DPM-CF-303 Long Term Administration of Inhaled Mannitol in Cystic Fibrosis - A Safety and Efficacy in Adult Cystic Fibrosis Subjects

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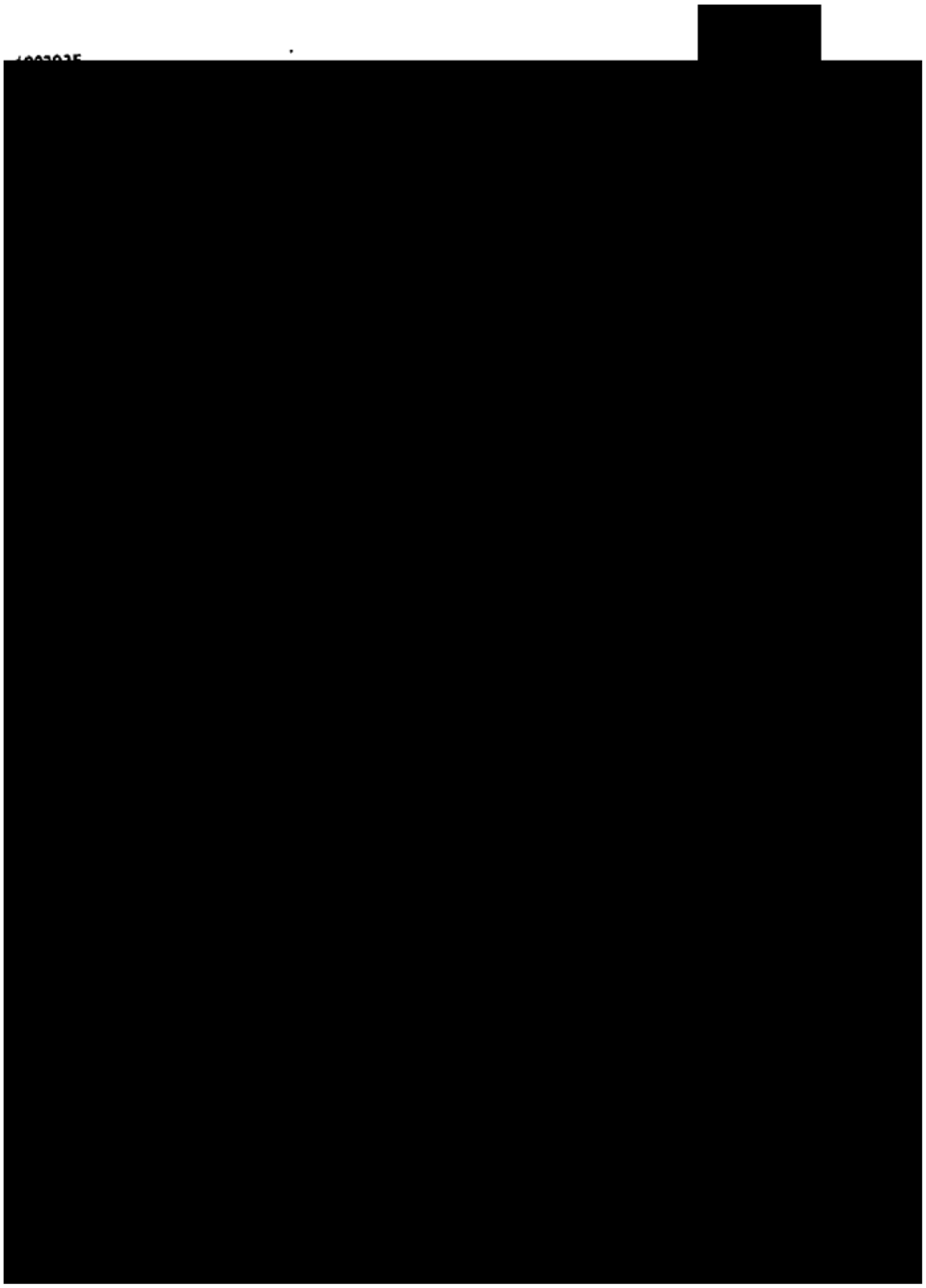

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1. GLOSSARY OF ABBREVIATIONS

Abbreviation	Description
AE	Adverse Event
ANCOVA	Analysis of Covariance
ATC	Anatomical Therapeutic Chemical
ATS/ERS	American Thoracic Society/European Respiratory Society
BDRM	Blind Data Review Meeting
b.i.d.	Twice daily
BOCF	Baseline Observation Carried Forward
CF	Cystic Fibrosis
CFTR	Cystic Fibrosis Transmembrane Conductance Regulator
CI	Confidence Interval
CRF	Case Report Form
DBP	Diastolic Blood Pressure
DMC	Data Monitoring Committee
FEF_{25-75}	Forced Expiratory Fraction from 25% to 75% of Vital Capacity
FEV_1	Forced Expiratory Volume in 1 second
FVC	Forced Vital Capacity
IMP	Investigational Medicinal Product
ITT	Intent-to-Treat
IUDR	Imputation Using Dropout Reason
IV	Intravenous
LS Means	Least Square Means
MDI	Metered Dose Inhaler
MAR	Missing at Random
MEAE	Mannitol Tolerance Test-emergent Adverse Event
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation

Statistical Analysis Plan

Abbreviation	Description
MMRM	Mixed Model Repeated Measures
MTT	Mannitol Tolerance Test
PDPE	Protocol Defined Pulmonary Exacerbation
PE	Pulmonary Exacerbation
PEF	Peak Expiratory Flow
PI	Principal Investigator
PP	Per Protocol
PT	Preferred Term
REML	Restricted Maximum Likelihood
rhDNase	Recombinant human deoxyribonuclease [redacted]
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Standard Deviation
SE	Standard Error
SOC	System Organ Class
SOP	Standard Operating Procedure
SpO_2	Oxygen Saturation
SAF	Safety Set
TEAE	Treatment-emergent Adverse Event
TLF	Table, Listing, and Figure
VAS	Visual Analogue Scale

2. PURPOSE

The purpose of this statistical analysis plan (SAP) is to ensure that the summary tables, data listings, and figures (TLFs) which will be produced, and the statistical methodologies that will be used, are complete and appropriate to allow valid conclusions regarding the trial objectives.

2.1. RESPONSIBILITIES

INC Research will perform the statistical analyses and are responsible for the production and quality control of all TLFs outlined in this document.

2.2. TIMINGS OF ANALYSES

For this trial, only a full analysis of safety and efficacy is planned after all subjects complete the final trial visit or withdraw early from the trial (no interim analyses will be performed). This SAP covers this analysis and has been finalized (on 23May2017) prior to the unblinding of the trial.

An independent data monitoring committee (DMC) reviewed descriptive summaries of subject disposition and accumulating safety data (including summaries of forced expiratory volume in 1 second [FEV_1] and forced vital capacity [FVC]) at a frequency recommended by the DMC. The final DMC charter Version 1.0, dated 29Jul2014, defined the timing and purpose of the DMC meetings and presented an outline of the reports to be provided for review at each meeting. Version 2.0, dated 15Dec2014, contained updates on meeting minute preparation and distribution, distribution of all safety data to the DMC, safety review meetings, and further updates on safety and pharmacovigilance. Version 3.0, dated 04Mar2015, contained updates on the Pharmaxis project manager and Version 2.0 of the protocol. Version 4.0, dated 23Jun2015, contained updates on the Pharmaxis project manager, the addition of summaries of FEV_1 and FVC to be included in open and closed reports, and other administrative changes. None of the updates to the DMC charter affected blinding procedures. The DMC is referred to in the Protocol as the data safety monitoring board. All analyses required for the DMC meetings are documented in a separate DMC SAP (final Version 3.0, dated 02Jul2015). The data reviewed by the DMC were fully unblinded and reported under the actual treatment groups. Therefore a separate unblinded team from INC Research biostatistics performed the analyses as described in the DMC SAP to maintain the blinding of the trial.

A fully blinded sample size re-estimation was planned after at least 300 subjects had been recruited and at least 100 subjects had Visit 4 (Week 26) spirometry data available. Further details are provided in Section 10 and in a separate sample size re-estimation plan (final Version 1.0, dated 07Dec2015).

3. TRIAL OBJECTIVES

3.1. PRIMARY OBJECTIVE

To determine whether inhaled mannitol (400 mg twice daily [b.i.d.]) is superior to control (50 mg inhaled mannitol b.i.d.) for improving lung function as measured by mean change from baseline FEV_1 (mL)* over the 26-week treatment period in adult subjects with cystic fibrosis (CF).

3.2. SECONDARY OBJECTIVE(S)

There are hierarchical and non-hierarchical secondary objectives. Analysis of hierarchical secondary objectives will continue until a non-significant p-value (i.e. $p>0.05$) is returned.

3.2.1. Hierarchical Secondary Objectives

1. To determine whether inhaled mannitol (400 mg b.i.d.) is superior to control (50 mg inhaled mannitol b.i.d.) for improving lung function as measured by mean change from baseline FVC (mL)* over the 26-week treatment period in adult subjects with CF;
2. To determine whether inhaled mannitol (400 mg b.i.d.) is superior to control (50 mg inhaled mannitol b.i.d.) in increasing the time to first pulmonary exacerbation** over the 26-week treatment period in adult subjects with CF;
3. To determine whether in adult subjects with CF, inhaled mannitol (400 mg b.i.d.) is superior to control (50 mg inhaled mannitol b.i.d.) for reducing the number of days on antibiotics (oral, inhaled, or intravenous [IV]) due to pulmonary exacerbation**;
4. To determine whether in adult subjects with CF, inhaled mannitol (400 mg b.i.d.) is superior to control (50 mg inhaled mannitol b.i.d.) for decreasing the number of days in hospital due to pulmonary exacerbation**; and
5. To determine whether inhaled mannitol (400 mg b.i.d.) decreases the rate of pulmonary exacerbations** over the 26-week treatment period compared to control (50 mg inhaled mannitol b.i.d.) in adult subjects with CF.

3.2.2. Non-hierarchical Secondary Objectives

To determine whether in adult subjects with CF, inhaled mannitol (400 mg b.i.d.) is superior to control (50 mg inhaled mannitol b.i.d.)

*Updated in this SAP to be reported in L rather than mL to match the units used in data collection (see Section 11).

**Clarified in this SAP that pulmonary exacerbations classified as protocol defined pulmonary exacerbations (PDPEs) will be used in the main analyses for these endpoints (see Section 11).

1. For decreasing the incidence of exacerbations** (i.e. the proportion of subjects with one or more exacerbation);
2. For improving ease of expectoration; and
3. For improving subject reported respiratory symptoms as measured by CFQ-R respiratory domain.

3.3. BRIEF DESCRIPTION OF TRIAL DESIGN

This is a phase III double-blind, randomized, parallel group, controlled, multicenter, and interventional clinical trial. Potential subjects will sign the informed consent form (ICF) and be assessed for eligibility. After satisfying all inclusion & exclusion criteria, subjects will be given a mannitol tolerance test (MTT). Those subjects that pass the MTT will be randomized in a 1:1 ratio to receive inhaled mannitol (400 mg b.i.d.) or control (50 mg inhaled mannitol b.i.d.) for a period of 26 weeks. Randomization will be stratified by Recombinant human deoxyribonuclease ([redacted] rhDNase) use and country.

3.4. SUBJECT SELECTION

3.4.1. Inclusion Criteria

The subject must meet all of the following criteria:

1. Have given written informed consent to participate in this trial in accordance with local regulations;
2. Have a confirmed diagnosis of CF (positive sweat chloride value ≥60 mEq/L) and/or genotype with two identifiable mutations consistent with CF, accompanied by one or more clinical features consistent with the CF phenotype);
3. Be aged at least 18 years old;
4. Have FEV_1 >40% and <90% predicted (using NHanes III[1]);
5. Be able to perform all the techniques necessary to measure lung function;
6. Be adherent with maintenance therapies (antibiotics and/or rhDNase), if used, for at least 80% of the time in the two weeks prior to Visit 1; and
7. If rhDNase and/or maintenance antibiotic are being used treatment must have been established at least 1 month prior to screening (Visit 0). The subject should remain on the rhDNase and/or maintenance antibiotics for the duration of the trial. The subject should not commence treatment with rhDNase or maintenance antibiotics during the trial.

*Updated in this SAP to be reported in L rather than mL to match the units used in data collection (see Section 11).

**Clarified in this SAP that pulmonary exacerbations classified as protocol defined pulmonary exacerbations (PDPEs) will be used in the main analyses for these endpoints (see Section 11).

3.4.2. Exclusion Criteria

The subject must NOT meet any of the following criteria:

1. Be investigators, site personnel directly affiliated with this trial, or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biologically or legally adopted;
2. Be considered "terminally ill" or eligible for lung transplantation;
3. Have had a lung transplant;
4. Be using maintenance nebulized hypertonic saline including in the 2 weeks prior to Visit 1;
5. Have had a significant episode of hemoptysis (>60 mL) in the three months prior to Visit 0;
6. Have had a myocardial infarction in the three months prior to Visit 0;
7. Have had a cerebral vascular accident in the three months prior to Visit 0;
8. Have had major ocular surgery in the three months prior to Visit 0;
9. Have had major abdominal, chest, or brain surgery in the three months prior to Visit 0;
10. Have a known cerebral, aortic, or abdominal aneurysm;
11. Be breast feeding or pregnant, or plan to become pregnant while in the trial;
12. Be using an unreliable form of contraception (female subjects at risk of pregnancy only);
13. Be participating in another investigative drug trial, parallel to, or within 4 weeks of Visit 0;
14. Have a known allergy to mannitol;
15. Be using non-selective oral beta blockers;
16. Have uncontrolled hypertension i.e. systolic blood pressure (SBP) >190 and/or diastolic blood pressure (DBP) >100;
17. Have a condition or be in a situation which in the Investigator's opinion may put the subject at significant risk, may confound results, or may interfere significantly with the subject's participation in the trial;
18. Have a failed or incomplete MTT.

3.5. DETERMINATION OF SAMPLE SIZE

Enrolment will continue until at least 350 subjects have been randomized to trial medication in a 1:1 ratio. Assuming that the change from baseline in FEV_1 on control (50 mg inhaled mannitol b.i.d.) is 0 mL and the change from baseline in FEV_1 on inhaled mannitol (400 mg b.i.d.) is 80 mL, then a sample size of 350 (175 Mannitol: 175 Control) subjects will yield 90% power at the 0.05 significance level to detect this difference between the treatment groups assuming a pooled standard deviation (SD) of 230 mL.

