients with non-abnormal/abnormal post-baseline values. Safety population.
11.3.55.	Blood Pressure: Listing of TEAEs for patients with abnormal blood pressure post-baseline values. Safety population.

ECG Parameters

Table	**Description**
11.3.56.	ECG parameters. Absolute values and change from baseline by time-point (heart rate, PR, QRS, QTcB, QTcF, and RR intervals). Safety population.
11.3.57.	ECG global abnormal findings not present at baseline by time-point in rhythm, ectopy, conduction, morphology, myocardial infarction, ST segment, T wave, and U wave. Safety population.
11.3.58.	Number (%) of patients with at least one potentially clinically significant ECG value (heart rate, PR, QRS, QTcB, and QTcF parameters) by time-point and treatment. Safety population.
11.3.59.	Number (%) of patients with ECG classified as abnormal clinically relevant. Safety population.
11.3.60.	ECG parameters. Listing of TEAEs for patients with at least one potentially clinically significant ECG value. Safety population.

12.2. PATIENT DATA LISTINGS

Discontinued patients

Listing	Description
12.2.1.	Discontinued patients.

Protocol deviations

Listing	Description
12.2.2.1.	Important protocol deviations (and patients excluded from PP population).
12.2.2.2.	Inclusion criteria at screening visit. Description.
12.2.2.3.	Inclusion criteria. Answer.
12.2.2.4.	Exclusion criteria at screening visit. Description.
12.2.2.5.	Exclusion criteria. Answer.

Patients excluded from safety and efficacy analyses

Listing	Description
12.2.3.1.	Patients excluded from the intent to treat or per protocol population.
12.2.3.2.	Randomization scheme. Patient identification and treatment assigned.
12.2.3.3.	Patients treatment allocation.
12.2.3.4.	Kit number allocation (including batches of medication).

Demographic Data

Listing	Description
12.2.4.1.	Demography, smoking history, informed consent.
12.2.4.2.	Medical history.
12.2.4.3.	COPD history and physical examination.
12.2.4.4.	Weight, height and BMI.

Patient exposure, patient compliance, prior medication, concomitant medication, and post-treatment medication

Listing	Description
12.2.5.1.	Patient compliance.
12.2.5.2.	Patient exposure.
12.2.5.3.	Prior medication by ATC text.
12.2.5.4.	Prior medication for COPD by therapeutic categories (including vaccines)
12.2.5.5.	Concomitant medication.
12.2.5.6.	Post-treatment medication.

Individual Efficacy response data

Listing	Description
12.2.6.1.	Pulmonary Function Test parameters. Derived values.
12.2.6.2.	SGRQ answers.
12.2.6.3.	CAT answers.
12.2.6.4.	Health status (total and three dimensions scores) as measured by the SGRQ over 24 weeks of treatment.
12.2.6.5.	COPD exacerbations by source: EDC and EXACT questionnaire.
12.2.6.6.	Hospitalization dates per patient.
12.2.6.7.	Drug accountability: Treatment compliance.
12.2.6.8.	e-Diary assessments: EXACT questionnaire.
12.2.6.9.	e-Diary assessments: E-RS Total Score & Breathlessness, Cough & Sputum, and Chest domains scores
12.2.6.10.	e-Diary assessments: Night-time and early morning COPD symptoms
12.2.6.11.	e-Diary assessments: Relief medication.

Adverse event listings

Listing	Description
Listing 12.2.7.	Adverse events by patient number and treatment group.

Laboratory Values

Listing	Description
12.2.8.1.	Laboratory values: Haematology.
12.2.8.2.	Laboratory abnormalities: Haematology.
12.2.8.3.	Laboratory values: Biochemistry (including theophylline levels).
12.2.8.4.	Laboratory abnormalities: Biochemistry (including theophylline levels).

Vitals Signs

Listing	Description
12.2.9.	Vital signs (Blood pressure over time) by treatment group.

ECG parameters

Listing	Description
12.2.10.1.	Electrocardiogram parameters by treatment group.
12.2.10.2.	Electrocardiogram global evaluation by treatment group.
12.2.10.3.	Patients showing outliers in ECG assessments by visit and treatment group.
12.2.10.4.	Description of rhythm, ectopy, conduction, morphology, myocardial infarction by treatment group.
12.2.10.5.	Description of ST segment, T wave and U wave observations by treatment group.

Final Evaluation

Listing	Description
12.2.10.1.	End of Study and End of Treatment forms.
12.2.10.2.	Study comments.