SAV005-04

A Phase III, randomized, double-blind, placebo-controlled study of AeroVanc for the treatment of persistent methicillin-resistant *Staphylococcus aureus* lung infection in cystic fibrosis patients

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Revision History

Version #	Date (dd-mmm-yyyy)	Document Owner	Revision Summary
0.1	30-Mar-2018	W. Schuck	Initial Release Version
0.2	04-May-2018	W. Schuck	Protocol Amendment requires SAP to be updated
0.3	08-Jun-2018	W. Schuck	Updated base on Savara comments
1.0	18-Sep-2018	W. Schuck	Updated base on Savara comments
1.1	18-Feb-2020	W. Schuck	- Clarification/update on Tipping Point analysis - Move Frequency of pulmonary exacerbations to be the first secondary endpoint to be tested - Add analysis and summary tables for all primary and secondary endpoints by Trikafta use
1.2	10-Apr-2020	W. Schuck	- Added sensitivity analyses using strata based on eCRF data instead of IWR reported strata used in actual randomization - Typographical updates
1.3	28-Apr-2020	W. Schuck	Updates regarding changes in the analysis due to COVID-19 pandemic, including the addition of Appendix B
1.4	08-May-2020	W. Schuck	Updated base on Savara comments to the COVID-19 pandemic changes
1.5	12-May-2020	W. Schuck	Updated base on Savara comments
2.0	15-May-2020	W. Schuck	Final for Sign-off
2.1	09Oct2020	W. Schuck	- Update definition of start of first pulmonary exacerbation - Update definition of a new pulmonary exacerbation - Incorporate use of PFT grades in selection of measures to be used in analyses.

Version #	Date (dd-mmm-yyyy)	Document Owner	Revision Summary
2.2	28Oct2020	W. Schuck	- Added baseline imputation method for CFRSD-CRISS and CRQ-R - Clarified adverse event count methods - included grading requirements for PFT use in analyses - Added programmatic definition of P. aeruginosa treatment for sensitivity analysis
3.0	05-Nov-2020	W. Schuck	Final for Sign-off

I confirm that I have reviewed this document and agree with the content.

APPROVALS		
Syneos Health		
Wayne Schuck	*Electronically signed by: Wayne Schuck Reason: I am the author Date: Nov 5, 2020 11:57 EST*	Nov 5, 2020
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0. PREFACE

In amendment 1, the analyses described here are those planned before the occurrence of the COVID-19 pandemic in early 2020. Consequent to COVID-19, recruitment to the trial has been stopped prematurely and some changes to rules for handling missed visits (and resulting missing data) have been introduced. Where appropriate, the new rules for handling missing data will be applied to the primary and secondary efficacy analyses that may differ from the protocol. For clarity, all changes resulting from COVID-19 issues are described in Appendix B of this document. For avoidance of doubt, the primary analyses will be based on the new rules for handling missing data (as described in Appendix B), and not necessarily as described in the original SAP text (as below) or in the protocol.

In amendment 2, any Pulmonary Function Test that scored for reliability and repeatability with a grade of F shall not be used in analyses. In the Per Protocol analyses, results with grades of C or D will also be excluded. This was not specified in the protocol.

1. GLOSSARY OF ABBREVIATIONS

Abbreviation	Description
ALT	Alanine Transaminase
AST	Aspartate transaminase
ATC	Anatomical Therapeutic Chemical
BID	Bis in die/twice daily
BMI	Body Mass Index
CFQ-R	Cystic Fibrosis Questionnaire-Revised
CFRSD-CRISS	Cystic Fibrosis Respiratory Symptom Diary-Chronic Respiratory Symptom Score
COVID-19	Coronavirus disease 2019
CV	Coefficient of Variation
DMC	Data Monitoring Committee
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
FEV_1	Forced expiratory volume in 1 second
ICH	International Conference on Harmonization
ITT	Intent-to-treat
i.v.	Intravenous
IWRS	Interactive Web Response System

Abbreviation	Description
MedDRA	Medical Dictionary for Regulatory Activities
MIC	Minimum Inhibitory Concentration
MIC50	The MIC that inhibits 50% of the tested isolates
MIC90	The MIC that inhibits 90% of the tested isolates
MMRM	Mixed Model for Repeated Measures
MRSA	Methicillin-resistant *Staphylococcus aureus*
N/A	Not Applicable
PFT	Pulmonary function test
PK	Pharmacokinetic
PP	Per Protocol Population
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
SOP	Standard Operating Procedure
TLF	Table, Listing and Figure
ULN	Upper Limit Normal
VAS	Visual Analog Scale
WHO	World Health Organization

2. PURPOSE

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

2.1. RESPONSIBILITIES

Syneos Health will perform the statistical analyses and is responsible for the production and quality control of all tables, figures, and listings on behalf of Savara Inc., the study sponsor.

2.2. TIMINGS OF ANALYSES

An independent Data Monitoring Committee (DMC) will review periodic descriptive summaries of safety, subject disposition, and limited efficacy data during the course of the study. Further description of the DSMB timing and analyses can be found in the DMC Statistical Analysis Plan Version 1.0 dated 25-Oct-2017 and the -DSMB charter Version 2.0 dated 24-Nov-2017. An unblinded team from Syneos Health biostatistics will perform the analyses for the DSMB to maintain the blinding of the study.

When 100% of subjects have completed Period 1 of the protocol or terminated early, the study will be unblinded as per Section 3.6. The primary analysis of safety and efficacy will be completed at that time.

Additional analyses of safety and efficacy will also be conducted after all subjects complete the final study visit in Period 2 (open-label), or terminate early from the study.

3. STUDY OBJECTIVES

3.1. PRIMARY OBJECTIVE

The primary objective of the study is to evaluate the efficacy of AeroVanc in improving lung function of CF patients ≤ 21 years of age with persistent MRSA lung infection.

3.2. SECONDARY OBJECTIVE(S)

The secondary objectives of the study are:

- To evaluate the time to first pulmonary exacerbation requiring use of another antibiotic medication (oral, intravenous, and/or inhaled) and the frequency of pulmonary exacerbations.
- To evaluate the efficacy of AeroVanc in the reduction of respiratory symptoms and improvement in quality of life.
- To evaluate the safety and tolerability of AeroVanc during 3 treatment cycles (24 weeks).

3.3. BRIEF DESCRIPTION

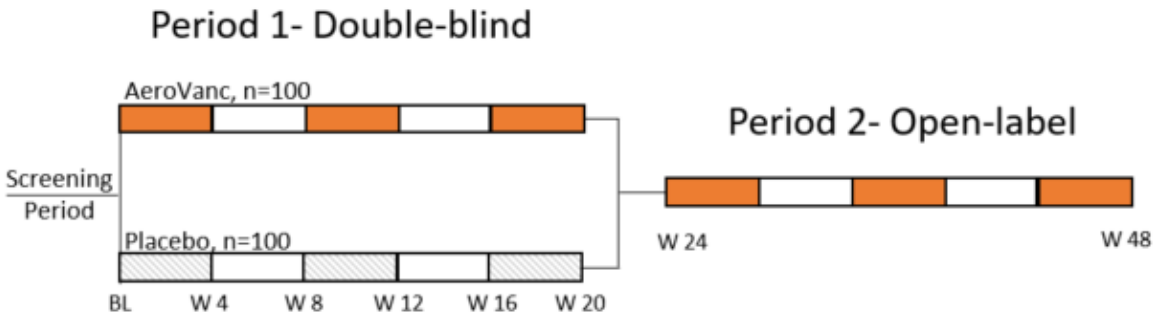
SAV005-04 is a Phase III, randomized, multicenter, double-blind, placebo-controlled, parallel-group study to examine the safety and efficacy of AeroVanc in the treatment of persistent MRSA lung infection in subjects diagnosed with cystic fibrosis.

After the Screening period (up to 42 days) to confirm study eligibility, subjects will be randomly assigned in a blinded fashion to receive either AeroVanc 30 mg twice daily (BID), or placebo BID (1:1 active to placebo) by inhalation for 24 weeks or 3 dosing cycles (Period 1). Upon completion of Period 1, subjects will receive open-label AeroVanc 30 mg BID for an additional 24 weeks or 3 dosing cycles (Period 2), to evaluate long-term safety of AeroVanc.