The sample size calculation was based on a t-test of the treatment contrast at Week 26. While this approach is not completely concordant with the primary analysis which computes the mean change in FEV_1 over all three post-baseline visits it can be considered a suitable method for estimating sample sizes for longitudinal analyses and is likely to be conservative.

The estimated pooled SD of 230 mL is based on the observed pooled SD in the pooled adult DPM-CF-301 and DPM-CF-302 data from subjects who completed the studies.

This minimum sample size is based upon the observed pooled SD from both DPM-CF-301 and DPM-CF-302 studies in subjects with baseline FEV_1 of more than 40% but less than 90%. However the observed SDs were different in these two previous studies, and were highly influenced by a few outlying values. In addition, this trial will be conducted at different sites and in different countries to the previous studies. Thus there is some uncertainty as to what the observed SD is likely to be in this trial. For these reasons a sample size re-estimation was planned to be completed after at least 300 subjects have been recruited and at least 100 subjects had Visit 4 (Week 26) spirometry data available. This blinded sample size re-estimation was based on the method of Kieser and Friede[2] which preserves the overall Type 1 error rate. Therefore no adjustments to the overall significance level for the trial are required. See Section 10 for more details.

[redacted]

3.6. TREATMENT ASSIGNMENT & BLINDING

Subjects are randomized in a 1:1 ratio to receive either inhaled mannitol (400 mg b.i.d.) or control (50 mg inhaled mannitol b.i.d.) using centralized randomization. Randomization will be stratified by rhDNase use and country. Note that in cases of misstratification, i.e. where the incorrect rhDNase use is entered in the randomization system, the correct rhDNase use recorded in the case report form (CRF) will be used in summaries and analyses.

During the trial, the subject, the investigative staff, and the Sponsor (or designee) will be blinded to the treatment allocation. Unblinding a subject should only be done in a medical emergency and, where possible, should be discussed with the sponsor prior to unblinding.

To ensure subject safety throughout the trial, an independent DMC will be established at the beginning of the trial to review all accumulating safety data. Unblinded data will be prepared by an INC statistician who is independent from the study team. All unblinded analyses will be stored in a restricted area. DMC charter Version 4.0 dated 23Jun2015 details the procedures to ensure maintenance of overall trial blinding.

3.7. ADMINISTRATION OF TRIAL MEDICATION

The inhalation technique for inhaled mannitol (400 mg b.i.d.) and control (50 mg inhaled mannitol b.i.d.) is identical.

The trial medication is to be administered in a standardized manner. The Investigator is responsible for instructing the subject on the correct trial medication inhalation technique, and on use of the bronchodilator (albuterol/salbutamol metered dose inhaler (MDI) or similar) 5 to 15 minutes prior to the trial medication administration.

The Investigator will prescribe the subject with a bronchodilator (albuterol/ salbutamol-MDI or similar) to be used as premedication prior to inhalation of the trial medication. This bronchodilator may also be used in the event of post-treatment chest tightness.

Subjects will take trial medication twice a day, once in the morning and once in the evening. The evening dose should be administered approximately 2 hours before sleep.

Each kit dispensed contains additional supply to account for the protocol allowed visit windows.

3.8. TRIAL PROCEDURES AND FLOWCHART

This trial consists of 5 visits over a period of 28-weeks.

Table 1 below provides the complete schedule of assessments for the trial.

[redacted]

Statistical Analysis Plan

Table 1: Time and Events Schedule

Event	Screening Visit 0	☎	Visit 1	☎	☎	Visit 2	☎	☎	Visit 3	☎	☎	☎	Visit 4	☎	IMP discontinuation visit[a]
Week	**-5 to- 2**	**-1**	**0[b]**	**2**	**4**	**6**	**8**	**12**	**14**	**16**	**20**	**24**	**26**	**27**	
Visit window		**± 1 day**		**± 3 days**	**± 3 days**	**± 7 days**	**± 3 days**	**± 3 days**	**± 7 days**	**± 3 days**	**± 3 days**	**± 3 day**	**- 7 days to + 28 days**	**± 1 day**	**Within 2 weeks of IMP discontinuation**
Informed consent	X														
Inclusion/exclusion criteria	X														
Medical history / demographics	X														
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination/ vital signs	X		X			X			X				X		X
Pulmonary function tests	X		X			X			X				X		X
Urine pregnancy test	X														
Pulmonary exacerbations review			X			X			X				X		X
MTT procedure	X														
Randomize subject			X[c]												
Dispense trial medication & bronchodilator			X			X			X						

[a] *The IMP discontinuation visit is used for all subjects that discontinue IMP early, but are remaining in the study.*

[b] *Subjects should be stable and clear of pulmonary exacerbations for at least two weeks prior visit 1. If a subject has an exacerbation after Visit 0 (screening), visit 1 should occur 2 to 5 weeks from the end of the treatment of the exacerbation or the end of the adverse event, whichever is later.*

[c] *Randomize eligible subjects if compliance with maintenance therapies (antibiotic & rhDNase) is at least 80% in the two weeks prior to visit 1.*

Event	Screening Visit 0	☎	Visit 1	☎	☎	Visit 2	☎	☎	Visit 3	☎	☎	☎	Visit 4	☎		IMP discontinuation visit[a]
Week	**-5 to- 2**	**-1**	**0[b]**	**2**	**4**	**6**	**8**	**12**	**14**	**16**	**20**	**24**	**26**	**27**		
Visit window		**± 1 day**		**± 3 days**	**± 3 days**	**± 7 days**	**± 3 days**	**± 3 days**	**± 7 days**	**± 3 days**	**± 3 days**	**± 3 day**	**- 7 days to + 28 days**	**± 1 day**		**Within 2 weeks of IMP discontinuation**
Administer treatment dose in clinic			X			X			X				X			
Sputum qualitative microbiology	X															
Screening blood sample	X															
Issue subject diary	X															
Review subject diary			X			X			X				X			X
Collect subject diary													X			
Adverse event assessment		X	X	X	X	X	X	X	X	X	X	X	X	X		X
Ease of expectoration VAS			X			X			X				X			X
CFQ-R respiratory domain			X			X			X				X			X
IMP compliance and accountability[d]						X			X				X			
Discuss adherence to treatment (if subject has discontinued IMP, schedule IMP discontinuation visit within 2 weeks of last IMP)				X	X		X	X		X	X	X				

[d] *IMP accountability and collection must occur at the next scheduled visit for any subjects that withdraw from the study or discontinue from IMP early*

Event	**Screening Visit 0**	☎	**Visit 1**	☎	☎	**Visit 2**	☎	☎	**Visit 3**	☎	☎	☎	**Visit 4**	☎		**IMP discontinuation visit[a]**
Week	**-5 to- 2**	**-1**	**0[b]**	**2**	**4**	**6**	**8**	**12**	**14**	**16**	**20**	**24**	**26**	**27**		
Visit window		**± 1 day**		**± 3 days**	**± 3 days**	**± 7 days**	**± 3 days**	**± 3 days**	**± 7 days**	**± 3 days**	**± 3 days**	**± 3 day**	**- 7 days to + 28 days**	**± 1 day**		**Within 2 weeks of IMP discontinuation**
Remind subject of next visit or phone call, withholding periods, to complete subject diary, and to return trial drug (if applicable)[e]		X	X	X	X	X	X	X	X	X	X	X	X			X
Discharge subject from trial														X		

[e] *The subject diary should be collected for all subjects, including those who withdraw early from the study*

4. ENDPOINTS

4.1. PRIMARY EFFICACY ENDPOINT

The primary endpoint is the mean absolute change from baseline FEV_1 (L)* over the 26-week treatment period (measured at Weeks 6, 14 and 26).

All spirometry for the trial will be performed according to the American Thoracic Society/European Respiratory Society (ATS/ERS) criteria[3], using a standardized spirometer throughout the trial that meets ATS/ERS requirements, and using a trained, experienced, qualified technician. Results of testing must meet the ATS/ERS criteria for acceptable spirometry (the number of trials, acceptability, and repeatability). The acceptability criteria will be applied before the repeatability criterion is checked.

Spirometry data for the trial will be collected on a computerized spirometry system, [redacted]® [redacted] and [redacted] ([redacted]) configured to the requirements of the trial and in accordance with guidelines published by the ATS/ERS[3].

Spirometry data for the trial will be centrally collected by [redacted] where each spirometry assessment will be reviewed by an over-reader to assess the quality. The over-reader either accepts or rejects each individual spirometry maneuver, which can change the original selection made by the site, and provides an over-read report to the site. The principal investigator (PI) or sub-PI of the site must then sign the over-read report to confirm that they agree to the over-reader's decision. If they do not agree to the over-reader's assessment, they have to notify [redacted] and the original data as recorded by the site will be retained. [redacted]

Following this process, the largest FEV_1, FVC, and Peak expiratory flow (PEF) from the three acceptable efforts will be recorded on the CRF, regardless of whether they come from the same curve. FEV_1/FVC will be derived within the CRF as the best individual FEV_1 divided by best individual FVC (where FEV_1 and FVC may be from different efforts). Forced expiratory fraction from 25% to 75% of vital capacity (FEF_{25-75}) will be reported from a single acceptable "best-curve" (defined as the curve with the largest sum of FEV_1 and FVC).

The spirometry data entered in the CRF will be used for the reporting described in this SAP and will therefore be reconciled with the [redacted] data to ensure consistency

*Updated in this SAP to be reported in L rather than mL to match the units used in data collection (see Section 11).

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and accuracy.

In addition to the primary endpoint, the following variables will be analyzed:

- Mean absolute change from baseline percent predicted FEV_1 (%) over 26 weeks.
- Mean relative change from baseline FEV_1 (L) over 26 weeks.
- Mean relative change from baseline percent predicted FEV_1 (%) over 26 weeks.

Percent predicted is a clinically accepted measure which adjusts for the subject age, height, gender, and race. The formula is:

$$\text{Percent predicted } FEV_1 = 100 \times (FEV_1 / \text{Predicted } FEV_1)$$

Predicted FEV_1 is derived using the formulae by Hankinson et al[1]:

$$\text{Predicted } FEV_1 = \alpha + \beta_1 \times age + \beta_2 \times age^2 + \beta_3 \times height^2$$

where height is taken as the screening value and measured in cm and age is calculated at the date of the spirometry measurement. The coefficients are as follows:

Table 2: Predicted FEV_1 Coefficients

Age	Race	Gender	α	β_1	β_2	β_3
18-19	Caucasian	Male	-0.7453	-0.04106	0.004477	0.00014098
18-19	African descent[a]	Male	-0.7048	-0.05711	0.004316	0.00013194
≥20	Caucasian	Male	0.5536	-0.01303	-0.000172	0.00014098
≥20	African descent[a]	Male	0.3411	-0.02309	-	0.00013194
≥18	Caucasian	Female	0.4333	-0.00361	-0.000194	0.00011496
≥18	African descent[a]	Female	0.3433	-0.01283	-0.000097	0.00010846

[a] *Referred to as African-American in Hankinson et al[1].*

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**Clarified in this SAP that pulmonary exacerbations classified as protocol defined pulmonary exacerbations (PDPEs) will be used in the main analyses for these endpoints (see Section 11).

Due to patient confidentiality regulations in Hungary, it is only possible to collect the year of birth for each subject in that country. In the trial database, the day and month of birth will be recorded as 31st December for all Hungarian subjects. Each Hungarian subject may therefore be allocated the predicted value of a younger age bracket for calculations. This would underestimate their predicted value, and overestimate their percent predicted value, as these would be based on the lung function expected of a younger subject. However since changes in this percent predicted value are the focus, rather than the absolute values themselves, this is expected to have minimal impact on trial results.

The percent predicted FEV_1 recorded by the investigator in the CRF at the screening visit, using the above formula, will be presented without recalculation. For post-screening timepoints, the predicted values will be calculated using the above formula. If race is different to those in Table 2, the Caucasian values presented here will be used for the coefficients in the formula. In addition, if race is recorded as East/South East Asian, or West Asian, then a correction factor will be applied and the formula will be:

$$\text{Predicted } FEV_1 = (\text{Predicted } FEV_1 \text{ derived using Caucasian coefficients}) \times 0.88$$

Mean relative change from baseline (% change) in FEV_1 (L) and percent predicted FEV_1 (%) will be calculated according to the following formula:

$$\text{relative change} = 100 \times (\text{absolute change from baseline} / \text{baseline value})$$

4.2. SECONDARY EFFICACY ENDPOINTS

4.2.1. Hierarchical Secondary Endpoints

1) Mean absolute change from baseline FVC (L)* over 26 weeks.

2) Time to first protocol defined pulmonary exacerbation (PDPE)** of any grade over the 26-week treatment period as recorded on the CRF. This is the time in days and is defined as:

   $$\text{Time} = (\text{date of PDPE}) - (\text{date of Trial Day 1}) + 1$$

   Trial Day 1 is defined in Section 6.2.2.

   A PDPE occurs when subjects are treated with IV antibiotics for four or more of the following twelve signs or symptoms[4]:

*Updated in this SAP to be reported in L rather than mL to match the units used in data collection (see Section 11).

**Clarified in this SAP that pulmonary exacerbations classified as protocol defined pulmonary exacerbations (PDPEs) will be used in the main analyses for these endpoints (see Section 11).

- Change in sputum production (volume, color, consistency).
- Increased dyspnea.
- New or increased hemoptysis.
- Malaise, fatigue, or lethargy.
- Fever ($\geq$38 ^{o}C).
- Anorexia or weight loss.
- Sinus pain or tenderness.
- Change in sinus discharge.
- FVC or FEV_1 decreased by >10% from previous recorded value.
- Radiographic signs indicative of pulmonary infection.
- Increased cough.
- Changes in physical examination of the chest.

PDPEs will be identified from the pulmonary exacerbation (PE) Review CRF page, where IV antibiotics were recorded as being given for a PE and, in addition, 4 or more of the above signs or symptoms were ticked.

Time to first PE will also be calculated, in a similar manner, and explored under this endpoint, however the hierarchical testing will be based on time to first PDPE. A PE is defined as any event recorded on the PE Review CRF page that has associated antibiotic use (oral, inhaled, or IV), whether or not it meets the above conditions.

3) Number of days on antibiotics (oral, inhaled, or IV) due to PDPE** over the 26-week treatment period. Medication use for a PE will be identified on the concomitant medication page by a yes/no box; a further check will be made to ensure medications are for a PDPE (i.e. that the PE event to which the medication is linked satisfies the above criteria for a PDPE). It will also be checked that both the PDPE and the medication use started on or after Trial Day 1 (defined in Section 6.2.2). Antibiotics are identified by their Anatomical Therapeutic Chemical (ATC) Level 2 code J01 (antibacterials for systemic use).

Number of days on one antibiotic = stop date–start date+1

The number of days for all occurrences will be summed. If multiple antibiotics are received for the same event, the durations will be computed separately and added together. If an antibiotic is ongoing at the end of the subject's participation in the trial, the subject's date of last participation in the trial will be used in the calculation instead of the stop date.

Date of last participation in the trial is defined in Section 6.2.5.

*Updated in this SAP to be reported in L rather than mL to match the units used in data collection (see Section 11).

**Clarified in this SAP that pulmonary exacerbations classified as protocol defined pulmonary exacerbations (PDPEs) will be used in the main analyses for these endpoints (see Section 11).

As a supportive analysis, the following endpoints will be calculated:

- Number of distinct days on antibiotics due to PDPE over the 26-week treatment period: if multiple antibiotics are received for the same event and overlap (i.e. stop date of one antibiotic≥start date of next antibiotic), days with more than one antibiotic will be counted only once.

  Number of distinct days on antibiotics = sum(days with at least one antibiotic intake for an event).

  If an antibiotic is ongoing at the end of the subject's participation in the trial, days will be counted up until the subject's date of last participation in the trial.

- Number of days on antibiotics (oral, inhaled, or IV) due to PE over the 26-week treatment period.

- Number of distinct days on antibiotics due to PE over the 26-week treatment period.

As supportive information, the following variables will be calculated:

- Number of distinct episodes of use of antibiotics due to PDPE, defined as any recorded use of antibiotics due to PDPE with a different start date from any other recorded use of antibiotics due to PDPE.

- Number of courses of antibiotics due to PDPE, defined as any recorded use of antibiotics due to PDPE with a start date 14 or more days after the stop date of all previous antibiotics for any PDPE.

All subjects experiencing a PDPE would have received IV antibiotics.

These supportive endpoints/variables will not be part of the hierarchical testing.

4) Number of days in hospital (admissions only) due to PDPE** over the 26-week treatment period. For each hospital admission, the number of days in hospital will be calculated as (end date)-(start date)+1. Each hospitalization with a reason of PE will be cross-referenced with a PE from the PE Review CRF page to determine if the hospitalization was due to a PDPE. If the start date of the hospitalization is included within the dates of any PDPE for that subject, then that hospitalization will be designated as due to PDPE. If the hospitalization is ongoing at the end of the subject's participation in the trial, the subject's date of last participation in the

*Updated in this SAP to be reported in L rather than mL to match the units used in data collection (see Section 11).

**Clarified in this SAP that pulmonary exacerbations classified as protocol defined pulmonary exacerbations (PDPEs) will be used in the main analyses for these endpoints (see Section 11).

trial will be used in the calculation instead of the end date.

As a supportive analysis, the following endpoint will be calculated:

- Number of days in hospital (admissions only) due to PE.

The hierarchical testing will be based on days in hospital due to PDPE.

5) Rate of PDPE** (per person year) over the 26-week treatment period.

The overall rate of PDPE (per person year) over the 26-week treatment period will be calculated for each treatment group as:

Overall Rate = total number of PDPE/total follow-up duration

where total follow-up duration (years) = ([last participation date]–[date of Trial Day 1]+1)/365.25 summed over all subjects in the treatment group.

Trial Day 1 is defined in Section 6.2.2.

Date of last dose of trial medication is defined in Section 6.2.1.

In the above calculations, rate will be rounded to two decimal places for displaying purposes.

The overall rate of PE (per person year) over the 26-week treatment period will also be calculated, in a similar manner, and explored under this endpoint, however the hierarchical testing will be based on the rate of PDPE.

4.2.2. Non-hierarchical Secondary Endpoints

1) Incidence of PDPEs** (yes or no, binary outcome) over the 26-week treatment period.

Incidence of PEs (yes or no, binary outcome) over the 26-week treatment period will also be explored under this endpoint, however the main focus will be on the incidence of PDPEs.

2) Ease of expectoration measured at Weeks 6, 14 and 26 using the absolute change from baseline visual analogue scale (VAS) score.

*Updated in this SAP to be reported in L rather than mL to match the units used in data collection (see Section 11).

**Clarified in this SAP that pulmonary exacerbations classified as protocol defined pulmonary exacerbations (PDPEs) will be used in the main analyses for these endpoints (see Section 11).

3) Mean absolute change from baseline CFQ-R respiratory domain score measured at Weeks 6, 14 and 26. This will be appropriately transformed according to the scoring manual[5], so that the best response will be uniformly the highest score and the worst response will be uniformly the lowest score. More details are provided in [redacted]

   The CFQ-R respiratory domain includes the Question 42 (CRF Question 3), "Have you had to cough up mucus?" The scoring algorithm scores an affirmative answer to this question as a negative outcome for the subject, however, due to the mechanism of action of mannitol (i.e. inducing coughing up mucus) an affirmative answer here may not be a negative outcome and hence this question is inappropriate here. Therefore, the endpoint will also be derived omitting this question.

4.3. SAFETY ENDPOINTS

Safety endpoints include adverse events (AEs; including deaths), extent of trial medication exposure and trial medication compliance, vital signs, and physical examination data.

*Updated in this SAP to be reported in L rather than mL to match the units used in data collection (see Section 11).

**Clarified in this SAP that pulmonary exacerbations classified as protocol defined pulmonary exacerbations (PDPEs) will be used in the main analyses for these endpoints (see Section 11).

5. ANALYSIS SETS

5.1. SAFETY SET

The Safety (SAF) set will include all subjects who were administered at least one dose (or part thereof) of randomized trial medication. Subjects will be analyzed according to trial medication received. The SAF set will be used for all analyses of safety endpoints.

5.2. INTENT-TO-TREAT SET

The Intent-to-Treat (ITT) set will include all randomized subjects. Subjects will be analyzed according to randomized trial medication. The ITT set will be used for all analyses of efficacy endpoints.

5.3. PER PROTOCOL SET

The Per Protocol (PP) set consists of all randomized subjects, excluding those who had deviations from the protocol that may affect the assessment of response to trial medication. The criteria for exclusion from the PP are defined in Section 5.5.

5.4. MANNITOL TOLERANCE TEST SET

The MTT set will include all subjects participating in the MTT prior to randomization regardless of their subsequent randomization status. It will include subjects who fail the MTT (MTT positive) or who have an incomplete procedure, along with those who pass the MTT (MTT negative). If subject is re-screened, only the re-screen subject number will be included in the MTT set, the original subject number will be excluded.

5.5. PROTOCOL DEVIATIONS

Protocol deviations identified by the clinical research associates during their monitoring visits were captured in [redacted] using broad category groupings.

All recorded protocol deviations were reviewed during the course of the trial. In addition, protocol deviations were identified through programmatic checks in order to assist in the assignment of subjects to the PP set. At the BDRM, held prior to the unblinding of the trial deviations were grouped into subcategories under each broad category grouping and decisions were made on whether to exclude each subject from the PP set by categorizing each recorded and programmed protocol deviation as major or minor, where major identifies a reason for exclusion from the PP set.

Statistical Analysis Plan

All major protocol deviations, from [redacted] and programmed, will be listed and summarized for the ITT set based on the [redacted] category and assigned subcategory. Important minor protocol deviations, including those related to trial inclusion or exclusion criteria, conduct of the trial, subject management or subject assessments, were identified at the BDRM and will be listed by [redacted] category and assigned subcategory.

Criteria to determine if a subject will be included in the PP set were detailed in a BDRM preparation plan together with details of the programmatic listings to be prepared. The adjusted criteria confirmed during the BDRM to determine if a subject will be excluded from the PP set were:

- Did not meet all the inclusion and exclusion criteria.
- Was randomized but did not take at least one dose of trial medication.
- Compliance to trial medication while taking trial medication <60%.
- No valid baseline FEV_1 measure, where a baseline measure was considered non valid if precluded medications were not withheld as detailed in the protocol.
- Started treatment with maintenance hypertonic saline where it was considered that there was a potential for efficacy assessments to be impacted.
- Started or stopped treatment with rhDNase or maintenance antibiotics where it was considered that there was a potential for efficacy assessments to be impacted.

Further details of the rules applied to determine inclusion in the PP set will be documented in the BDRM Highlights and will be agreed and finalized prior to database lock.

Only FEV_1 measurements taken in the absence of precluded medications will be considered valid. Precluded medications and required withholding periods are detailed in Table 3 (as detailed in the protocol and CRF).

Table 3: Medication-withholding periods

Medication	Time interval from last dose until spirometry
Short-acting ß2 agonists (isoproterenol, isoetharine, metaproterenol, salbutamol, albuterol, levalbuterol, terbutaline) Short-acting anticholinergics including combination therapies (e.g. ipratropium)	At least 6 hours
Long acting ß2 agonists (e.g. salmeterol or eformoterol) Long acting anticholinergics (e.g. tiotropium)	At least 12 hours
Oral bronchodilators (e.g. theophylline and ß-agonist tablets)	At least 12 hours

Any precluded medications taken not in accordance with the above withholding periods were reviewed at the BDRM, and an assessment was made on the validity of the associated spirometry measurements.

At the BDRM, a local major deviation was defined for the visit if the spirometry assessment was determined to be non valid, leading to the exclusion of all the specific assessment's data collected at the visit from the PP analysis. Of note, local major deviations will not lead to the exclusion of the subject from the PP set; any derived variables based on these excluded measurements will be treated as missing data and will not be imputed for the PP analysis. Local major deviations will be flagged in the data listing of major protocol deviations, but not included in the corresponding summary table.

The finalization of protocol deviations and exclusions of subjects from the PP set and of individual visit data from the PP analysis will be made [redacted]

[redacted]

The number and percentage of subjects included in and excluded from the SAF and PP sets will be presented for the ITT set, including a breakdown of all categorized reasons for exclusion from the PP set. All reasons for each subject will be included, but each subject will only be counted once within each reason category.

6. GENERAL ASPECTS FOR STATISTICAL ANALYSIS

6.1. GENERAL METHODS

Unless otherwise specified, all demographic and baseline data will be presented by treatment group and overall. Efficacy and safety data will be presented by treatment group. All subjects entered into the database will be included in subject data listings.

Continuous variables will be summarized using the number of observations (n), n missing (n miss), mean, SD, median, minimum, and maximum. Categorical variables will be summarized using the number (n) and percentage (%) of subjects with non-missing data per category. Where relevant, the number of missing values will be included as a "Missing" category. Unless otherwise specified, the denominator for each percentage will be the number of non-missing observations within the analysis set and treatment group.

All tests of hypotheses will be 2-sided and conducted at the 5% significance level, and all confidence intervals (CIs) will be 2-sided at the 95% level.

[redacted].

6.2. KEY DEFINITIONS

6.2.1. Dates of First and Last Trial Medication Intake

In this document, trial medication refers to the randomized trial medication (inhaled mannitol [400 mg b.i.d.] and control [50 mg inhaled mannitol b.i.d.]) and does not include the MTT.

The date of first trial medication is taken as the date of first administration of trial medication after randomization.

The date of last trial medication is taken as the date of last administration of trial medication.

If date of last administration of trial medication is missing, the date will be imputed using the last available known start or end date of trial medication.

6.2.2. Trial Day

Trial day is defined as the number of days from the date of randomization to the event date and will be calculated as follows:

- If the event date≥date of randomization, trial day = event date–date of randomization+1. Trial Day 1 is therefore defined as the day of randomization.
- If the event date<date of randomization, trial day = event date-date of randomization.

6.2.3. Treatment Day

Treatment day is defined as the number of days from the date of first dose to the event date and will be calculated as follows:

- If the event date≥date of first dose, treatment day = event date–date of first dose+1. Treatment Day 1 is therefore defined as the day of first dose.
- If the event date<date of first dose, treatment day = event date-date of first dose.

6.2.4. Baseline

The baseline value for all efficacy endpoints will be taken as Visit 1. It will be assumed that assessments performed on this visit were prior to first trial medication administration, with the exception of post-dose spirometry. Therefore, efficacy baseline will be the Visit 1 measurement unless the Visit 1 measurement is missing, where the Visit 0 measurement will be used as baseline.

The baseline value for safety endpoints (vital signs and physical examination) will be taken as the latest available measurement prior to or on Treatment Day 1 (i.e. day of first trial medication dose). It will be assumed that safety assessments performed on Treatment Day 1 were prior to trial medication administration. Baseline will be the Visit 1 measurement.

6.2.5. Date of Last Participation in the Trial

A subject's date of last participation in the trial is the last date of contact that the subject has with the trial and is recorded as the date of completion or date of withdrawal on the completion page of the CRF.

6.2.6. Follow-up Phase

The follow-up phase covers the whole time that a subject is in the trial between Trial Day 1 and their date of last participation in the trial.

follow-up duration = (last participation date)–(date of Trial Day 1)+1

6.2.7. On-treatment and Off-treatment Period

Subjects discontinuing the trial medication were encouraged to continue in the trial to provide all scheduled measurements. This will result in some subjects having information recorded both while taking trial medication and after trial medication has been discontinued.

The following definition of "on-treatment" and "off-treatment" periods are applied:

<u>For Safety data:</u>

- On-treatment period: period of time while the subject is on trial medication; it starts with the first intake of trial medication after randomization and ends 28 days after the last trial medication intake.

All safety analyses will be conducted considering the measurements and AEs observed during the on-treatment period (excluding MTT-emergent AEs [MEAEs]).

<u>For Efficacy data:</u>

- On-treatment period: period of time while the subject is on trial medication; it starts with the first intake of trial medication after randomization and ends 7 days after the last trial medication intake.

- Off-treatment period: period of time while the subject is not on trial medication; it starts the eighth day after the last trial medication intake and ends on the date of last participation in the trial.

All efficacy analyses will be conducted considering all measurements collected (i.e. including both on-treatment and off-treatment period data).

In addition, for the primary endpoint, supportive analyses will be conducted considering only measurements collected during the on-treatment period.