A dosing cycle is defined as 28 days of treatment followed by 28 days of observation. Subjects meeting the inclusion / exclusion criteria will be stratified upon randomization on the basis of (a) age (6–21; > 21), (b) Baseline FEV_1 (≥60%; <60%), (c) prior exacerbations treated with antibiotics during the previous 12 months (1-2; ≥ 3) and (d) *P. aeruginosa* treatment (not treated; treated).

Subjects on a 28-day cyclical on/off anti-Pseudomonal antibiotic regimen will enter the Screening period at a time such that the Baseline visit coincides with the end of their anti-Pseudomonas antibiotic cycle. Study drug will thereby be administered during the off-cycle, and subjects can then resume anti-Pseudomonal therapy during the 28-day

observation period (Week 5 through Week 8). Subjects continuing alternating anti-Pseudomonal therapy can continue their treatment during the study drug administration, and observation periods. The primary efficacy and safety parameters will be measured during the 3-cycle, double-blind treatment portion of the study (Period 1). Upon completion of the double-blind portion, subjects will have the option to continue into an open-label portion in which subjects will receive AeroVanc 30 mg BID for 3, 28-day dosing cycles (Period 2).



Note: Period 2 dosing ends at Week 44 not Week 48 as indicated in the figure above. There is a 4 week follow-up until Week 48,

200 subjects (150 subjects ≤ 21 years old, 50 subjects > 21 years old)

3.4. SUBJECT SELECTION

3.4.1. Inclusion Criteria

Subjects must meet all of the following criteria to be considered eligible to participate in the study:

1. Subjects ≥ 6 years of age at time of Informed Consent Form (ICF) or Assent Form signing.

2. Confirmed diagnosis of CF, determined by having clinical features consistent with the CF phenotype, plus 1 of the following:

    a. Positive sweat chloride test (value ≥ 60 mEq/L),

    b. Genotype with 2 mutations consistent with CF (ie, a mutation in each of the cystic fibrosis transmembrane conductance regulator [CFTR] genes).

3. Positive sputum culture or a throat swab culture for MRSA at Screening.

4. In addition to the Screening sample, have at least 2 prior sputum or throat swab cultures positive for MRSA, of which at least 1 sample is more than 6 months prior to Screening. At least 50% of all MRSA cultures (sputum or throat swab culture) collected from the time of the first positive culture (in the previous 1 year) must have tested positive for MRSA. (Note: Screening sample may count towards 50% positive count)

5. Forced expiratory volume in 1 second (FEV_1) ≥ 30% and ≤ 90% of predicted that is normal for age, gender, race, and height, using the Global Lung Function Initiative (GLI) equation.

6. At least 1 episode of acute pulmonary infection treated with non-maintenance antibiotics within 12 months prior to the Baseline visit. (Initiation of treatment with intermittent inhaled anti-Pseudomonal therapy will not qualify as treatment with non-maintenance antibiotics).

7. If female of childbearing potential, an acceptable method of contraception must be used during the study and must be combined with a negative pregnancy test obtained during Screening; sexually active male subjects of reproductive potential who are non-sterile (i.e., male who has not been sterilized by vasectomy for at least 6 months, and were not diagnosed with infertility through demonstration of azoospermia in a semen sample and/or absence of vas deferens through ultrasound) must be willing to use a barrier method of contraception, or their female partner must use an acceptable method of contraception, during the study.

   For purposes of this study, the Sponsor defines “acceptable methods of contraception” as:

   a. Oral birth control pills administered for at least 1 monthly cycle prior to administration of the study drug

   b. A synthetic progestin implanted rod (eg, Implanon®) for at least 1 monthly cycle prior to the study drug administration but not beyond the 4th successive year following insertion

   c. Intrauterine devices (IUDs), inserted by a qualified clinician for at least 1 monthly cycle prior to study drug administration

   d. Medroxyprogesterone acetate (eg, Depo-Provera®) administered for a minimum of 1 monthly cycle prior to administration of the study drug and continuing through 1 month following study completion.

   e. Hysterectomy or surgical sterilization

f. Abstinence

g. Double barrier method (diaphragm with spermicidal gel or condoms with contraceptive foam)

NOTE: For subjects prescribed Orkambi: Orkambi may substantially decrease hormonal contraceptive exposure, reducing the effectiveness and increasing the incidence of menstruation-associated adverse reactions. Hormonal contraceptives, including oral, injectable, transdermal, and implantable, should not be relied upon as an effective method of contraception when co-administered with Orkambi.

8. Able and willing to comply with the protocol, including availability for all scheduled study visits and be able to perform all techniques necessary to use the AeroVanc inhaler and measure lung function.

9. Agree not to smoke during any part of the clinical trial (Screening visit through end of study).

10. Subjects with a *P. aeruginosa* co-infection must either be stable on a regular suppression regimen of inhaled antibiotics or must be, in the opinion of the Investigator, stable despite the lack of such treatment.

3.4.2. Exclusion Criteria

In addition to those unable to meet the Inclusion Criteria, subjects who meet any of the following criteria will be excluded from participating in the study:

1. Use of anti-MRSA treatments prescribed as maintenance therapy (IV or inhaled treatment within 28 days; oral treatment within 14 days) prior to the Baseline visit.

2. Use of non-maintenance antibiotic for pulmonary infection or extrapulmonary MRSA infection (IV or inhaled antibiotic within 28 days; oral antibiotic within 14 days) prior to the Baseline visit.

3. History of previous allergies or sensitivity to vancomycin, or other component(s) of the study drug or placebo except for a history of red-man syndrome.

4. Inability to tolerate inhaled products.

5. First time sputum culture or throat swab culture yielding *B. cepacia*, or nontuberculous Mycobacteria in the previous 6 months to Screening.

6. History of lung or other solid organ transplantation or currently on the list to receive lung or other solid organ transplantation.

7. Resistance to vancomycin at Screening (vancomycin resistant *Staphylococcus aureus* [VRSA], or vancomycin intermediate resistant *Staphylococcus aureus* [VISA], with minimum inhibitory concentration [MIC] ≥ 8 μg/mL).

8. Oral corticosteroids in doses exceeding 10 mg prednisone per day or 20 mg prednisone every other day, or equipotent doses of other corticosteroids.

9. Changes in antimicrobial, bronchodilator, anti-inflammatory, or corticosteroid medications within 14 days, or changes in CFTR modulators within 28 days, prior to the Baseline visit.

10. Abnormal laboratory findings or other findings or medical history at Screening that, in the Investigator's opinion, would compromise the safety of the subject or the quality of the study data.

11. Inability to tolerate inhalation of a short acting beta2 agonist.

12. SpO_2 <90% at Screening.

13. Changes in physiotherapy technique or physiotherapy scheduled within 1 week of the Baseline visit.

14. Administration of any investigational drug or device within 4 weeks prior to the Screening visit and during the course of the study

15. Female with positive pregnancy test result during Screening, pregnant (or intends to become pregnant), lactating or intends to breastfeed during the course of the study.

16. Renal insufficiency, defined as creatinine clearance < 50 mL/min using the Cockcroft-Gault equation for adults or Schwartz equation for children at the Screening visit.

17. Abnormal liver function, defined as ≥ 4x upper limit of normal (ULN), of serum aspartate aminotransferase (AST) or serum alanine aminotransferase (ALT), or known cirrhosis at Screening.

18. Diagnosed with clinically significant hearing loss.

19. History of positive result for human immunodeficiency virus (HIV), hepatitis B virus (HBV) or hepatitis C virus (HCV).

20. Planned hospitalizations for prophylaxis antibiotic treatment within 28 days prior to Baseline visit or during the open-label period (Period 1).

3.5. DETERMINATION OF SAMPLE SIZE

A total of 200 subjects will be enrolled into the study (150 subjects ≤ 21 years old, 50 subjects > 21 years old). The primary analysis population will be the subjects ≤ 21 years of age. In the single cycle Phase II study, with missing data imputed using conservative rules adopted by the FDA, a difference in the mean absolute change in FEV_1 percent predicted of 4.3% and a root mean square deviation of 6.3% were observed between the treatment arms in subjects < 21 years of age. Based on these numbers, a sample size of 45 subjects per arm would provide 89% power to detect a statistically significant difference at alpha level of 0.05. To account for potential drop outs and/or smaller effect size in a three-cycle study, a sample size of 75 per arm will be enrolled in the primary analysis population, which if all completed would provide 90% power to detect a difference of 3.4% at 20 weeks assuming the same standard deviation of 6.3%.