6.3. MISSING DATA

Missing or partial dates will be resolved in the most conservative manner. Additional details regarding partial or missing dates for the different safety data are given in Sections 6.2.1, 7 and 9 where applicable.

Details of imputation of missing values for efficacy endpoints are given in Section 8. Subjects who discontinue trial medication should remain in the trial and continue to provide all scheduled measurements. While all efforts will be made to ensure subjects remain in the trial, the following planned imputation strategy will allow for appropriate analyses of FEV_1, FVC, ease of expectoration VAS score, and CFQ-R respiratory domain in the presence of missing data.

To calculate baseline values, missing Visit 1 measurements will be replaced by Visit 0 (screening) measurements, if available.

Missing post-baseline measurements as a result of withdrawal from the trial will be imputed in both ITT and PP analyses using an imputation using dropout reason (IUDR) methodology. For subjects who withdraw from the trial due to AE, death, physician decision, or lack of efficacy, missing post-baseline measures as a result of withdrawal from the trial will be imputed using the baseline measurement (baseline observation carried forward [BOCF] procedure). Missing measurements as a result of other causes of withdrawal from the trial (i.e. lost to follow-up, relocation, pregnancy, major protocol deviation, sponsor decision, withdrawal of consent, or other) will not be imputed. Missing data at intermediate visits (i.e. where data is available at a later visit) will not be imputed. Any measurements excluded from the PP analysis at the BDRM, and any derived variables based on these excluded measurements, will be treated as missing data but will not be included in the imputation process.

Imputation of missing FEV_1 measurements by means of BOCF is a reasonable assumption in studies of adult subjects with CF, as those subjects who withdraw from the trial will no longer receive trial medication and are thus likely to promptly return to their baseline lung function. Imputation by BOCF specifically inhibits any assumed prolongation of an observed early trial medication benefit implicitly conferred by a mixed model.

A framework of imputation by BOCF in combination with the IUDR strategy seeks to specifically address the primary question of interest, that is to provide a reliable estimation of the treatment group effect over 26 weeks as observed in all randomized subjects.

For time to first PDPE, subjects who do not have a PDPE during the trial will be censored at the date of last participation in the trial.

For rate of PDPE, if a subject withdraws from the trial before Week 14 with no observed instances of a PDPE the number of PDPEs will be imputed using half the subject's historical (previous 12 months) PE count (rounded upwards) and their follow-up duration will be imputed as 26 weeks. If a subject withdraws from the trial after Week 14 with no observed instances of a PDPE the number of PDPEs will be imputed using one quarter the subject's historical (previous 12 months) PE count (rounded upwards) and their follow-up duration will be imputed as 26 weeks.

For the secondary efficacy analyses of number of days on antibiotics due to PDPE, number of days in hospital due to PDPE, and incidence of PDPEs, no imputation of missing data will be performed.

Imputed data will not be displayed in data listings unless otherwise specified.

6.4. VISIT WINDOWS

All ITT analyses will be performed using the visit as recorded on the CRF. In the case where a subject performed the IMP discontinuation visit, the following visit windows will be used to assign this visit to the most appropriate visit number for the purposes of analysis:

Table 4: Visit windows for assigning IMP discontinuation visits to visit numbers

Visit	Target Trial Day	Window
Visit 1 (Baseline)	1	≤Treatment Day 1
Visit 2 (Week 6)	43	Day 14 – Day 70
Visit 3 (Week 14)	99	Day 71 – Day 140
Visit 4 (Week 26)	183	Day 141 – Day 211

If this re-assignment of the IMP discontinuation visit to a visit number results in two spirometry assessments being available for the same visit then the following rules for selecting which assessment to use in the analysis will be used:

- If one assessment is recorded during the on-treatment period and the other is recorded during the off-treatment period, the assessment recorded during the on-treatment period will be used.
- Otherwise, if both assessments are recorded during the on-treatment period or both are recorded during the off-treatment period then, the one closest to the planned or scheduled visit date will be used. If the two observations are equidistant from the target day the one after the target day will be used in the analysis.

6.5. POOLING OF CENTERS

No investigation of center effects is planned, however the stratification factor of country will be included in statistical analysis models as detailed in the following sections. Low numbers of subjects were recruited for at least one country, so countries will be pooled together as United States versus the rest of the world for the stratification factor.

6.6. SUBGROUPS

Subgroup analyses of primary and hierarchical secondary endpoints will be performed to assess consistency of response between subgroups of subjects:

- With and without rhDNase use.
- With differing disease severity (percent predicted FEV_1 at baseline). The following cut point will be used: >70% and ≤70%.

In addition subgroup analyses of the primary endpoint will be performed to assess the consistency of response between subgroups of subjects:

- With and without *Pseudomonas aeruginosa* infection as specified on the sputum qualitative microbiology collected at screening. *Pseudomonas aeruginosa* infection is assumed if there is a recording of mucoid or non-mucoid *Pseudomonas aeruginosa* infection at screening regardless of organism presence or clinical significance. Subjects who did not have a sputum sample analyzed at screening will be excluded from these subgroup summaries and analyses.

All subgroup analyses will be carried out by subsetting the overall population according to the above subgrouping factors and repeating the analysis for each level of the factor. Where applicable (i.e. for rhDNase use and disease severity) the related variable in the analysis model will be dropped.

7. DEMOGRAPHIC, OTHER BASELINE CHARACTERISTICS, AND MEDICATION

7.1. SUBJECT DISPOSITION AND WITHDRAWALS

7.1.1. Subject Disposition

The number of screened subjects who participated in the MTT and MTT status (negative [passed], positive [failed], or incomplete) will be presented for the MTT set. Percentages will be based on the number of subjects participating in the MTT.

The number and percentage of subjects randomized, not randomized, and treated in the trial will be presented, together with the number and percentage of subjects randomized in each center within each country, and the number and percentage of subjects included in each of the analysis sets. Percentages will be based on the number of subjects randomized.

7.1.2. Withdrawal from the Trial

The number and percentage of randomized subjects who completed the trial and who withdrew from the trial early, including a breakdown of the corresponding reasons for withdrawal, will be presented for the ITT set. All reasons for withdrawal listed in the CRF will be included in the summary, whether or not any subjects withdrew for each reason.

Time to withdrawal from the trial in days will be calculated as:

Time = (date of withdrawal from the trial)–(date of Trial Day 1)+1

A Kaplan-Meier plot of time to withdrawal from the trial for the ITT set will be presented. Subjects who do not withdraw will be censored at the date of last participation in the trial. The number of subjects who withdraw and who are censored will be summarized. Kaplan-Meier product limit estimators of the survivor function (probability of staying in the trial) will be summarized for 25th percentile, median, and 75th percentile, and their 95% CIs.

For the study periods [0-6) weeks, [6-14) weeks, [14-26) weeks, [26-31) weeks, and [31-∞) weeks, the number of subjects in the trial at the beginning of the period, the cumulative number of withdrawn subjects at the end of the period, and the probability of withdrawal at the end of the period with the associated 95% CIs will be presented for the ITT set.

The number and percentage of subjects in categories of time to withdrawal {[0-2) weeks, [2-4) weeks, [4-8) weeks, etc. in 4 weekly intervals} and the number and percentage of subjects withdrawing between each visit will also be presented for the ITT set.

In addition, the follow-up duration will be summarized for the ITT set using summary statistics for continuous variables and also for categorical variables using monthly categories (i.e. 0-1, >1-2, etc.). This will be calculated as:

Follow-up duration (months) = ([last participation date]–[date of Trial Day 1]+1) x12/365.25

Follow-up duration in months will be rounded to one decimal place for displaying purposes.

The number of subjects who attended Visits 2, 3, and 4 will be summarized for the ITT set using summary statistics for categorical variables.

7.1.3. Discontinuation from Trial Medication

The number and percentage of subjects who completed the trial on trial medication will be presented for the ITT set.

The number and percentage of subjects who discontinued from trial medication (whether or not they continued in the trial), including a breakdown of the corresponding reasons for discontinuation will be presented for the ITT set. If reason for discontinuation is missing for subjects who withdrew from the trial at the same time as trial medication discontinuation, the reason for withdrawal will be used. In addition, the number and percentage of subjects who discontinued trial medication without off-trial medication efficacy data and the number and percentage of subjects who discontinued trial medication with off-trial medication efficacy data, including a breakdown of the corresponding reasons for discontinuation will be presented for the ITT set. In each case, all reasons for discontinuation listed in the CRF will be included in the summary, whether or not any subjects discontinued for each reason.

For those subjects with off-trial medication efficacy data, the number and percentage of subjects who went on to complete the trial while off trial medication and the number and percentage of subjects who subsequently withdrew early from the trial while off trial medication will be presented for the ITT set.

If applicable, a similar breakdown for subjects who never started trial medication will be presented for the ITT set.

Time to discontinuation from trial medication in days will be calculated for subjects receiving at least one dose of trial medication as:

Time = (date of discontinuation from trial medication)–(date of Treatment Day 1)+1

Subjects not starting trial medication will have a time to discontinuation of 0 (not censored). Subjects who do not discontinue will be censored at the date of last dose in the trial.

A Kaplan-Meier plot of time to discontinuation from trial medication for the ITT set will be presented. The number of subjects with an event and censored will be summarized. Kaplan-Meier product limit estimators of the survivor function (probability of staying event free) will be summarized for 25^{th} percentile, median, and 75^{th} percentile, and their 95% CIs.

For the study periods [0-6) weeks, [6-14) weeks, [14-26) weeks, [26-31) weeks, and [31-∞) weeks, the number of subjects in the trial at the beginning of the period, the cumulative number of discontinued subjects at the end of the period, and the probability of discontinuation at the end of the period with the associated 95% CIs will be presented for the ITT set.

The number and percentage of subjects in categories of time to discontinuation {[0-2) weeks, [2-4) weeks, [4-8) weeks, etc. in 4 weekly intervals} and the number and percentage of subjects discontinuing between each visit will also be presented for the ITT set.

7.2. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demography (gender, race, ethnicity, country, age [years] at screening, weight [kg] at screening and height [cm] at screening), percent predicted FEV_1 at screening, percent predicted FEV_1 at screening cut points (>90%, >80% to ≤90%, >70% to ≤80%, >40% to ≤70%, and ≤40%), disease severity (percent predicted FEV_1 at baseline), and disease severity (percent predicted FEV_1 at baseline) cut points (>90%, >80% to ≤90%, >70% to ≤80%, >40% to ≤70%, and ≤40%) will be summarized for the ITT, PP, and SAF sets, and also for the subset of the MTT set who did not go on to be randomized (with the exception of the disease severity at baseline variables). Age, weight, and height will be summarized using summary statistics for continuous variables. Gender, race, ethnicity, and country will be summarized using summary statistics for categorical variables.

Age at screening = (date of MTT-date of birth+1)/365.25 truncated to complete years.

Note that due to patient confidentiality regulations in Hungary, it is only possible to collect the year of birth for each subject in that country. In the trial database, the day

and month of birth will be recorded as 31st December for all Hungarian subjects, therefore age values will be an underestimation.

Screening medications will be summarized for the ITT set, and for the subset of the MTT set who did not go on to be randomized, by anatomical main group, therapeutic subgroup and preferred drug name terms using summary statistics for categorical variables. Screening medications are defined in Section 7.7.2. A subject who took more than one screening medication will be counted only once if these medications belong to the same anatomical main group, therapeutic subgroup or preferred drug name. Tables will be sorted alphabetically by anatomical main group, therapeutic subgroup and preferred drug name.

Screening sputum qualitative microbiology data will be summarized for the ITT set using summary statistics for categorical variables. Clinically significant screening laboratory tests, screening sputum qualitative microbiology, and screening urine pregnancy test data will be listed.

7.3. PRIMARY DIAGNOSIS

The primary diagnosis information collected at screening will be summarized for the ITT and SAF sets, and also for the subset of the MTT set who did not go on to be randomized. This will include time since diagnosis (years), age at diagnosis (years), cystic fibrosis transmembrane conductance regulator (CFTR) mutation (both deltaF508, one deltaF508, at least one other known mutation, and both unknown), use of rhDNase, previous diagnosis of bronchiectasis, number of hospitalizations in last 12 months due to PE, number of PEs treated with IV antibiotics in last 12 months, previous hypertonic saline use, and hypertonic saline use at screening.

Time since diagnosis (years) and age at diagnosis (years), will be summarized using summary statistics for continuous variables. All other endpoints will be summarized using summary statistics for categorical variables. Appropriate categories will be defined based on available data for number of hospitalizations in last 12 months due to PE and number of PEs treated with IV antibiotics in last 12 months.

Time since diagnosis will be calculated as:

Time since diagnosis = (age at screening-age at diagnosis)

where age at diagnosis = (date of first diagnosis-date of birth+1)/365.25 truncated to complete years.

If date of first diagnosis is partially missing, the most conservative case will be considered when calculating time since diagnosis: if a partial date is missing a start day,

'01' will be used for the day; if a partial date is missing a month, 'January' will be used for the start month. If date of first diagnosis is fully missing, the value of age at diagnosis as recorded on the CRF will be used in the above calculation.

If both date of first diagnosis and age at diagnosis (CRF) are missing, then the derived age at diagnosis and time since diagnosis will be missing.

7.4. HEMOPTYSIS HISTORY

Hemoptysis history will be summarized for the ITT and SAF sets. This will include the number and percentage of subjects with a history of hemoptysis, and for those subjects, the type of event (single or multiple), the incidence of any hemoptysis events not concurrent with an exacerbation, and the incidence of any massive hemoptysis events (defined as acute bleeding ≥240 mL in a 24-hour period and/or recurrent bleeding ≥100 mL per day over several days). For those subjects experiencing a massive hemoptysis, the number and percentage of subjects with all massive hemoptysis concurrent with an exacerbation, the number and percentage of subjects with at least one massive hemoptysis not concurrent with an exacerbation, and the time of the most recent massive hemoptysis (within the last 12 months or more than 12 months ago) will be summarized.

7.5. MEDICAL HISTORY AND CONCOMITANT DISEASES

Medical history and concomitant diseases will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 11.1.

Medical history will be defined as any clinically significant past medical conditions that ended before screening. Medical history will be summarized for the ITT and SAF sets with number and percentage of subjects with at least one medical history item, and number and percentage of subjects by system organ class (SOC) and preferred term (PT). The terms will be sorted alphabetically by SOC and PT.

Concomitant diseases will be defined as any clinically significant current medical conditions that were ongoing at screening. Concomitant diseases will be summarized for the ITT and SAF sets with number and percentage of subjects with at least one concomitant disease, and number and percentage of subjects by system organ class (SOC) and preferred term (PT). The terms will be sorted alphabetically by SOC and PT.

Concomitant diseases will be flagged on the medical history and concomitant diseases data listing.

7.6. RESPONSE TO SCREENING MANNITOL TOLERANCE TEST

The MTT parameters FEV_1 and oxygen saturation (SpO_2) will be summarized by timepoint and by MTT result (negative [passed], positive [failed], and incomplete) for the MTT set. In addition the maximum percentage fall in FEV_1 and greatest absolute drop in SpO_2, from the 40 mg, 120 mg, 240 mg and 400 mg doses attempted, will be summarized by MTT result (negative, positive, and incomplete) for the MTT set.

Percentage fall in FEV_1 will be calculated as:

$$\text{Percentage fall in } FEV_1 = 100\times((\text{Baseline } FEV_1 - \text{post Baseline } FEV_1)/\text{Baseline } FEV_1)$$

Percentage fall in FEV_1 will be rounded to two decimal places for displaying purposes.

Absolute drop in SpO_2 will be calculated as:

$$\text{Absolute drop in } SpO_2 = \text{Baseline } SpO_2 - \text{post Baseline } SpO_2$$

7.7. MEDICATION

Prior and concomitant medications will be coded using WHO Drug Dictionary version DD B2March 2010. Medication will be presented by anatomical main group (ATC Level 1), therapeutic subgroup (ATC Level 2) and preferred drug name. If anatomical main group, therapeutic subgroup or preferred drug name is unavailable, "uncoded" will be used. A subject who took more than one medication will be counted only once if these medications belong to the same anatomical main group, therapeutic subgroup or preferred drug name. Tables will be sorted alphabetically by anatomical main group, therapeutic subgroup and preferred drug name.

If either the start or stop date of medication is missing, the most conservative case will be considered when assigning medications to categories: for a missing start date (where stop date is after date of Trial Day 1) the date will be imputed as the date of Trial Day 1; for a missing stop date the date will be imputed as the date of last participation in the trial. If a partial date is recorded, the following convention will be used to assign the medication:

- If a partial date is missing a start day, '01' will be used for the day; if a start date is missing a month, 'January' will be used for the start month.
- If a partial date is missing a stop day, last day of the given month will be used for the stop day; if a stop date is missing a month 'December' will be used for the stop month.

7.7.1. Prior Medication

Prior medications will be defined as medications that stop before Trial Day 1. Prior

medications will be flagged on the concomitant medication listing.

The number and percentage of subjects with prior medications will be summarized for the ITT set by anatomical main group, therapeutic subgroup and preferred drug name.

7.7.2. Screening Medication

Screening medications will be defined as any medications that were started prior to the screening visit and were ongoing at the time of screening, or any that were started on the day of the screening visit, or stopped on the day of the screening visit. Screening medications will be flagged on the concomitant medication listing.

The number and percentage of subjects with screening medications will be summarized by anatomical main group, therapeutic subgroup and preferred drug name for the ITT set and for the subset of the MTT set who did not go on to be randomized.

7.7.3. Concomitant Medication

Concomitant medications taken during the follow-up phase will be defined as any medications that were taken on or after Trial Day 1. All concomitant therapies will be listed.

The number and percentage of subjects with concomitant medications during the follow-up phase will be summarized for the ITT and SAF sets by anatomical main group, therapeutic subgroup and preferred drug name. In addition, separate summaries will be presented for the ITT set for the number and percentage of subjects with the following categories of concomitant medications by anatomical main group, therapeutic subgroup and preferred drug name:

- Maintained medications - defined as concomitant medications started before Trial Day 1.
- New medications during trial medication - defined as concomitant medications started on or after Treatment Day 1 and before or on date of last trial medication.
- New medications whilst off trial medication - defined as concomitant medications started after last date of trial medication or started on or after Trial Day 1 and before first dose of trial medication.

All concomitant medications recorded should fall into one of the above categories.

7.7.4. Antibiotic Use

Concomitant antibiotic use due to PDPE and PE will be summarized for the ITT set by preferred drug name. These medications will be identified as detailed in Section 4.2.1.

8. EFFICACY

The hypotheses for the primary efficacy endpoint and the key secondary efficacy endpoints will be formally tested using a hierarchical testing approach to preserve the Type 1 error rate. Objectives will be tested in the order in which they are ranked in Section 4. Analysis of hierarchical secondary objectives will continue until a non-significant p-value (i.e. $p>0.05$) is returned.

All efficacy analyses will be performed on the ITT set unless otherwise specified.

8.1. PRIMARY EFFICACY ENDPOINT AND ANALYSIS

The primary endpoint is the absolute change from baseline FEV_1 (L) over the 26-week treatment period (measured at Weeks 6, 14 and 26). The primary analysis will include assessments as specified up until the time of last participation for each subject, including those performed off trial medication. For subjects who have an IMP discontinuation visit, the spirometry assessment done at this visit can be used instead of the assessment performed at the scheduled visit in line with the rules defined in Section 6.4.

In order to assess the potential impact of missing data on the results, sensitivity analyses will be performed (see Section 8.1.2 for more details):

- Pattern Mixture Model.
- Tipping Point Analysis.
- Mixed model repeated measures (MMRM) without imputation.
- Responder Analysis.

The following supportive analyses will also be performed:

- Using the PP set.
- Absolute change from baseline FEV1 (L) at 26 weeks and at 6 and 14 weeks.
- Absolute change from baseline percent predicted FEV1 (%) over 26 weeks.
- Relative change from baseline FEV1 (L) over 26 weeks.
- Relative change from baseline percent predicted FEV1 (%) over 26 weeks.

In addition, the following supportive analyses on the absolute change from baseline FEV_1 (L) over the 26 week treatment period will be conducted based on on-treatment period data only:

- MMRM with BOCF+IUDR imputation.
- Pattern mixture model.
- MMRM without BOCF.

The primary analysis of absolute change in FEV1 over the 26 week treatment period and the supportive analysis of relative change in FEV1 over the 26 week treatment period will be repeated by the subgroups specified in Section 6.6 on the ITT set only.

The results from the primary analysis, the sensitivity analyses, the supportive analyses, and the subgroup analyses for the primary endpoint will be presented in forest plots to graphically explore the consistency of the estimated treatment effect.

8.1.1. Primary Analysis of the Primary Endpoint

Descriptive Summaries:
FEV_1 (L) absolute change from baseline and relative change from baseline (% change) and percent predicted FEV_1 (%) absolute change from baseline and relative change from baseline (% change) will be summarized by visit using summary statistics for continuous variables. Two summaries will be produced based on actual data and imputed missing data as described below. All these summaries will be performed on the ITT and PP sets. In addition, FEV_1 (L) absolute change from baseline and relative change from baseline (% change) will be summarized for on trial medication data only (i.e. excluding data >7 days after trial medication stop date), by visit, using summary statistics for continuous variables, based both on actual data and imputed missing data, for the ITT set.

Primary Analysis Method:
The mean absolute change from baseline FEV_1 (L) over 26 weeks (including assessments at Weeks 6, 14 and 26) will be compared between the two treatment groups with a restricted maximum likelihood (REML) based MMRM approach.

The model will include the fixed, categorical effects of treatment group, rhDNase use, pooled country, visit, and treatment group-by-visit interaction, as well as the continuous, fixed covariate of baseline FEV_1 and also disease severity (percent predicted FEV_1 at baseline). Subject will be included in the model as a random effect. An unstructured (co)variance structure will be used to model the within-subject errors. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. [redacted].

[redacted]:

[redacted]

Least squares means (LS means) and mean treatment group difference, standard error (SE), 95% CIs, and p-value for the treatment group effect averaged across the trial, with the same weight applied to each visit, will be presented.

Plots of the LS means (95% CI) for the primary endpoint against visit will be presented for the ITT and PP sets, highlighting significant differences between the treatment groups at any timepoint.

Missing Data:
The analysis will use spirometry data which are consistent with the visit assignment as described in Section 6.4. Subjects who discontinue trial medication should remain in the trial and continue to provide all scheduled FEV_1 measurements. The primary analysis will include all available on-treatment and off-treatment period data, regardless of adherence to or discontinuation of trial medication. While all efforts will be made to ensure subjects remain in the trial, the following planned imputation strategy will allow for an appropriate primary analysis in the presence of missing FEV_1 data.

To calculate baseline values, missing Visit 1 measurements for the primary efficacy variable (FEV_1) will be imputed using Visit 0 (screening) measurements, if available.

Missing post-baseline measurements as a result of withdrawal from the trial for the primary efficacy variable (FEV_1) will be imputed using an IUDR methodology. For subjects who withdraw from the trial due to AE, death, physician decision, or lack of efficacy, missing post-baseline FEV_1 measures as a result of withdrawal from the trial will be imputed using the baseline FEV_1 measurement (BOCF procedure). Missing FEV_1 measurements as a result of withdrawal from the trial, where the withdrawal was as a result of other causes (i.e. lost to follow-up, relocation, pregnancy, major protocol deviation, sponsor decision, withdrawal of consent, or other) will not be imputed. Missing data at intermediate visits (i.e. where data is available at a later visit) will not be imputed.

Imputation of missing FEV_1 measurements by means of BOCF is a reasonable assumption in studies of adult subjects with cystic fibrosis, as those subjects who discontinue will no longer receive treatment and are thus likely to promptly return to their baseline lung function. Imputation by BOCF specifically inhibits any possible prolongation of an observed early treatment benefit implicitly conferred by a mixed model. Considering the higher drop-out rate observed with the experimental treatment compared to control in previous studies (DPM-CF-301 and DPM-CF-302), BOCF is not likely to favour the mannitol arm.

The primary analysis will target the de facto estimand assessing the effect of a treatment policy (Estimand 1 in Mallinckrodt [6]) by:

- Including all available on-treatment and off-treatment period data.
- Handling missing data based on a clinically reasonable assumption not biased in favor of the mannitol arm.

8.1.2. Sensitivity Analyses of the Primary Endpoint

To elicit insights into the effect of imputation via the planned BOCF+IUDR framework, the following sensitivity analyses of the primary endpoint will be conducted:

- Sensitivity Analysis 1: Pattern Mixture Model.
- Sensitivity Analysis 2: Tipping Point Analysis.
- Sensitivity Analysis 3: MMRM without imputation.
- Sensitivity Analysis 4: Responder Analysis.

As for the primary analysis, these sensitivity analyses target the de facto estimand assessing the effect of a treatment policy. These analyses will include all available on-treatment and off-treatment period data, regardless of adherence to or discontinuation of trial medication.

Planned approaches for handling missing data in Sensitivity analyses 1, 2, and 4 are not likely to favor the experimental arm (for more details see specific sections below.)

In the first 3 analyses, the mean absolute change from baseline FEV_1 (L) over 26 weeks (including assessments at Weeks 6, 14 and 26) and at each post-baseline visit will be compared between the two treatment groups. For the responder analysis, the comparison between treatment groups will be performed at Week 26 (however subjects who withdraw from the trial earlier are assumed to be non-responders).

Sensitivity Analysis 1: Pattern Mixture Model
A potential disadvantage of employing a single imputation method such as BOCF is the risk of underestimating the variability. To assess the possible impact of this effect,

missing FEV_1 values at post-baseline visits will be imputed using multiple imputation (MI) from the distribution of baseline values, using the method of Ratitch et al[7] for pattern imputation based on reasons for dropout.

This approach is in line with the one defined for the primary endpoint analysis, where subjects withdrawing from the trial for AE, death, physician decision or lack of efficacy are considered to stop benefiting from the trial medication and return to their baseline status (i.e. BOCF approach; see GRP2 imputation model below), while for subjects withdrawing from the trial for other reasons, it is assumed that they would have continued to benefit from the trial medication in line with subjects completing the trial (see GRP4 and GRP6 imputation models below).

In a preliminary step, imputation based on the missing at random (MAR) assumption will be performed using the joint modeling approach in order to obtain monotone missing data patterns. The imputation model will include the following variables: treatment group, rhDNase use, pooled country, FEV_1 (L) from Visit 0 to Visit 4.

Then, a regression-based imputation will be performed for the remaining missing FEV_1 values. The strategy for imputation will be based on the definition of the following groups of observed data and patterns of missingness:

(GRP1) Subjects from both treatment groups with non-missing baseline FEV_1 values

(GRP2) Subjects from both treatment groups who withdraw from the trial due to AE, death, physician decision, or lack of efficacy

(GRP3) Subjects in the control group who completed the trial

(GRP4) Subjects in the control group who withdraw from the trial because of other reasons

(GRP5) Subjects in the mannitol group who completed the trial

(GRP6) Subjects in the mannitol group who withdraw from the trial because of other reasons

Imputation will be performed:

- In pattern (GRP2) using a model for baseline FEV_1 including rhDNase use, pooled country and FEV_1 (L) at Visit 0, estimated on the (GRP1) group.
- In pattern (GRP4) using a model including rhDNase use, pooled country, FEV_1 (L) from Visit 0 to Visit 4, estimated on the (GRP3) group.

- In pattern (GRP6) using the same model described in the previous bullet point, estimated on the (GRP5) group.

One thousand imputations will be performed and for each imputed dataset the analysis of the change from baseline FEV_1 (L) over 26 weeks (the mean of values at Weeks 6, 14 and 26) will be based on an ANCOVA model including the following variables: treatment group, rhDNase use, pooled country, baseline FEV_1 and disease severity (percent predicted FEV_1 at baseline). Also the changes at each post-baseline visit will be analyzed using the same ANCOVA model. Estimates from the models will be then combined using Rubin's rule.

[redacted]

Sensitivity Analysis 2: Tipping Point Analysis

If a significant difference between treatments is found in the primary analysis, a tipping point analysis will be performed.

The hypothesis behind this approach is that subjects withdrawing from the trial will have a worse outcome (FEV1) compared to subjects completing the trial by a certain amount of mL, with penalties applied to the missing information varying between the two treatment arms. This analysis will explore the influence of missingness, providing evidence of the 'tipping' point where there is no longer evidence of a treatment effect on improvement from baseline of FEV1.