In addition, approximately 25 patients per arm in the over 21-year age group will be included.

3.6. TREATMENT ASSIGNMENT & BLINDING

After the Screening period (up to 42 days) to confirm study eligibility, subjects will be randomly assigned, using Interactive Web Response System (IWRS), in a blinded fashion to receive either AeroVanc 30 mg twice daily (BID), or placebo BID (1:1 active to placebo) by inhalation for 24 weeks or 3 dosing cycles (Period 1). Upon completion of Period 1, subjects will receive open-label AeroVanc 30 mg BID for an additional 24 weeks or 3 dosing cycles (Period 2), to evaluate long-term safety of AeroVanc.

A dosing cycle is defined as 28 days of treatment followed by 28 days of observation. Subjects meeting the inclusion/exclusion criteria will be stratified upon randomization on the basis of (a) age (6–21; > 21), (b) Baseline FEV_1 percent predicted (≥60%; <60%), (c) prior exacerbations treated with antibiotics during the previous 12 months (1-2; ≥ 3) and (d) *P. aeruginosa* treatment (not treated; treated).

During the course of the study, all personnel will remain blinded except for DSMB members, Syneos Health unblinded DSMB statistician, Syneos Health unblinded DSMB programmer, and Syneos Health unblinded Senior Statistical Reviewer.

The unblinding of the treatment code will occur and the data will be analyzed after all the following have been completed:

- The last subject's Week 20 visit has been completed or study discontinuation
- The study database for the Period 1 Double-blind Treatment Period has been locked for the first reporting phase
- The final SAP has been signed off and the subjects in the analysis populations have been identified

3.7. ADMINISTRATION OF STUDY MEDICATION

AeroVanc, 30 mg or matching placebo (2 capsules) BID will be administered using the reloadable, capsule inhaler. Subjects will be instructed to take a short-acting bronchodilator agent pre-treatment (2 puffs of the short acting bronchodilator albuterol, or equivalent) no less than 10 minutes and up to 45 minutes prior to study drug administration. A short-acting bronchodilator, such as albuterol may also be used as rescue medication in the event of bronchoconstriction caused by the study drug.

3.8. STUDY PROCEDURES AND FLOWCHART

This study will consist of up to 6 cycles over a total of 48 weeks. A dosing cycle is defined as 28 days of treatment followed by 28 days of observation.

During Period 1, visits occur at the beginning and end of each cycle with an additional visit at Week 2. During Period 2, visits are scheduled at the beginning of each cycle, after Cycle 6 and a follow-up visit at Week 48.

A Schedule of Events representing the required testing procedures to be performed for the duration of the study is presented in Table 1 Schedule of Events

Table 1 Schedule of Events

	Scrn/BL	Period 1 (Double-Blind Treatment)							Follow-up	Period 2 (Open-Label Treatment)			Follow-up
	Screening	Baseline	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20 or Early Termination	Week 24/BL	Week 28	Week 36	Week 44 or Early Termination	Week 48
	-42		± 2 day	± 2 day	± 2 day	± 2 day	± 2 day	± 2 day	± 2 day	± 3 day	± 3 day	± 3 day	± 3 day
Informed Consent/Assent	X												
Review Inclusion/Exclusion Criteria	X	X											
Medical History	X												
Demographic Review	X												
Physical Examination	X					X		X				X	
Symptom Oriented Physical Examination		X		X	X		X		X	X	X		
Height	X							X				X	
Weight and vitals	X			X	X	X	X	X	X	X	X	X	X
Blood Collection for Hematology and Biochemistry	X	X		X		X		X		X	X	X	X
Urinalysis	X	X				X		X	X		X	X	
Pregnancy Test[1]	X					X		X			X	X	
12-lead ECG	X	X						X				X	
CFQ-R[5]		X	X	X	X	X	X	X	X	X	X	X	X
CFRSD -CRISS[5]		X	X	X	X	X	X	X	X	X	X	X	X
EQ-5D-5L & EQ-5Dy[5]		X	X	X	X	X	X	X	X	X	X	X	X
Train and issue e-Diary	X												
PFT (spirometry)[2]	X	X	X	X	X	X	X	X	X	X	X	X	X
Obtain sputum sample for MRSA levels[3]	X	X		X	X	X	X	X	X	X		X	
Obtain culture swab for MRSA resistance	X	X		X	X	X	X	X	X	X		X	
Obtain sputum for PK sample[3]			X								X		
Plasma pk collection (trough measure)			X										
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X
Complete drug accountability and drug compliance			X	X	X	X	X	X	X	X	X	X	
Administer short-acting bronchodilator 30 mins prior to study drug administration		X	X	X	X	X	X	X	X	X	X	X	
Dispense study drug		X[4]			X[4]		X[4]		X[4]	X[4]	X[4]		
Collect Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X

[1]Serum pregnancy test performed on women of child bearing potential
[2]PFT performed prior to dosing study drug
[3]Sample may be collected by the subject at home the morning of the visit or during the office visit
[4]Subjects will be administered study drug during the clinic visit after completion of all study procedures
[5]CFQ-R conducted every two weeks; CFRSD and EQ-5D-5L/y conducted during clinic visits only

4. ENDPOINTS

The primary efficacy endpoint is the mean absolute change from baseline in FEV_1 percent predicted based on the ITT population of all randomized subjects ≤ 21 years of age. The endpoint will be analyzed sequentially at Week 4 (end of Cycle 1), Week 12 (end of Cycle 2), and at Week 20 (end of Cycle 3).

If AeroVanc is superior to placebo after Cycle 1, then the mean change in the FEV_1 percent predicted after Cycle 2 will be analyzed and if AeroVanc is superior to placebo after Cycle 2, then the mean change in the FEV1 percent predicted after Cycle 3 will be analyzed.

4.1. SECONDARY EFFICACY ENDPOINTS

The following parameters will be analyzed as secondary efficacy endpoints based on the ITT population of all randomized subjects ≤ 21 years of age:

- Time to first pulmonary exacerbation requiring use of another antibiotic medication (oral, IV, and/or inhaled).
- Change from Baseline in the Cystic Fibrosis Questionnaire-Revised (CFQ-R) scores at Weeks 4, 12, and 20.
- Change from Baseline in the Cystic Fibrosis Respiratory Symptom Diary-Chronic Respiratory Symptom Score (CFRSD-CRISS) scores at Weeks 4, 12, and 20.
- Relative change from Baseline in FEV_1 percent predicted at Weeks 4, 12, and 20.
- The number of successful response cycles a subject achieves over Period 1 (Weeks 4, 12, and 20).
- Frequency of pulmonary exacerbations.
- Area under the FEV_1 – time profile, i.e. the mean treatment difference in FEV_1 across all post-baseline visits.

4.2. EXPLORATORY ENDPOINTS

The following parameters will be analyzed as exploratory efficacy endpoints based on the ITT population of all randomized subjects ≤ 21 years of age:

- Changes from Baseline in EQ-5D-5L/EQ-5Dy scores at Weeks 4, 12, and 20.

- Change from Baseline in MRSA sputum density at Weeks 4, 12, and 20.
- Change from Baseline in body weight at Weeks 8, 16 and 24.
- Change from Baseline in MIC for Vancomycin at Weeks 4, 12 and 20.
- Emergence of additional pathogens in sputum.

4.3. PHARMACOKINETIC ENDPOINTS

Pharmacokinetics will be studied as a sub-study of approximately 100 subjects, with trough plasma and sputum samples collected as per the Schedule of Events.

4.4. SAFETY ENDPOINTS

To evaluate safety and tolerability, safety assessments will be conducted on the safety population including analysis of all adverse events (AEs), as well as standard hematology, biochemistry, and urine analyses, vital signs, physical examination, spirometry, pulmonary function tests (PFT) and electrocardiogram (ECG).

5. ANALYSIS POPULATIONS

5.1. ALL ENROLLED POPULATION

The All Enrolled Population will include all subjects who signed informed consent and were screened. Unless specified otherwise, this population will be used for subject listings and for summaries of subject disposition.

5.2. SAFETY POPULATION

The Safety Population will include all subjects who were administered at least one dose of study medication. Subjects will be analyzed according to treatment received. The Safety Population will be used for all analyses of safety endpoints and for the presentation of subjects in all subject listings except where noted. The Safety population may also be split out by age (≤ 21 years, > 21 years).

5.3. INTENT-TO-TREAT POPULATION

The Intent-to-Treat (ITT) Population will include all randomized subjects. Subjects will be analyzed according to randomized treatment. The ITT population will also be split out by age (≤ 21 years, > 21 years). The ITT Population of subjects ≤ 21 years will be used for all main analyses of efficacy endpoints.

5.4. PER PROTOCOL POPULATION

The Per Protocol Population (PP) will include all ITT subjects who adhere to all key protocol procedures. As with the ITT population, the PP population will also be split out by age (≤ 21 years, >21 years). Subjects will be analyzed according to randomized treatment. Criteria for exclusion from the PP include the following:

- Study drug compliance of less than 80% during Period 1.
- Any other criteria deemed to affect the primary efficacy analysis in some meaningful way. Criteria and subjects will be identified during a review of protocol violations during a population selection meeting to be held prior to database lock and unblinding but after all subjects have terminated the study.

Inclusion in the PP, along with all other populations, will be determined prior to database lock.

5.5. PHARMACOKINETIC POPULATION

The Pharmacokinetic (PK) Population will include all subjects who received at least one dose of the study drug and have at least one PK concentration measured.

PK concentrations are listed for all subjects in PK population.

5.6. PROTOCOL DEVIATIONS

Protocol Deviations will be collected and classified on the eCRF. Subjects with protocol deviations listed in Section 5.4 will be excluded from the PP population. All other protocol deviations will be reviewed to identify other subjects to be excluded from the PP population. If necessary, a Blind Data Review Meeting will be held to review the protocol deviation to identify subjects to be included or excluded from the PP population.

Protocol Deviations related to telemedicine or missed visits due to COVID-19 epidemic will be used to identify missing data as COVID-19 missing. COVID-19 missing data will be imputed differently than originally planned. Analysis of efficacy data using missing data due to COVID-19 is detailed in Appendix B.

6. GENERAL ASPECTS FOR STATISTICAL ANALYSIS

6.1. GENERAL METHODS

This section describes analysis issues that relate to all or some of the analysis sections that follow. It describes general guidelines for analysis as well as the following items:

- SAS version 9.3 or later will be used.
- Unless otherwise specified, summaries will be presented for each treatment. For Period 2, summaries will be presented based on the treatment group to which patients were randomized in Period 1.
- All statistical testing will be two-sided and will be performed at the 0.05 significance level.
- Continuous variables will be summarized with means, standard deviations, medians, minimums, and maximums. For primary and secondary endpoints, the 25^{th} and 75^{th} percentile will be include for the non-supporting analyses summaries. Categorical variables will be summarized by counts and by percentage of subjects in corresponding categories.
- All relevant subject data will be included in listings. All subjects entered into the database will be included in subject data listings.
- The nominal visit data will be used for analysis.
- Visits will be assigned to Period 1 when the visit date or assessment date is on or after the date of first dose of study medication and on or prior to the date of completion/early discontinuation of Period 1 as identified on the eCRF. Visits will be assigned to Period 2 when the visit date or assessment date is on or after the date of first dose of study medication after the end date of Period 1 and on or prior to the date of completion/early discontinuation of Period 2 as identified on the eCRF.

6.2. KEY DEFINITIONS

Study Day 1 and First dose date for Period 1: Date of randomization and first dose of study medication respectively.

Last dose date for Period 1: Date as indicated for “Date of Period 1 last double-blind study drug dose” on the eCRF page Period 1: End of Treatment.

First dose date for Period 2: Date of first dose of study medication after completion date of Period 1.

Last dose date for Period 2: Date as indicated on the eCRF page Period 2: End of Study. In case of no date available then use last study medication dispense date for the purpose of the end of Period 2 data analysis.

The onset of a pulmonary exacerbation is defined as the date after randomization where both an antibiotic concomitant medication and pulmonary exacerbation adverse event occur concurrently in the subject at one point in time. An antibiotic concomitant medication is defined as any concomitant medication from classes 9 (ANTIBACTERIALS FOR SYSTEMIC USE) or 20 (ANTIMYCOBACTERIALS) as found in the variable CMDECOD, prescribed for a pulmonary infection indication, and indexed to the pulmonary exacerbation adverse event with a route of administration equal to "ORAL", "G TUBE", "GASTROSTOMY TUBE", "THROUGH G TUBE" , "INTRA VENOUS", or "RESPIRATORY (INHALATION)"). The use of study drug is not included in the definition of antibiotic concomitant medication. A pulmonary exacerbation adverse event is defined as an affirmative response to the corresponding eCRF question (“Is this a pulmonary exacerbation?” = “Yes”).

The end of a pulmonary exacerbation is defined as the last date of concurrent pulmonary exacerbation adverse event and antibiotic concomitant medication, regardless of the number of different consecutive antibiotic treatments required.

Intervals of < 14 days between periods of concurrent antibiotic concomitant medication and pulmonary exacerbation adverse event, will be considered a relapse of the same event. Intervals of >= 14 days between periods of concurrent antibiotic concomitant medication and pulmonary exacerbation adverse event will be counted as a new event.

The onset of a *first* pulmonary exacerbation is defined as the *earliest* date after randomization where both an antibiotic concomitant medication **and** pulmonary exacerbation adverse event occur concurrently in the subject at one point in time. An antibiotic concomitant medication is defined as any concomitant medication from classes 9 (ANTIBACTERIALS FOR SYSTEMIC USE) or 20 (ANTIMYCOBACTERIALS), prescribed for a pulmonary infection indication, and indexed to the pulmonary exacerbation adverse event with a route of administration equal to "ORAL", "G TUBE", "GASTROSTOMY TUBE", "THROUGH G TUBE" , "INTRA VENOUS", or "RESPIRATORY (INHALATION)"). The use of study drug is **not** included in the definition of antibiotic concomitant medication. A pulmonary exacerbation adverse event is defined as an affirmative response to the corresponding eCRF question (“Is this a pulmonary exacerbation?” = “Yes”).

6.3. MISSING DATA

6.3.1. Primary Endpoint Data

Sensitivity analyses of the primary endpoint will be conducted where missing data will be imputed in different ways. These will include:

- Worst reasonable case analysis: subjects in the AeroVanc group with a missing FEV_1 percent predicted will be assigned the visit median for the placebo group and subjects in the placebo group with a missing FEV_1 percent predicted will be assigned the visit median for the AeroVanc group.
- Best reasonable case analysis: subjects in the AeroVanc group with a missing FEV_1 percent predicted will be assigned the visit median for the AeroVanc group and subjects in the placebo group with a missing FEV_1 percent predicted will be assigned the visit median for the placebo group.
- Tipping point analysis: In the event that statistical significance in favor of AeroVanc is determined from the primary analysis, subjects in the AeroVanc group with a missing FEV_1 percent predicted will be assigned successively more extreme values, whilst subjects in the placebo group with a missing FEV1 percent predicted will be assigned successively less extreme values, to find the point at which statistical significance is lost (i.e. the 2-sided P-value becomes greater than 0.05).

Monotone missing data occurs when the result of a variable is missing for a particular individual and this implies that all subsequent results are missing for that individual. Alternatively, when a result is observed for a particular individual, it is assumed that all previous results are also observed for that individual. Non-monotone missing occurs when result of a variable is missing for a particular individual but this does not imply that all subsequent results are missing for that individual and at least one subsequent result is not missing.

The tipping point analysis will be implemented using the steps delineated below:

Step 1: Non-monotone missing data in AeroVanc treatment and placebo groups will be imputed using the Markov Chain Monte Carlo (MCMC) method within each treatment group.

Step 2: Monotone missing data will be imputed using the regression method on the basis of the predicted future pattern for the same treatment group. The regression model will use treatment, visit, Baseline FEV_1 percent predicted, age, age group (6–21; > 21), Baseline FEV_1 (≥60%; <60%), prior exacerbations treated with antibiotics during the previous 12 months (1-2; ≥ 3), and *P. aeruginosa* treatment (not treated; treated) as the independent variables. Week 4 values will be imputed first, without visit in the model. Then Week 8 values will be imputed using all Week 4 values. Finally, Week 12 values will

be imputed using all values for Weeks 4 and 8.