In a preliminary step, imputation based on the missing at random (MAR) assumption will be performed in order to obtain monotone missing data patterns as above described for Sensitivity Analysis 1.

Then, a regression-based imputation will be performed for the remaining missing FEV_1 values (regardless of the reason for withdrawal from the trial). The imputation model will include the following variables: treatment group, rhDNase use, pooled country, FEV_1 (L) from Visit 0 to Visit 4. Subjects who withdraw from the trial will then have their unobserved post-baseline FEV_1 values worsened by an amount δ compared to the observed FEV_1 of subjects who continue. The analysis will find a tipping point in the spectrum of assumptions on the magnitude of δ in the mannitol group at which conclusions change from being favorable to mannitol to being inconclusive (non-statistically significant mean difference between treatments over 26 weeks). The tipping point will be determined in the scenarios described in Table 5:

Table 5: δ-adjustments to Identify the Tipping Point

δ-adjustment in the control group	δ-adjustment in the mannitol group (in order to identify the tipping point)
0	-0.020, -0.040, -0.060, … L
-0.020 L	-0.020, -0.040, -0.060, -0.080, … L
-0.040 L	-0.040, -0.060, -0.080, -0.100, … L
-0.060 L	-0.060, -0.080, -0.100, -0.120, … L
-0.080 L	-0.080, -0.100, -0.120, -0.140, … L
-0.100 L	-0.100, -0.120, -0.140, -0.160, … L

where the δ-adjustments for the mannitol group will decrease by 20 mL up to reaching the non-statistical significance of the treatment comparison.

In each scenario one thousand imputations will be performed and the analysis of the change from baseline FEV_1 (L) over 26 weeks will be conducted using an ANCOVA model in line with the specification made for Sensitivity Analysis 1.

[redacted]

Sensitivity Analysis 3: MMRM Without BOCF Imputation
The same MMRM as for the primary analysis will be used without performing any imputation of post-baseline measurements.

This analysis is based on a MAR assumption on missing data, i.e. on the assumption that unobserved outcomes of subjects who withdraw from the trial do not systematically differ from observed outcomes of subjects who remained in the trial.

Sensitivity Analysis 4: Responder Analysis
A subject will be defined as:

- A responder if they have a change from baseline FEV_1 (L)≥threshold at Week 26.
- A non-responder if they have a change from baseline FEV1 (L)<threshold at Week 26 or missing change from baseline FEV_1 at Week 26.

The hypothesis is that subjects withdrawing from the trial are not expected to benefit from the treatment, and so are considered as 'Non-responders'.

Three different thresholds will be considered: 0.100, 0.075 and 0.050 L.

Considering the higher drop-out rate observed with the experimental treatment compared to control in previous studies (DPM-CF-301 and DPM-CF-302), responder analysis is not likely to favor the experimental arm.

The proportion of responders will be summarized and compared between treatment groups using logistic regression. The model will include the same covariates as specified in the primary analysis. The treatment group effect odds ratio and its 95% CI and p-value will be presented.

[redacted]

[redacted]

8.1.3. Supportive Analyses of the Primary Endpoint

8.1.3.1. Supportive Analyses of the Primary Endpoint – PP Set

Supportive Analysis 1: MMRM with BOCF+IUDR Imputation, PP set

Same statistical model as for the primary analysis (Section 8.1.1), but considering the PP set. This will provide an extra robustness check on the primary results from the ITT set. Any measurements excluded from the PP analysis at the BDRM will be treated as missing data but will not be included in the imputation process.

8.1.3.2. Supportive Analyses of the Primary Endpoint – Results at Each Visit

Supportive Analysis 2: MMRM with BOCF+IUDR Imputation, at Week 6/Week 14/Week 26

Using the same statistical model as for the primary analysis (Section 8.1.1), results will be presented also for the treatment group effect at each of the 3 post-baseline visits.

[redacted]

8.1.3.3. Supportive Analyses of the Primary Endpoint – Additional FEV_1 Evaluations

In addition to the evaluation of the mean absolute change from baseline FEV_1 (L) over 26 weeks, the following supportive analyses based on the FEV_1 parameter will be analyzed:

Supportive Analysis 3: Absolute Change from Baseline Percent Predicted FEV_1 (%) Over 26 Weeks

Supportive Analysis 4: Relative Change from Baseline FEV_1 (L) Over 26 Weeks

Supportive Analysis 5: Relative Change from Baseline Percent Predicted FEV_1 (%) Over 26 Weeks

Supportive analyses 3, 4 and 5 will follow the same approach as for the primary analysis (Section 8.1.1). For the analyses of percent predicted FEV_1, the FEV_1 baseline [redacted] will not be included in the model; the baseline measure of the outcome will be included as baseline percent predicted FEV_1 (disease severity).

8.1.3.4. Supportive Analyses of the Primary Endpoint – On-treatment Period Data Only

To elicit insights into the effects of including data from subjects after cessation of trial medication (by including these data, the effects of subsequent therapy are attributed to trial medication); the analyses outlined in Section 8.1.1 and 8.1.2 will be repeated for on trial medication data only (i.e. *excluding* data >7 days after trial medication discontinuation).

Supportive Analysis 6: MMRM with BOCF+IUDR Imputation, On-treatment Period Data
Same approach as for the primary analysis (Section 8.1.1), but considering reason for discontinuation from trial medication.

Supportive Analysis 7: Pattern Mixture Model, On-treatment Period Data
Same approach as for Sensitivity Analysis 1 (Section 8.1.2), but considering reason for

discontinuation from trial medication.

Supportive Analysis 8: MMRM Without BOCF, On-treatment Period Data
Same approach as for Sensitivity Analysis 3 (Section 8.1.2).

8.2. HIERACHICAL SECONDARY EFFICACY ENDPOINT(S) AND ANALYSES

All summaries and main analyses outlined below for the hierarchical secondary efficacy endpoints will be repeated by the subgroups of rhDNase use and disease severity (percent predicted FEV_1 at baseline) as specified in Section 6.6. For each hierarchical secondary endpoint, the results from the main analysis, the sensitivity analyses, the supportive analyses (where possible i.e. where these are on the same scale as the main analysis results), and the subgroup analyses will be presented in a forest plot for comparison.

8.2.1. Forced Vital Capacity and Other Spirometry Parameters

Descriptive Summaries:
FVC absolute change from baseline (L) and relative change from baseline (% change) will be summarized by visit using summary statistics for continuous variables. Two summaries will be produced for the ITT set based on actual data and imputed missing data as described for the primary endpoint in Section 8.1.1.

PEF (L/s), FEV_1/FVC ratio (%) and FEF_{25-75} (L/s) absolute change from baseline and relative change from baseline (% change) will also be summarized by visit using summary statistics for continuous variables without imputation of missing data.

Analysis Method:
The mean absolute change from baseline FVC (L) over 26 weeks (including assessments at Weeks 6, 14, and 26) will be compared between the two treatment groups using the same model as the primary analysis (with a covariate of baseline FVC, rather than baseline FEV_1). Missing data will be handled in the same way as for the primary endpoint.

The mean absolute change from baseline FVC (L) will also be presented for the treatment group effect at each of the 3 post-baseline visits.

The other pulmonary function tests (PEF, FEV_1/FVC ratio, and FEF_{25-75}) will not be analyzed.

The criterion for moving to the next endpoint in the analysis will be based on a p-value less than 0.05 for the comparison between the two treatment groups; sensitivity and supportive analyses will not be part of the testing hierarchy.

8.2.1.1. Sensitivity Analyses of FVC

Sensitivity Analysis 1: Pattern Mixture Model
To assess the possible impact of employing a single imputation method, a pattern mixture model analysis will be conducted, following the same approach as for Sensitivity Analysis 1 (Section 8.1.2) for the primary endpoint (and with a covariate of baseline FVC, rather than baseline FEV1).

Sensitivity Analysis 2: MMRM Without BOCF
To elicit insights into the effect of imputation via the planned BOCF+IUDR framework, the main FVC analysis outlined above will be repeated with no imputation of missing post-baseline FVC. This analysis will be performed as described for Sensitivity Analysis 3 of the primary endpoint in Section 8.1.2 (with a covariate of baseline FVC, rather than baseline FEV1).

8.2.1.2. Supportive Analysis of FVC

8.2.1.2.1. Supportive Analysis – Results at Each Visit

Supportive Analysis: MMRM with BOCF+IUDR Imputation, at Week 6/Week 14/Week 26
Least squares means (LS means) and mean treatment group difference, SE, 95% CIs, and p-value will be presented not only for the treatment groups averaged across the trial, but also for the treatment group effect at each of the 3 post-baseline visits. These results will be obtained by adding specific contrasts to the main model, in line with the approach followed for the primary analysis (Sections 8.1.1 and 8.1.3.2).

8.2.2. Time to First Protocol Defined Pulmonary Exacerbation

Descriptive Summaries:
Subjects who do not have a PDPE during the trial will be censored at the date of last participation in the trial. The number of subjects with an event and censored will be summarized. Kaplan-Meier product limit estimators of the survivor function (probability of staying event free) will be summarized for 25^{th} percentile, median, and 75^{th} percentile, and their 95% CIs. The plot of Kaplan-Meier estimates for the two treatment groups will also be presented.

As supportive information the above summaries will be repeated for time to first PE (i.e. all PEs recorded on the CRF with associated antibiotic use, whether or not they met the criteria for a PDPE).

Analysis Method:
The time (in days) to first PDPE will be analyzed using the Cox's Proportional Hazards model. The model will include the terms treatment group, pooled country, rhDNase use, and number of IV antibiotic treated PEs in year prior to screening (continuous) as factors. The treatment group hazard ratio will be presented with 95% CI and p-value for the treatment group effect.

[redacted]

The criterion for moving to the next endpoint in the analysis will be based on a p-value less than 0.05 for the comparison between the two treatment groups; supportive will not be part of the testing hierarchy.

8.2.2.1. Supportive Analysis of Time to First Protocol Defined Pulmonary Exacerbation

8.2.2.1.1. Supportive Analysis – All Pulmonary Exacerbations

Supportive Analysis: Time to First Pulmonary Exacerbation
As supportive information the above analysis will be repeated for time to first PE.

8.2.3. Number of Days on Antibiotics Due to Protocol Defined Pulmonary Exacerbation

Descriptive Summaries:
The number of days on antibiotics due to PDPE will be summarized using summary statistics for continuous variables (for all subjects in the ITT set and repeated only for

those with at least one distinct episode of antibiotic usage to treat PDPE) and also for categorical variables using weekly categories (0, 1-7 days, 8-14 days, etc.).

The number of distinct episodes of use of antibiotics due to PDPE will be summarized using summary statistics for categorical variables (e.g. 0, 1-5, etc. or as appropriate to data).

The number of courses of antibiotics due to PDPE will be summarized using summary statistics for categorical variables (no antibiotic use, 1, 2, 3, >3).

As supportive information the above summaries will be repeated for the number of distinct days on antibiotics due to PDPE (excluding overlaps), the number of days on antibiotics due to PE (i.e. all PEs recorded on the CRF with associated antibiotic use, whether or not they met the criteria for a PDPE), and the number of distinct days on antibiotics due to PE (excluding overlaps).

Analysis Method:
The number of days on antibiotics due to PDPE will be compared between treatment groups using a negative binomial model. [redacted] The model will include the categorical effects treatment group, pooled country, rhDNase use, and the continuous covariate number of IV antibiotic treated PEs in year prior to screening. An offset variable of the natural log of follow-up duration (years) will be used in the model to adjust for different lengths of follow-up. The rate ratio will be presented with 95% CI and p-value for the treatment group effect.

There will be no imputation of missing data.

[redacted]

[redacted]

The criterion for moving to the next endpoint in the analysis will be based on a p-value less than 0.05 for the comparison between the two treatment groups; supportive analyses will not be part of the testing hierarchy.

8.2.3.1. Supportive Analyses of Number of Days on Antibiotics Due to Protocol Defined Pulmonary Exacerbation

8.2.3.1.1. Supportive Analysis – Additional Evaluation of the Number of Days on Antibiotics Due to Protocol Defined Pulmonary Exacerbation

Supportive Analysis 1: Number of Distinct Days on Antibiotics Due to Protocol Defined Pulmonary Exacerbation
Same approach described in Section 8.2.3 'Analysis Method', but considering the number of distinct days on antibiotics due to PDPE (i.e. excluding overlaps).

8.2.3.1.2. Supportive Analyses – All Pulmonary Exacerbations

Supportive Analysis 2: Number of Days on Antibiotics Due to Pulmonary Exacerbation
Same approach described in Section 8.2.3 'Analysis Method', but considering the number of days on antibiotics due to PE (i.e. all PEs recorded on the CRF with associated antibiotic use, whether or not they met the criteria for a PDPE).

Supportive Analysis 3: Number of Distinct Days on Antibiotics Due to Pulmonary Exacerbation
Same approach described in Section 8.2.3 'Analysis Method', but considering the number of distinct days on antibiotics due to PE (i.e. excluding overlaps and considering all PEs recorded on the CRF with associated antibiotic use, whether or not they met the criteria for a PDPE).

8.2.4. Number of Days in Hospital Due to Protocol Defined Pulmonary Exacerbation

Descriptive Summaries:
The number of days in hospital due to PDPE will be summarized using summary statistics for continuous variables (for all subjects in the ITT set and repeated only for those with at least one hospitalization due to PDPE) and also for categorical variables using weekly categories (0, 1-7 days, 8-14 days, etc.). The number of hospitalizations per subject will also be summarized using categories 0, 1, 2, 3, and >3.

As supportive information the above summaries will be repeated for hospitalizations due to PE (i.e. all PEs recorded on the CRF with associated antibiotic use, whether or not they met the criteria for a PDPE).

Analysis Method:
The number of days in hospital (admissions only) due to PDPE will be compared between treatment groups using a negative binomial model. The model will include the categorical effects treatment group, pooled country, rhDNase use, and the continuous covariate number of IV antibiotic treated PEs in year prior to screening. An offset variable of the natural log of follow-up duration (years) will be used in the model to adjust for different lengths of follow-up. The rate ratio will be presented with 95% CI and p-value for the treatment group effect.

[redacted]

There will be no imputation of missing data.

The criterion for moving to the next endpoint in the analysis will be based on a p-value less than 0.05 for the comparison between the two treatment groups; supportive analyses will not be part of the testing hierarchy.