Step 3: The imputed values for the AeroVanc treatment group will be subtracted progressively by a delta = k (0%, 10%, 20%, …, 100%) * LSMeans estimate for treatment difference in the primary analysis ($x_{tipping\ point} = x_{imputed} - (LSMeans * k)$). The imputed values for the placebo treatment group will be held fixed ($x_{tipping\ point} = x_{imputed}$).

Step 3 will be repeated iteratively while increasing the penalty (e.g., 10%, 20%, …, 100%) for the missing data in the AeroVanc treatment group and keeping all the other imputed data unchanged, until the tipping point value (i.e., where p-value > 0.05) is identified.

Step 4: One hundred (100) imputed datasets will be generated for each MI analysis. Each imputed dataset is analyzed separately using the Mixed Model for Repeated Measures (MMRM) model specified in Section 8.1.1. The final estimate of treatment difference will be the average of the estimates based on the 100 individual imputed datasets. The pooling of the individual estimates and inferences based on the combined estimate will be handled by SAS procedure MIANALYZE.

Analyses using each of these imputation methods are described in Section 8.1.2.

6.3.2. Other Efficacy Data

Several subjects missed collecting their baseline values for CFRSD-CRISS and CFQ-R because they lacked the device to collect the questionnaire at that time. For subjects without any baseline visit data for either of these questionnaires the baseline will be imputed using the median scores of the subjects meeting the same strata criteria as identified for randomization.

All other missing data associated with various scores and scales will be handled as prescribed by the respective scoring methodology. These details are described in the related sub-section of 8.2 below.

6.3.3. Safety Data

Complete dates will be imputed from partial dates of medications solely for the purpose of defining prior/concomitant status for medications. Dates will be defined using the hierarchy of derivations below.

Concomitant Medications

If the start date of a concomitant medication is missing, then the start date will be set to the first dose date. If the stop date of a concomitant medication is missing, then the medication will be treated as ongoing. Missing or incomplete dates will be defined using the hierarchy of derivations below.

- For missing start day where month and year are present, the start day will be set to the 1st of the month, unless the month and year are the same as the first dose month and year and the 1st of the month is before the first dose date, in which case, the start date will be set to the first dose date.
- For missing start day and month where year is present, the start day and month will be set to January 1st, unless the year is the same as the first dose year and January 1st is before the first dose date, in which case, the start date will be set to the first dose date.
- For missing end day where month and year are present, the end day will be set to the last day of the month, unless the month and year are the same as the trial termination month and year, in which case, the end date will be set to the trial termination date.
- For missing end day and month, where year is present, the end date will be set to the trial termination date if the years are the same. If the trial termination year is greater than the end year, the end day and month will be set to December 31st.

6.4. VISIT WINDOWS

The Cystic Fibrosis Respiratory Symptom Diary – Chronic Respiratory Infection Symptom Score (CFRSD-CRISS) is scheduled to be collected weekly. The visit week window will be the expected date ±3 days with the exception of Week 1. For example Week 2 data should be collected on Day 15. The visit window for Week 2 will be Day 12 through Day 18. For Week 1, the window will include Day1 through Day 11. If 2 questionnaires are collected in a given window, the visit closest to the expected collection day will be used for analysis. If both questionnaires are equidistant from the expected collection day, the earlier of the 2 questionnaires will be used in the analyses.

The Cystic Fibrosis questionnaire - revised (CFQ-R) is scheduled to be collected every 2 weeks. The visit window will be the expected date -7 days through +6 days with the exception of Week 2. For example, Week 4 data should be collected on Day 29. The visit window for Week 4 will be Day 22 through Day 35. For Week 2, the window will include Day1 through Day 21. If 2 questionnaires are collected in a given window, the visit closest to the expected collection day will be used for analysis. If both questionnaires are equidistant from the expected collection day, the earlier of the 2 questionnaires will be used in the analyses.

For all other data, nominal visit will be used.

6.5. POOLING OF CENTRES

Not applicable since center effects are not included in any analyses.

6.6. SUBGROUPS

The primary efficacy population is the 6-21 years age group. All efficacy analyses, excluding sensitivity analyses, will also be repeated using the >21 years age group. All efficacy summary tables will be provided separately by age group. Subjects will be assigned to either 6–21 years or > 21 years.

Efficacy summary tables, for all primary, secondary and exploratory endpoints, will also be provided by other stratification factors (Baseline FEV_1 (≥60%; <60%), prior exacerbations treated with antibiotics during the previous 12 months (1-2; ≥ 3), *P. aeruginosa* treatment (not treated; treated)). With the FDA approval for Trikafta (elexacaftor/tezacaftor/ivacaftor and ivacaftor), primary and secondary efficacy variables, along with demographics will be summarized for subjects who received Trikafta and those subjects who did not receive Trikafta at baseline or during Period 1.Subjects who receive intravenous (i.v.) vancomycin during Period 1 will also be identified. Efficacy analyses, for all primary, secondary and exploratory endpoints will also be provided for those who did and did not receive i.v. vancomycin during Period 1.

7. DEMOGRAPHIC, OTHER BASELINE CHARACTERISTICS AND MEDICATION

7.1. SUBJECT DISPOSITION AND WITHDRAWALS

Subject disposition will be presented for all subjects by age group and overall, which include the following:

- Number of subjects in the All Enrolled Population
- Number (%) of subjects randomized by Period 1 treatment

Among the randomized subjects, the following will be summarized by Period 1 treatment

- Number (%) of subjects in the Safety Population
- Number (%) of subjects in the ITT Population
- Number (%) of subjects in the Per-Protocol Population
- Number (%) of subjects in the PK Population
- Number (%) of subjects who completed Period 1
- Number (%) of subjects who discontinued treatment in Period 1 and their reason
- Number (%) of subjects who entered Period 2
- Number (%) of subjects who completed Period 1 but choose not to enter Period and their reason
- Number (%) of subjects who completed Period 2
- Number (%) of subjects who discontinued from the study early in Period 2 and their reason
- Number (%) of subjects ongoing in Period 2 (End of Period 1 Analysis only)

A separate by-subject listing of subject disposition and withdrawal will also be provided. Subjects who screen failed will be listed along with the date and reason for the screen failure.

Protocol deviations will also be summarized and listed. Randomized subjects not included in the Per Protocol population and their reason for exclusion will be listed.

7.2. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographics and other baseline characteristics will be summarized for the Safety Population by age group, Trikafta use at baseline or during Period 1, and overall, and Period 1 treatment. Summary statistics and by-subject listings will be provided.

Demographics and baseline characteristics will include age, age group (6-21 years, >21 years), sex, ethnicity, race, weight height, body mass index (BMI), *Pseudomonas aeruginosa* infection present at Screening, *Pseudomonas aeruginosa* treatment (treated, not treated), number of pulmonary infections in the last year, prior exacerbations treated with antibiotics - previous 12 Months (1-2, ≥3), baseline FEV_1 and baseline FEV_1 group (≥60%, <60%).

Age = (informed consent date - date of birth + 1) / 365.25 and truncated to complete years.

Height (in cm) = height (in inches) * 2.54

Weight (in kg) = weight (in lbs.) * 0.4536

BMI (kg/m^2) = Weight (kg)/[Height$(m)^2$]

7.3. MEDICAL HISTORY AND CONCOMITANT DISEASES

Previous diseases/conditions will be sorted alphabetically by system organ class and preferred term. History of MRSA and Cystic Fibrosis will be collected for all subjects.

A summary table of the number and percentage of subjects by medical history, including MRSA and Cystic Fibrosis, system organ class (SOC) and preferred term will be produced for the Safety Population. Medical history will be sorted alphabetically by SOC and in descending order of subjects per preferred term with each SOC.

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 20.0 or higher.

A separate by-subject listing of medical history will also be provided.

7.4. MEDICATION

All prescription and non-prescription medications taken within 6 months prior to Baseline through the follow-up visit will be documented in the eCRF.

All prior and concomitant medications will be classified using the Anatomical Therapeutic Chemical (ATC) classification and preferred drug name from the World Health Organization Drug Dictionary, version MAR 2017, or later.

A separate by-subject listing of medications will also be provided.

7.4.1. Prior Medication

Prior medications will be defined as medication on the eCRF as starting prior or ending prior to the first dose of study medication. Prior medications will be summarized by ATC level 2 and preferred drug name for the Safety Population.

Prior medications which continue after first dose of study medication may also be classified as a concomitant medication.

7.4.2. Concomitant Medication

Concomitant medications will be defined as medication on the eCRF as starting prior to the first dose of study medication and ongoing at the time of first dose of study medication or started after first dose of study medication. Concomitant medications will be summarized by ATC level 2 and preferred drug name for the Safety Population.

8. EFFICACY

The efficacy analyses described here are those planned before the occurrence of the COVID-19 pandemic in early 2020. Consequent to the outbreak of COVID-19, recruitment to the trial has been stopped prematurely and some changes to rules for handling missed visits (and resulting missing data) have been introduced. Where appropriate, the new rules for handling missing data will be applied to the primary and secondary analyses. For clarity, all changes resulting from COVID-19 issues are described in Appendix B of this document. For avoidance of doubt, the primary analyses will be based on the new rules for handling missing data (as described in Appendix B), and not necessarily as described in the original SAP text (as below) or in the protocol.

For the purposes of transparency, in addition to the revised analysis, the primary and affected secondary efficacy analyses described here will be provided, but not the associated sensitivity analyses. Changes in the sensitivity analyses will be detailed in Appendix B.

Each set of PFTs are scored for reliability and repeatability. Scores consist of letter grades of A, B, C, D, and F. All PFT results with a grade of F will be treated as missing for all analyses except for baseline F grade PFT measurements – in this instance, the F grade baseline PFT measurements will be replaced by the most recent previous acceptable and reproducible screening value (grade not equal to F).

For the Per-Protocol analyses, only results with a grade of A or B will be used. All other grade PFTs will be treated as missing, except for baseline C, D, or F grade PFT measurements – in this instance, the C, D, or F grade baseline PFT measurements will be replaced by the most recent previous A or B grade screening value.

The main analysis will only be performed using the 6-21 year age group. Strata for the primary and secondary analyses will be based on strata identified for randomization. Supportive summaries and analyses will be performed on the >21 year age group.

8.1. PRIMARY EFFICACY ENDPOINT AND ANALYSIS

8.1.1. Primary Analysis of the Primary Efficacy Endpoint

The primary efficacy endpoint is the mean absolute change from baseline in FEV_1 percent predicted. The primary analysis will be based on the ITT population of ≤ 21 years of age using all observed data with a PFT scoring grade of A, B, C, or D, at Weeks 4, 12, and 20.

All subjects will undergo standardized pulmonary function testing FEV_1. Pulmonary function testing will be performed according to American Thoracic Society (ATS) guidelines (2005). Subjects will be tested using the same spirometry equipment provided by the Sponsor. Up to 8 efforts should be performed to obtain 3 acceptable and reproducible test results. The best results from the acceptable and reproducible efforts for PFTs will be recorded in the Biomedical Systems (BMS) spirometry system and transferred to the clinical database, - and a copy of the spirometry reports will be retained with the subject's source documents.

For any subjects who have one or more missing FEV_1 result(s) (whether that be because they withdrew early from the trial, or for any other reason), their missing FEV_1 will be imputed using the least favorable group visit median change from baseline. This imputation can occur for more than one visit (if necessary); in such cases, the "least favorable group" will be determined on a visit-by-visit basis (i.e. the "least favorable" group could be different at weeks 4, 12 and 20).

The absolute change from baseline in FEV_1 percent predicted will be analyzed using a Mixed Model for Repeated Measures (MMRM) with the absolute change from baseline in FEV_1 percent predicted for a given visit as the dependent variable. Treatment, visit, treatment by visit interaction, Baseline FEV_1 percent predicted, age, Baseline FEV1 (≥60%; <60%), prior exacerbations treated with antibiotics during the previous 12 months (1-2; ≥ 3), and *P. aeruginosa* treatment (not treated; treated) will be the independent variables. The Kenward-Roger approximation will be used to adjust the denominator degrees of freedom. An unstructured (general) covariance structure will be assumed initially to model the within-subject errors. If the model fails to run properly, the following corrective actions will be take in order; drop Baseline FEV_1 percent predicted, then other covariance structure (ie, AR(1), CS) will be tested and used in the final model as appropriate.

The absolute change from baseline in FEV_1 percent predicted will be tested sequentially at Week 4 (end of Cycle 1), Week 12 (end of Cycle 2), and at Week 20 (end of Cycle 3) using the MMRM model stated above. If a statistically significant difference is observed in favor of AeroVanc compared to placebo after Cycle 1, then the change from baseline in the FEV_1 percent predicted -after Cycle 2 will be tested. Similarly, if the effect after Cycle 2 is statistically significant, then the analysis of Baseline to end of Cycle 3 will be tested.

As a supportive analysis, three Analysis of Covariance (ANCOVA) models (one at each of weeks 4, 12 and 20) with the absolute change from baseline in FEV_1 percent predicted for a given visit as the dependent variable will be performed. Treatment, Baseline FEV_1 percent predicted, age, Baseline FEV1 (≥60%; <60%), prior exacerbations treated with antibiotics during the previous 12 months (1-2; ≥ 3) and *P. aeruginosa* treatment (not treated; treated) will be used as independent variables. If an ANCOVA model fails to run properly, the variable Baseline FEV_1 percent predicted will be dropped. The same

missing value imputation strategy as for the primary analysis (i.e. imputing least favorable group visit mean change from baseline) will be used to allow clearer comparisons between analysis strategies.

All analyses will be performed for Period 1 only.

Absolute change from baseline in FEV_1 percent predicted will be summarized using descriptive statistics by other stratification factors (Baseline FEV_1 (≥60%; <60%), prior exacerbations treated with antibiotics during the previous 12 months (1-2; ≥ 3), *P. aeruginosa* treatment (not treated; treated)). Figures will be provided for mean in FEV_1 percent predicted and mean absolute change from baseline in FEV_1 percent predicted during Period 1 by other stratification factors. A by-subject listing will be included with the listing of pulmonary function tests.

8.1.2. Sensitivity Analysis of the Primary Efficacy Endpoint

For confirmation of the primary endpoint, sensitivity analyses will be performed where missing data will be imputed using worst reasonable case analysis, best reasonable case analysis, and tipping point analysis as described in Section 6.3 .

An additional sensitivity analysis will be performed using the Per-Protocol Population in place of the ITT and including only results with a PFT scoring grade of A or B.

Given the FDA approval of Trikafta, sensitivity analyses will be performed for subjects who did not use Trikafta at baseline or during Period 1.

Sensitivity analyses will be performed to assess the effect of actual stratification as based on eCRF data, instead of strata reported at time of randomization. These analyses will be repeated for all primary supportive analyses. Since P. aeruginosa treatment is not directly collected, if a subject has reported using one of the following antibiotics, based on ATC3 coding, and route of administration of Respiratory (Inhalation) prior to start of study medication, they will be considered as receiving *P. aeruginosa* treatment.

- Aztreonam
- Aztreonam Lysine
- Colistimethate Sodium
- Colistin
- Gentamicin

- Tobramycin

A sensitivity analyses will also be provided for those who did and did not receive i.v. vancomycin during Period 1.

All sensitivity analyses will be performed using the same analysis methodology as the primary analysis (Section 8.1.1).

8.1.3. Multiplicity / Control of Type I error rate

The sequence of statistical testing will be as follows:

- Age group 6–21:
    - Primary endpoint (mean absolute change from Baseline in FEV_1 percent predicted) at 4 weeks, then 12 weeks, then 20 weeks.
    - Secondary endpoints:
        - Frequency of pulmonary exacerbations requiring use of another antibiotic medication (oral, IV, and/or inhaled.
        - Time to first pulmonary exacerbation requiring use of another antibiotic medication (oral, IV, and/or inhaled).
        - Change from Baseline in the Cystic Fibrosis Questionnaire-Revised (CFQ-R) scores at Weeks 4, 12, and 20.
        - Change from Baseline in the Cystic Fibrosis Respiratory Symptom Diary-Chronic Respiratory Symptom Score (CFRSD-CRISS) scores at Weeks 4, 12, and 20.
        - Relative change from Baseline in FEV_1 percent predicted at Weeks 4, 12, and 20.
        - The number of successful response cycles a subject achieves over Period 1 (Weeks 4, 12, and 20).
        - Area under the FEV_1 – time profile, i.e. the mean treatment difference in FEV_1 across all post-baseline visits.