8.2.4.1. Supportive Analysis of Number of Days in Hospital due to Protocol Defined Pulmonary Exacerbation

8.2.4.1.1. Supportive Analysis – All Pulmonary Exacerbations

Supportive Analysis: Number of Days in Hospital Due to Pulmonary Exacerbation
As supportive information the analysis outlined in Section 8.2.4 'Analysis Method' will be repeated for hospitalizations due to PE (i.e. all PEs recorded on the CRF with associated antibiotic use, whether or not they met the criteria for a PDPE).

8.2.5. Rate of Protocol Defined Pulmonary Exacerbation

Descriptive Summaries:
Number of PDPEs (0, 1, etc.) and incidence of PDPEs (yes or no) will be summarized using summary statistics for categorical variables.

The number of subjects with PDPEs, the total number of PDPEs, the total follow-up duration (in years), and the overall rate of PDPEs (per person year) will be presented.

As supportive information the above summaries will be repeated for overall rate of PEs (i.e. all PEs recorded on the CRF with associated antibiotic use, whether or not they met the criteria for a PDPE).

Analysis Method:
The rate of PDPEs will be compared between treatment groups using a negative binomial model. The model will include the categorical effects treatment group, pooled country, rhDNase use, and the continuous covariate number of IV antibiotic treated PEs in year prior to screening. An offset variable of the natural log of follow-up duration (years) will be used in the model to adjust for different lengths of follow-up. The rate ratio will be presented with 95% CI and p-value for the treatment group effect.

[redacted]

The criterion for moving to the next endpoint in the analysis will be based on a p-value less than 0.05 for the comparison between the two treatment groups; supportive and sensitivity analyses will not be part of the testing hierarchy.

Missing Data:
In the event a subject withdraws from the trial before Week 14 with no observed instances of a PDPE the number of PDPEs will be imputed using half the subject's historical (previous 12 months) PE count (rounded upwards) and their follow-up duration will be imputed as 26 weeks.

In the event a subject withdraws from the trial after Week 14 with no observed instances of a PDPE the number of PDPEs will be imputed using one quarter the subject's historical (previous 12 months) PE count (rounded upwards) and their follow-up duration will be imputed as 26 weeks.

8.2.5.1. Sensitivity Analyses of Rate of Protocol Defined Pulmonary Exacerbations

Sensitivity Analysis 1: No Imputation
To elicit insights into the effect of the imputation method described above, the analysis will be repeated with no imputation of missing data.

Sensitivity Analysis 2: Zero Inflated Negative Binomial Model
To account for the possibility of an excess reporting of zero rates, the main analysis outlined above will be repeated using a zero inflated negative binomial model. This models the data as a mixture of two separate distributions; as a negative binomial distribution that can generate both zero and nonzero counts, and as a constant distribution that generates only zero counts. First an investigation of the data will be carried out to assess whether the probability of observing zero counts is conditional on any of the covariates in the model, by plotting the marginal and conditional distributions of the response variable.

[redacted]

Sensitivity Analysis 3: Multiple Imputation

To assess the possible impact of employing a single imputation method (i.e. risk of variability underestimation), an analysis based on MI will be performed.

For all subjects who withdrew from the trial with a follow-up duration shorter than 183 days (i.e. 26 weeks+1 day), the number of PDPEs from withdrawal up to day 183 will

be imputed.

The imputation will be performed using a model for the number of IV antibiotic treated PEs in the year prior to screening including rhDNase use and pooled country. Therefore, the imputation will be based on the distribution of historical PE count.

One thousand imputations will be performed and the analysis of the total number of PDPEs (observed+imputed events) will be based on the same negative binomial model described in the 'Analysis Method' paragraph above. Estimates from the models will then be combined using Rubin's rule.

[redacted]

8.2.5.2. Supportive Analysis of Rate of Protocol Defined Pulmonary Exacerbations

8.2.5.2.1. Supportive Analysis – Rate of Pulmonary Exacerbations

Supportive Analysis: Single imputation, Pulmonary Exacerbations
Same approach as for the analysis described in 'Analysis Method' (Section 8.2.5), considering PEs (i.e. all PEs recorded on the CRF with associated antibiotic use, whether or not they met the criteria for a PDPE).

8.3. NON-HIERACHICAL SECONDARY EFFICACY ENDPOINT(S) AND ANALYSES

8.3.1. Incidence of Protocol-Defined Pulmonary Exacerbations

Descriptive Summaries:
Incidence of PDPEs (yes or no) will be summarized as described in Section 8.2.5.

Analysis Method:
Proportions will be compared between treatment groups using logistic regression. The model will include the categorical effects pooled country, rhDNase use, and the continuous covariate number of IV antibiotic treated PEs in year prior to screening. The treatment group effect odds ratio, 95% CI, and p-value will be presented.

No imputation of missing data will be performed.

8.3.1.1. Supportive Analysis of Incidence of Protocol Defined Pulmonary Exacerbations

Supportive Analysis: Incidence of Pulmonary Exacerbations
The summary and analysis defined in Section 8.3.1 will be repeated for incidence of PEs (i.e. all PEs recorded on the CRF with associated antibiotic use, whether or not they met the criteria for a PDPE).

8.3.2. Ease of Expectoration Visual Analogue Scale

Descriptive Summaries:
The ease of expectoration VAS score and absolute change from baseline will be summarized by visit using summary statistics for continuous variables, based both on actual data and imputed missing data.

Analysis Method:
The mean absolute change from baseline VAS score over Weeks 6, 14 and 26 will be compared between the two treatment groups with a REML based MMRM approach. The analysis will be the same as described for the primary endpoint in Section 8.1.1. The model will include the fixed, categorical effects of treatment group, rhDNase use, pooled country, visit, and treatment group-by-visit interaction, as well as the continuous, fixed covariates of baseline VAS score and disease severity (percent predicted FEV_1 at baseline). Missing data will be handled in the same way as for the primary analysis of the primary endpoint.

8.3.2.1. Sensitivity Analysis of Ease of Expectoration Visual Analogue Scale

Sensitivity Analysis: MMRM Without BOCF
To elicit insights into the effect of imputation via the planned BOCF+IUDR framework, the main analysis outlined in Section 8.3.2 'Analysis Method' will be repeated with no imputation of missing data.

8.3.3. CFQ-R Respiratory Domain

Descriptive Summaries:
The CFQ-R respiratory domain scaled score and absolute change from baseline will be summarized by visit using summary statistics for continuous variables, based both on actual data and imputed missing data.

Analysis Method:
The mean absolute change from baseline in the CFQ-R respiratory domain score over Weeks 6, 14 and 26 will be compared between the two treatment groups with a REML

based MMRM approach. The analysis will be the same as described for the primary endpoint in Section 8.1.1. The model will include the fixed, categorical effects of treatment group, rhDNase use, pooled country, visit, and treatment group-by-visit interaction, as well as the continuous, fixed covariates of baseline CFQ-R respiratory domain score and disease severity (percent predicted FEV_1 at baseline). Missing data will be handled in the same way as for the primary analysis of the primary endpoint.

8.3.3.1. Sensitivity Analysis of CFQ-R Respiratory Domain

Sensitivity Analysis: MMRM Without BOCF

To elicit insights into the effect of imputation via the planned BOCF+IUDR framework, the main analysis outlined above will be repeated with no imputation of missing data.

8.3.3.2. Supportive Analysis of CFQ-R Domain

Supportive Analysis: MMRM with BOCF+IUDR Imputation, Question 42 Excluded

The above summary and analysis will be repeated for the CFQ-R respiratory domain score omitting Question 42 (CRF Question 3: "Have you had to cough up mucus?"), where the baseline covariate will be baseline CFQ-R respiratory domain score omitting Question 42.

8.4. SUMMARY OF ANALYSES

Table 6: Summary of Analyses

Analysis Designation	Endpoint	Model	Imputation Process Used	Off-trial Medication Data Included	Analysis Set
Primary					
Primary	FEV_1 Absolute Change from Baseline	MMRM	IUDR (trial withdrawal reason)/ BOCF	Yes	ITT
Primary – Sensitivity 1	FEV_1 Absolute Change from Baseline	ANCOVA	Pattern Mixture: MI Based on Reasons for Trial Withdrawal	Yes	ITT

Analysis Designation	Endpoint	Model	Imputation Process Used	Off-trial Medication Data Included	Analysis Set
Primary – Sensitivity 2	FEV_1 Absolute Change from Baseline	ANCOVA	Tipping point	Yes	ITT
Primary – Sensitivity 3	FEV_1 Absolute Change from Baseline	MMRM	None	Yes	ITT
Primary – Sensitivity 4	FEV_1 Responders	Logistic Regression	Missing = non-response	Yes	ITT
Primary – Supportive 1	FEV_1 Absolute Change from Baseline	MMRM	IUDR (trial withdrawal reason)/ BOCF	Yes	PP
Primary – Supportive 2	FEV_1 Absolute Change from Baseline – At Week 6/Week 14/Week 26	MMRM	IUDR (trial withdrawal reason)/ BOCF	Yes	ITT
Primary – Supportive 3	Percent Predicted FEV_1 Absolute Change from Baseline	MMRM	IUDR (trial withdrawal reason)/ BOCF	Yes	ITT
Primary – Supportive 4	FEV_1 Relative Change from Baseline	MMRM	IUDR (trial withdrawal reason)/ BOCF	Yes	ITT
Primary – Supportive 5	Percent Predicted FEV_1 Relative Change from Baseline	MMRM	IUDR (trial withdrawal reason)/ BOCF	Yes	ITT
Primary – Supportive 6	FEV_1 Absolute Change from Baseline	MMRM	IUDR (trial medication discontinuation reason)/ BOCF	No	ITT

Statistical Analysis Plan

Analysis Designation	Endpoint	Model	Imputation Process Used	Off-trial Medication Data Included	Analysis Set
Primary – Supportive 7	FEV_1 Absolute Change from Baseline	ANCOVA	Pattern Mixture: MI Based on Reasons for Trial Medication Discontinuation	No	ITT
Primary – Supportive 8	FEV_1 Absolute Change from Baseline	MMRM	None	No	ITT
Primary – by Subgroups	FEV_1 Absolute Change from Baseline	MMRM by Subgroups (see Section 6.6)	IUDR (trial withdrawal reason)/ BOCF	Yes	ITT
Primary – by Subgroups	FEV_1 Relative Change from Baseline	MMRM by Subgroups (see Section 6.6)	IUDR (trial withdrawal reason)/ BOCF	Yes	ITT
Secondary Hierarchical					
Secondary 1 Hierarchical	FVC Absolute Change from Baseline	MMRM	IUDR (trial withdrawal reason)/ BOCF	Yes	ITT
Secondary 1 - Sensitivity 1	FVC Absolute Change from Baseline	ANCOVA	Pattern Mixture: MI Based on Reasons for Trial Withdrawal	Yes	ITT
Secondary 1 - Sensitivity 2	FVC Absolute Change from Baseline	MMRM	None	Yes	ITT
Secondary 1 - Supportive	FVC Absolute Change from Baseline - At Week 6/Week 14/Week 26	MMRM	IUDR (trial withdrawal reason)/ BOCF	Yes	ITT

Statistical Analysis Plan

Analysis Designation	Endpoint	Model	Imputation Process Used	Off-trial Medication Data Included	Analysis Set
Secondary 1 – by Subgroups	FVC Absolute Change from Baseline	MMRM by Subgroups (see Section 6.6)	IUDR (trial withdrawal reason)/ BOCF	Yes	ITT
Secondary 2 Hierarchical	Time to First PDPE	Cox's Proportional Hazards	censoring at date of last participation	Yes	ITT
Secondary 2 – Supportive	Time to First PE	Cox's Proportional Hazards	censoring at date of last participation	Yes	ITT
Secondary 2 – by Subgroups	Time to First PDPE	Cox's Proportional Hazards by Subgroups (see Section 6.6)	censoring at date of last participation	Yes	ITT
Secondary 3 Hierarchical	Number of Days of Antibiotic Use Due to PDPE	Negative Binomial Model	None	Yes	ITT
Secondary 3 – Supportive 1	Number of Days of Antibiotic Use Due to PDPE Excluding Overlaps	Negative Binomial Model	None	Yes	ITT
Secondary 3 – Supportive 2	Number of Days of Antibiotic Use Due to PE	Negative Binomial Model	None	Yes	ITT
Secondary 3 – Supportive 3	Number of Days of Antibiotic Use Due to PE Excluding Overlaps	Negative Binomial Model	None	Yes	ITT
Secondary 3 - by Subgroups	Number of Days of Antibiotic Use Due to PDPE	Negative Binomial Model by Subgroups (see Section 6.6)	None	Yes	ITT

Statistical Analysis Plan

Analysis Designation	Endpoint	Model	Imputation Process Used	Off-trial Medication Data Included	Analysis Set
Secondary 4 Hierarchical	Number of Days in Hospital Due to PDPE	Negative Binomial Model	None	Yes	ITT
Secondary 4 – Supportive	Number of Days in Hospital Due to PE	Negative Binomial Model	None	Yes	ITT
Secondary 4 – by Subgroups	Number of Days in Hospital Due to PDPE	Negative Binomial Model by Subgroups (see Section 6.6)	None	Yes	ITT
Secondary 5 Hierarchical	PDPE Rate	Negative Binomial Model	Half historical count over 26 weeks for withdrawals before Week 14 or one quarter historical count over 26 weeks for withdrawals after Week 14	Yes	ITT
Secondary 5 – Sensitivity 1	PDPE Rate	Negative Binomial Model	None	Yes	ITT

Statistical Analysis Plan

Analysis Designation	Endpoint	Model	Imputation Process Used	Off-trial Medication Data Included	Analysis Set
Secondary 5 – Sensitivity 2	PDPE Rate	Zero Inflated Negative Binomial Model	Half historical count over 26 weeks for withdrawals before Week 14 or one quarter historical count over 26 weeks for withdrawals after Week 14	Yes	ITT
Secondary 5 – Sensitivity 3	PDPE Rate	Negative Binomial Model	Multiple imputation based on historical PE count	Yes	ITT
Secondary 5 – Supportive	PE Rate	Negative Binomial Model	Half historical count over 26 weeks for withdrawals before Week 14 or one quarter historical count over 26 weeks for withdrawals after Week 14	Yes	ITT

Statistical Analysis Plan

Analysis Designation	Endpoint	Model	Imputation Process Used	Off-trial Medication Data Included	Analysis Set
Secondary 5 – by Subgroups	PDPE Rate	Negative Binomial Model by Subgroups (see Section 6.6)	Half historical count over 26 weeks for withdrawals before Week 14 or one quarter historical count over 26 weeks for withdrawals after Week 14	Yes	ITT
Secondary Non-hierarchical					
Secondary Non-hierarchical 1	Incidence of PDPEs	Logistic Regression	None	Yes	ITT
Secondary Non-hierarchical 1 – Supportive	Incidence of PEs	Logistic Regression	None	Yes	ITT
Secondary Non-hierarchical 2	Ease of Expectoration VAS Score Absolute Change from Baseline	MMRM	IUDR (trial withdrawal reason)/ BOCF	Yes	ITT

Statistical Analysis Plan

Analysis Designation	Endpoint	Model	Imputation Process Used	Off-trial Medication Data Included	Analysis Set
Secondary Non-hierarchical 2 – Sensitivity	Ease of Expectoration VAS Score Absolute Change from Baseline	MMRM	None	Yes	ITT
Secondary Non-hierarchical 3	CFQ-R Respiratory Domain Scaled Score Absolute Change from Baseline	MMRM	IUDR (trial withdrawal reason)/ BOCF	Yes	ITT
Secondary Non-hierarchical 3 – Sensitivity	CFQ-R Respiratory Domain Scaled Score Absolute Change from Baseline	MMRM	None	Yes	ITT
Secondary Non-hierarchical 3 – Supportive	CFQ-R Respiratory Domain Scaled Score Excluding Question 42 Absolute Change from Baseline	MMRM	IUDR (trial withdrawal reason)/ BOCF	Yes	ITT

9. SAFETY

The SAF set will be used for all safety analyses. Safety will be assessed on the basis of AE reports, extent of exposure and compliance, physical examinations, and vital signs.