The statistical decision rule for moving to each analysis will be based on the sequence listed above and each cycle within each parameter. The testing order with each parameter will proceed from Week 4 (Cycle 1) to Week 12 (Cycle 2) then to Week 20

(Cycle 3 prior to advancing to the next parameter. Statistical testing will stop when the threshold of P < 0.05 is not reached. Sensitivity analyses will not impact on the decision to move forward or stop testing. Subgroup analyses for the stratification factors (other than age group) are for descriptive and supportive purposes and will not impact the decision to move forward or stop testing.

Although the above sequence is implemented to control type I error, results of all the analyses will be included in the final report.

In addition to the above, all analyses will be repeated in the group of patients > 21 years of age and using strata as identified on the eCRF. Estimates of treatment effects and 95% confidence intervals will be produced. Nominal p-values will also be produced but only for descriptive purposes. No Type I error control will be implemented for the patients >21 years of age or the eCRF based strata analyses.

8.2. SECONDARY EFFICACY ENDPOINT(S) AND ANALYSES

8.2.1. Frequency of Pulmonary Exacerbations

The Generalized Linear Model, based on the negative binomial distribution, will use the number of pulmonary exacerbations requiring use of another antibiotic medication (oral, IV, and/or inhaled) as the dependent variable and will include treatment group and the stratification factors (Baseline FEV1 (≥60%; <60%), prior exacerbations treated with antibiotics during the previous 12 months (1-2; ≥ 3), P. aeruginosa treatment (not treated; treated)) as fixed effects. The analysis will be adjusted for each subject's length of follow-up in Period 1 defined as last dose Period 1- first dose Period 1 + 28 days. The risk ratio (AeroVanc group: placebo) of treatment effect will be derived from the model along with the 95% 2-sided Confidence Interval for the risk ratio. Model adjusted mean rates for each treatment group will be derived and their 95% 2-sided confidence interval; calculated.

A descriptive summary will be provided by age group, and other stratification factors (Baseline FEV_1 (≥60%; <60%), prior exacerbations treated with antibiotics during the previous 12 months (1-2; ≥ 3), *P. aeruginosa* treatment (not treated; treated)). A separate by-subject listing will also be provided.

Secondary analysis will be performed using subjects ≤21 years old. Subjects >21 years old, subjects not using Trikafta at baseline or during Period 1 will be analyzed separately as supportive analyses. An additional supportive analysis using eCRF-identified strata in place of strata identified at randomization will also be provided. A supportive analyses will also be provided for those who did and did not receive i.v. vancomycin during Period 1.

8.2.2. Time to First Pulmonary Exacerbation

The distributions of time to first pulmonary exacerbation will be compared between the treatment arms using a Cox proportional hazards regression model including the effects of treatment group, age, and the stratification factors for Period 1 except for age group. The hazard ratio and the associated 95% confidence interval will be provided along with the associated log-rank test p-value.

The number of days from the date of randomization until the date of the first pulmonary exacerbation will be calculated and summarized for Period 1 using a Kaplan-Meier life table presentation and Kaplan-Meier curves for subjects in each age group separately. Subjects who do not experience an exacerbation prior to discontinuation from the study will be censored at the date of their study drug discontinuation.

A descriptive summary will be provided by age group and other stratification factors (Baseline FEV_1 (≥60%; <60%), prior exacerbations treated with antibiotics during the previous 12 months (1-2; ≥ 3), *P. aeruginosa* treatment (not treated; treated)). A separate by-subject listing will also be provided.

Secondary analysis will be performed using subjects ≤21 years old. Subjects >21 years old, subjects not using Trikafta at baseline or during Period 1 will be analyzed separately as supportive analyses. An additional supportive analysis using eCRF-identified strata in place of strata identified at randomization will also be provided. A supportive analyses will also be provided for those who did and did not receive i.v. vancomycin during Period 1.

8.2.3. Change from Baseline in the Cystic Fibrosis Questionnaire-Revised (CFQ-R) Scores at Weeks 4, 12, and 20

The CFQ-R is a disease-specific health-related quality of life measure for children, adolescents, and adults with CF. The CFQ-R measures functioning in a variety of domains, including Physical Functioning, Vitality, Health Perceptions, Respiratory Symptoms, Treatment Burden, Role Functioning (teen/adult version only), Emotional Functioning, Social Functioning (teen/adult version only), Body, Eat, Weight, Digest, and School (parent version only). A parent version of the CFQ-R will be used for subjects ≤ 13 years and the teen/adult version for subjects ≥ 14 years.

Score each question based on the responses to the question:

Very True = 1, Mostly True = 2, Somewhat True = 3, Not at all True = 4

Always = 1, Often = 2, Sometimes = 3, Never = 4

When an item is indicted to be reverse-coded the numeric values are reversed from what is indicated above (derived as 5 – item score). Missing values are replaced with the median value for the responses within a given domain within each treatment group. If the median would end in a value of .5, round the imputed value to the next higher value. If more than half of the values within a domain are missing then leave the domain score as missing.

In creation of the electronic diary (eDiary) used for the collection of the CFQ-R questionnaire, question 27 (“People are afraid I am contagious”) had the question text replace with the text from question 26 (“I feel bad about my personal appearance”) for some early versions of the eDiary. These values will be flagged in the data by the vendor (CRF Health). For calculations, summaries, analyses, and data presentations, these values will be treated as missing and the general rules for missing data (impute least favorable group mean will not be used in these cases).

Table 2 CFQ-R Scoring

Domain	Parent CFQ-R Question Numbers	Parent CFQ-R Scaled Score	Teen/Adult CFQ-R Question Numbers	Teen/Adult CFQ-R Scaled Score
Physical Functioning	1 2 3 4 5 14 15* 16	if number miss ≤ 4 then physical = (mean (1, 2, 3, 4, 5, 14, 15*, 16)-1)/3*100;	1 2 3 4 5 13* 19 20	if number miss ≤ 4 then physical = (mean (1, 2, 3, 4, 5, 13*, 19, 20)-1)/3*100;
Vitality	8 9 10* 11 12*	if number miss ≤ 2 then vitality = (mean (8, 9, 10*, 11, 12)-1)/3*100;	6* 9 10* 11	if number miss ≤ 2 then vitality = (mean (6*, 9, 10*, 11)-1)/3*100;
Health Perceptions	22* 24* 32*	if number miss ≤ 1 then health = (mean (22*, 24*, 32*)-1)/3*100;	18* 32* 34*	if number miss ≤ 1 then health = (mean (18*, 32*, 34*)-1)/3*100;
Respiratory Symptoms	34 35 36 38 39 40	if number miss ≤ 3 then respirat = (mean (34, 35, 36, 38, 39, 40)-1)/3*100;	40 41 42 44 45 46	if number miss ≤ 3 then respirat = (mean (40, 41, 42, 44, 45, 46)-1)/3*100;
Treatment Burden	18 30 31*	if number miss ≤ 1 then treat = (mean (18, 30, 31*)-1)/3*100;	15* 16 17*	if number miss ≤ 1 then treat = (mean (15*, 16, 17*)-1)/3*100;
Role Functioning	--	--	35* 36 37 38	if number miss ≤ 2 then role = (mean (35*,36, 37, 38)-1)/3*100;
Emotional Functioning	6* 7 23 25 26	if number miss ≤ 2 then emotion = (mean (6*, 7, 23, 25, 26)-1)/3*100;	7 8 12 31 33	if number miss ≤ 2 then emotion = (mean (7, 8, 12, 31, 33)-1)/3*100;

Domain	Parent CFQ-R Question Numbers	Parent CFQ-R Scaled Score	Teen/Adult CFQ-R Question Numbers	Teen/Adult CFQ-R Scaled Score
Social Functioning	--	--	22 23* 27 28* 29 30*	if number miss ≤ 3 then social = (mean (22, 23*, 27, 28*, 29, 30*)-1)/3*100;
Body	19 20 21	if number miss ≤ 1 then body = (mean(19, 20, 21)-1)/3*100;	24 25 26	if number miss ≤ 1 then body = (mean (24, 25, 26)-1)/3*100;
Eat	17 44	if number miss ≤0 then eat = (mean(17, 44)-1)/3*100;	14 21 50	if number miss ≤ 1 then eat = (mean (14, 21, 50)-1)/3*100;
Weight	33	if number miss ≤ 0 then weight = (mean (33)-1)/3*100;	39	if number miss = 0 then weight= (mean (39)-1)/3*100;
Digest	41 42 43	if number miss ≤ 1 then digest = (mean (41, 42, 43)-1)/3*100;	47 48 49	if number miss ≤ 1 then digest = (mean (47, 48, 49)-1)/3*100; run;
School	13 27 28* 29	if number miss ≤ 2 then school = (mean (13, 27, 28*, 29)-1)/3*100;	--	--
• Items that are reversed coded prior to calculating score. Reverse coding will be performed by using 5-response as the value used to generate the scaled scores.				