No inferential statistical testing is planned on the safety data.

9.1. EXTENT OF EXPOSURE

Duration of exposure (months) will be summarized and will be calculated for the SAF set as follows:

Duration of exposure = (last date trial medication–first date trial medication+1)x12/365.25

Duration of exposure in months will be rounded to one decimal place for displaying purposes.

Duration of exposure will be summarized for the SAF set using summary statistics for continuous variables and also for categorical variables using monthly categories (e.g. 0-1, >1-2, etc.).

If last date of trial medication is missing or partial then the algorithm specified in Section 6.2.1 will be applied.

9.2. TRIAL MEDICATION COMPLIANCE

Trial medication compliance (%) will be summarized for the SAF set using summary statistics for continuous variables. Compliance to trial medication while taking trial medication will be calculated based on the subject reported last date of trial medication as follows:

$$\text{Compliance} = 100\% \times \frac{\sum_{i=1}^{3}(D_i) - \sum_{i=2}^{4}(R_i)}{2 \times 10 \times ([\text{last date of trial med}^*] - [\text{date of Trial Day 1}] + 1)}$$

* Date of last dose of trial medication is as defined in Section 6.2.1

where:

D_i = number of capsules dispensed at Visit i.
R_i = number of unused capsules returned at Visit i.

This calculation assumes 10 capsules were to be taken at each trial medication administration time; dosing was b.i.d., hence 20 capsules were to be taken each day. Trial medication to be taken on dates corresponding with clinic visits are administered at the clinic. Unreturned capsules and/or blister packs will be assumed to have been used by the subject.

9.3. ADVERSE EVENTS

AEs will be coded using MedDRA v11.1.

AEs will be considered MTT-emergent if they started within 2 days after MTT (MTT day and the day after) but before Treatment Day 1.

AEs will be considered treatment-emergent unless there is clear indication that the event occurred prior to Treatment Day 1 (i.e. AEs starting on Treatment Day 1 will be assumed to have occurred after the first dose of trial medication) or the start date is >28 days after permanent discontinuation of trial medication. MEAEs cannot be treatment-emergent AEs (TEAEs) unless they worsen on or after Treatment Day 1. AEs present prior to Treatment Day 1 that increased in intensity or relationship to trial medication while the subject was on trial medication or within 28 days of permanent discontinuation from trial medication will be classed as TEAE. Events with missing or partial dates will be handled such that in the absence of contradictory information an AE is treatment-emergent. So for a missing start date (where stop date is after date of Treatment Day 1) the date will be imputed as the date of Treatment Day 1; for a missing stop date the date will be imputed as the date of last participation in the trial. If a partial date is recorded, the following convention will be used to assign the AE:

- If a partial date is missing a start day and month/year is the same as the date of Treatment Day 1 then use the date of Treatment Day 1, else '01' will be used for the day; if a start date is missing a month and the year is the same as the date of Treatment Day 1 then use the date of Treatment Day 1, else January will be used for the start month.
- If a partial date is missing a stop day and month/year is same as last participation date then use last participation date, else last day of the given month will be used for the stop day; if a stop date is missing a month and year is the same as last participation date then use last participation date, else December will be used for the stop month.

AEs will be summarized by SOC and PT. Subjects will be counted once at the SOC level and once at each PT within the SOC level. Where applicable, summaries will include number and percentage of subjects who report at least one AE, number and percentage of subjects reporting at least one AE in a SOC, number and percentage of subjects reporting at least one AE in a PT, and total number of events within a SOC and within a

PT. Tables will be sorted by decreasing frequency (overall) of SOC, and then, within a SOC, descending frequency (overall) of PT.

Trial medication related AEs are defined as those that are 'possibly related', 'probably related', or 'definitely related'. Relationship to trial medication is not expected to be missing after data cleaning, however, if relationship is confirmed as missing, the AE will be considered as related.

An overall summary table of TEAEs will be presented detailing the number and percentage of subjects, and number of events for the following categories:

- At least one TEAE.
- TEAEs related to trial medication.
- Serious TEAEs.
- Related serious TEAEs.
- TEAEs leading to permanent discontinuation of trial medication.
- TEAEs leading to withdrawal from the trial.
- TEAEs leading to death.

The incidence of all TEAE by SOC and PT will be presented for the following:

- All TEAEs.
- TEAEs related to trial medication.
- Serious TEAEs.
- Related serious TEAEs.
- TEAEs leading to permanent discontinuation of trial medication.
- TEAEs leading to withdrawal from the trial.

In addition, a summary of all TEAEs by maximum intensity (mild, moderate, severe), SOC, and PT will be presented, where the maximum intensity per subject will be counted at each level of summarization. AEs leading to death (all AEs with outcome recorded as 'Fatal' on the CRF), serious AEs (all AEs marked as serious on the CRF), and AEs Leading to withdrawal from the trial (all AEs with 'Did the subject withdraw from the study due to this event?' recorded as 'Yes' on the CRF) will be listed separately.

MEAEs will be summarized by SOC and PT for the MTT set.

Additional information has been collected for AEs that are considered to be hemoptysis events in this trial i.e. information on infection, hemoptysis volume, and whether the hemoptysis occurred concurrently with an exacerbation. These data will be listed and summarized separately.

9.4. VITAL SIGNS

Vital signs assessment and absolute change from baseline in SBP (mmHg), DBP (mmHg), heart rate (beats/min), respiratory rate (breaths/minute), SpO_2 (%), temperature (°C) and weight (kg) will be summarized by visit using summary statistics for continuous variables.

9.5. PHYSICAL EXAMINATION

Physical examination data (decrease in breath sounds/wheezing, crackles, retraction, and clinically significant findings) will be summarized by visit using summary statistics for categorical variables.

10. SAMPLE SIZE RE-ESTIMATION

A formal sample size re-estimation was planned to be performed after at least 300 subjects have been recruited and at least 100 subjects had Visit 4 (Week 26) spirometry data available.

This blinded sample size re-estimation was based on the methods of Kieser and Friede[2] which preserve the overall Type 1 error rate. Thus no adjustments to the overall significance level for the trial are required.

Further details are provided in a separate sample size re-estimation plan (final Version 1.0, dated 07Dec2015).

The outcome of the sample size re-estimation was to increase the sample size required to 440 subjects. In total, 423 subjects were randomized.

11. CHANGE FROM ANALYSIS PLANNED IN PROTOCOL

1. The analysis of spirometry endpoints has been updated to report relevant endpoints using L, as recorded in the CRF, rather than mL, as specified in the protocol, to keep consistency between data collection and final reporting.

2. The 4 hierarchical secondary endpoints and one non-hierarchical secondary endpoint listed below have been clarified to refer to PDPEs rather than PEs. All analyses will be repeated for PEs (defined as all events recorded on the PE Review CRF page that have associated antibiotic use) however the hierarchical testing will be based on the PDPE endpoints (Section 4.2):

   - Time to first PDPE.
   - Number of days on antibiotics (oral, inhaled, or IV) due to PDPE.
   - Number of days in hospital (admissions only) due to PDPE.
   - Rate of PDPE (per person year) over the 26-week treatment period.
   - Incidence of PDPEs over the 26-week treatment period.

3. The criteria to determine if a subject will be included in the PP set were adjusted during the BDRM and local major deviations were defined for the visit if the spirometry assessment was determined to be non valid, leading to the exclusion of all the specific assessment's data collected at the visit from the PP analysis. All the decisions made are documented in the [redacted] which will be finalized prior to unblinding the trial.

4. Time to event derivations will be based on date of randomization (Trial Day 1) for all subjects rather than date of first treatment (Treatment Day 1), except for time to discontinuation from trial medication, to allow consistency of derivations between randomized and treated and randomized but non-treated subjects.

5. Baseline FEV_1 has been added as a continuous, fixed covariate in the REML based MMRM model, or the appropriate baseline value of the analysis variable (i.e. baseline percent predicted FEV_1, baseline FVC, baseline VAS score, or baseline CFQ-R respiratory domain score).

6. For IUDR, BOCF imputations will be done for AE, death, physician decision, and lack of efficacy, while not for lost to follow-up; the logic behind this choice is the fact that motivation for the latter is not related to safety.

7. The BOCF imputation based on IUDR methodology will not be applied to all the missing post-baseline FEV_1 measurements, but only to those which are missing as a result of withdrawal from the trial (i.e. missing intermediate FEV_1 will not be

imputed). It is assumed that a MAR missingness pattern is the most probable in this context.

8. Protocolled primary sensitivity analyses #1 remains unchanged but has become primary sensitivity analysis #3. It will be performed to elicit insights into the effect of imputation via the planned BOCF+IUDR framework and the primary analyses will be repeated without imputation of missing post-baseline FEV_1.

9. Protocolled primary sensitivity analyses #2, #3, #5, #7, and #9 have been removed to provide a more targeted and focused set of analyses to test the robustness of the primary results to varying assumptions (Section 8.1).

    a. Protocolled primary sensitivity analysis #2 was to elicit insights into the effects of including data from subjects after cessation of trial treatment and the primary analyses was to be repeated excluding these data both with imputation of missing post-baseline FEV_1 assessments and without imputation. These analyses will now be included as supportive analyses (Supportive analyses 6 and 8).

    b. Protocolled primary sensitivity analysis #3 was sensitivity of the primary result to choice of "across Weeks 6 to 26" versus "at Week 26" estimates of the treatment effect, gauged by computing the LS mean treatment group difference at Week 26; this result will be presented as part of the primary endpoint primary analysis and is now included as a supportive analysis (Supportive analysis 2).

    c. Protocolled primary sensitivity analysis #5 was to determine if the primary results are sensitive to any observed changes between screening and Visit 1 in FEV_1, and the primary analysis was to be repeated using the mean FEV_1 measurement from screening (Visit 0) and Visit 1.

    d. Protocolled primary sensitivity analysis #7 was a responder analysis where the cut-off for classification as a responder was to be change from baseline FEV_1 greater than: -300, -250, -200, -150, -100, -50, 0, 50, 100, 150, 200, 250, and 300 mL respectively.

    e. Protocolled primary sensitivity analysis #9 was to explore the effect of different imputation methods, the primary analysis was to be repeated using a worst observation carried forward+IUDR method rather than the BOCF+IUDR framework.

10. Primary sensitivity analysis #4 has become primary sensitivity analysis #1 and has been changed to use the Ratitch method[7] (Section 8.1.2). The intention of this

sensitivity analysis remains the same (i.e. to assess the impact of the use of a single imputation method in the primary analysis), only the methodology has been updated. Protocolled primary sensitivity analyses #4 was a two-sample t-test at Week 26 computing point estimates from the data with BOCF but computing variation only from subjects who completed the trial. Furthermore a non-parametric equivalent (e.g. Wilcoxon rank sum test) was to be undertaken on the data with BOCF imputation. These results were to be compared to the Week 26 contrast computed by the primary efficacy model.

11. Primary sensitivity analysis #6 has become primary sensitivity analysis #4, with a different set of responder analyses (Section 8.1.2). Protocolled primary sensitivity analyses #6 defined two responder analyses, the first where a responder was defined as those who have an increase from baseline FEV_1 of greater than 100 mL, and the second where a non-responder was defined as those who have a reduction from baseline FEV_1 of more than 100 mL. In addition, the definition of responder has been revised: subjects having a change greater than or equal to (≥) the threshold are considered responders, instead of subjects having a change greater than (>) the threshold.

12. Primary sensitivity analysis #8 has become primary sensitivity analysis #2, with a change in the rules of attribution of the penalties to missing observations in order to match a *Tipping point* analysis (Section 8.1.2). Protocolled primary sensitivity analysis #8 was to explore the impact of patterns of "missingness" amongst the data using MI with penalties. Missing data across Weeks 6 to 26 were to be imputed by MI, then the impact of various penalties was to be explored, including linking penalties to reason for "missingness", and increasing penalties for subjects with multiple missing data who could be less likely to benefit from treatment. The imputed longitudinal data was to be analyzed by MMRM. In primary sensitivity analysis #2 all missing data as a result of withdrawal from the trial will be imputed regardless of reason for withdrawal, different penalties will be investigated for the mannitol and control arms and the analysis method will be ANCOVA.

13. The continuous covariate of historical exacerbation rate, used for the analyses of some secondary efficacy endpoints, has been reworded to number of IV antibiotic treated PEs in year prior to screening.

14. A secondary sensitivity analysis on FVC has been added. The main FVC analysis will be repeated using a pattern mixture model similar to primary sensitivity analysis #1.

15. A secondary sensitivity analysis on PDPE rate has been added. An analysis based on MI will be performed.

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Statistical Analysis Plan

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