CFQ-R is recorded every 14 days in the trial and has a recall period of 14 days.

The scaled score for each domain of the CFQ-R will be analyzed the same as the primary efficacy analysis, including the same rules for missing domain values at each scheduled

collection time point (See Section 8.1.1) using the domain baseline value instead of the baseline FEV_1 result in the model for subjects <13 years old, subjects 14-21 years old, and subjects >21 years old. Additionally, the respiratory domain, domain of primary interest, will also be analyzed by combining the results of both the CFQ-R (Teen/Adult Version) and CFQ-R (Parents Version) for all subjects ≤ 21 years old, subjects not using Trikafta at baseline or during Period 1. An additional supportive analysis using eCRF-identified strata in place of strata identified at randomization will also be provided. A supportive analyses will also be provided for those who did and did not receive i.v. vancomycin during Period 1.

Summary tables will also be provided by period and age group, Trikafta use at baseline or during Period 1, and by other stratification factors (Baseline FEV_1 (≥60%; <60%), prior exacerbations treated with antibiotics during the previous 12 months (1-2; ≥ 3), *P. aeruginosa* treatment (not treated; treated)). Summary figures will be provided for mean change from baseline in the Respiratory Domain for each period.

A separate by-subject listing will also be provided.

8.2.4. Chronic Respiratory Symptom Score (CFRSD-CRISS) scores at Weeks 4, 12, and 20

The CFRSD-CRISS is an 8-item patient-reported outcome (PRO) symptom measure that is part of the Cystic Fibrosis Respiratory Symptom Diary (CFRSD). The CFRSD-CRISS is designed to evaluate the effect of treatment on the severity of symptoms of respiratory infection in subjects with Cystic Fibrosis (CF). Assessments in the CFRSD-CRISS comprise the 8 symptom items of the CFRSD: difficulty breathing, cough, cough up mucus, chest tightness, wheeze, feeling feverish, tired, and chills/sweats.

The Rasch-derived CFRSD-CRISS is computed by rescoring the eight respiratory symptom items of the CFRSD, summing the rescored items, and converting to a 0 to 100 scale. The CFRSD-CRISS should not be calculated if more than one item response is missing. The rescaling schema and conversion table are provided below. Rescore item responses as follows:

Q1.

Response	Raw Score	Item Score
None	0	0
A little	1	1
Somewhat	2	1
A good deal	3	2
A great deal	4	3

Q2.

Response	Raw Score	Item Score
None	0	0
A little	1	1
Somewhat	2	1
A good deal	3	1
A great deal	4	2

Q3.

Response	Raw Score	Item Score
None	0	0
A little	1	1
Somewhat	2	1
A good deal	3	2
A great deal	4	3

Q4.

Response	Raw Score	Item Score
None	0	0
Slightly	1	1
Moderately	2	1
Very	3	2
Extremely	4	3

Q5.

Response	Raw Score	Item Score
None	0	0
Slightly	1	1
Moderately	2	2
Very	3	3
Extremely	4	4

Q6.

Response	Raw Score	Item Score
None	0	0
A little	1	1
Somewhat	2	2
A good deal	3	3
A great deal	4	4

Q7.

Response	Raw Score	Item Score
None	0	0
A little	1	1
Somewhat	2	1
A good deal	3	2
A great deal	4	3

Q8.

Response	Raw Score	Item Score
None	0	0
Slightly	1	1
Moderately	2	1
Very	3	1
Extremely	4	2

Sum the item scores. Then convert the summed score to the CFRSD_CRISS score as indicated below.

Table 3 Conversion of Raw Summed Score to CFRSD-CRISS.

Raw Summed Score	CFRSD-CRISS		Raw Summed Score	CFRSD-CRISS
0	0		13	59
1	14		14	61
2	23		15	63
3	29		16	65
4	34		17	68
5	37		18	70
6	41		19	73
7	44		20	76
8	46		21	80
9	49		22	85
10	52		23	91
11	54		24	100
12	56			

CFRSD-CRISS is recorded every 7 days at home on the ePRO diary. It has a recall period of 7 days.

The CFRSD-CRISS will be analyzed using the same methods as the primary efficacy analysis, including the same rules for missing CFRSD-CRISS values at each scheduled collection time point (See Section 8.1.1) using the CFRSD-CRISS baseline value instead of the baseline FEV_1 result in the model. Summary tables will also be provided by period and age group, and by other stratification factors (Baseline FEV_1 (≥60%; <60%), prior exacerbations treated with antibiotics during the previous 12 months (1-2; ≥ 3), *P. aeruginosa* treatment (not treated; treated)). A supportive analyses will also be provided for those who did and did not receive i.v. vancomycin during Period 1. Summary figures will be provided for mean change from baseline for each period.

An additional supportive analysis using eCRF-identified strata in place of strata identified at randomization will also be provided.

A separate by-subject listing will also be provided.

8.2.5. Relative Change from Baseline in FEV1 Percent Predicted at Weeks 4, 12, and 20

Relative change from Baseline in FEV_1 percent predicted is defined as (Visit FEV_1 percent predicted – Baseline FEV_1 percent predicted)/Baseline FEV_1 percent predicted.

Relative change from Baseline in FEV_1 percent predicted will be analyzed using the same methods as the primary efficacy analysis, including the same rules for missing values (See Section 8.1.1). Summary tables will also be provided by age group and other stratification factors (Baseline FEV_1 (≥60%; <60%), prior exacerbations treated with antibiotics during the previous 12 months (1-2; ≥ 3), *P. aeruginosa* treatment (not treated; treated)).

Secondary analysis will be performed using subjects ≤21 years old. Subjects >21 years old, subjects not using Trikafta at baseline or during Period 1 will be analyzed separately as supportive analyses. An additional supportive analysis using eCRF-identified strata in place of strata identified at randomization will also be provided. A supportive analyses will also be provided for those who did and did not receive i.v. vancomycin during Period 1.

A separate by-subject listing will also be provided.

8.2.6. Number of Successful Response Cycles a Subject Achieves over Period 1

A response in a cycle is defined by at least a 5% relative improvement from baseline in FEV_1 percent predicted at the end of each cycle. If the relative FEV_1 improvement is less than 5%, the subject is considered a failure in that cycle, but the failure does not preclude success in future cycles. If a subject experiences an exacerbation, and concomitant antibiotic therapy is given, the subject is considered a failure in that cycle but not subsequent cycles.

The number of successful response cycles each subject achieves over the 3 cycles of therapy will be used to create a 2 × 4 contingency table consisting of the 2 treatments (AeroVanc and Placebo) and the counts of all Subjects across the 4 levels of response (0, 1, 2, or 3 successful treatment cycles). Summary tables will be provided by age group and other stratification factors (Baseline FEV_1 (≥60%; <60%), prior exacerbations treated with antibiotics during the previous 12 months (1-2; ≥ 3), *P. aeruginosa* treatment (not treated; treated)).

The number of successful response cycles in Period 1 will be analyzed using the Wald Chi-squared test based on an Ordinal logistic regression with treatment as the independent variable and number of cycles as the dependent variable.

Secondary analysis will be performed using subjects ≤21 years old. Subjects >21 years old, subjects not using Trikafta at baseline or during Period 1 will be analyzed separately as supportive analyses. An additional supportive analysis using eCRF-identified strata in place of strata identified at randomization will also be provided. A supportive analyses will also be provided for those who did and did not receive i.v. vancomycin during Period 1.

8.2.7. Area under the FEV_1-time Profile

Area under the FEV_1–time profile will be calculated for each subject over the course of each period. The area will be the sum of each FEV_1 multiplied by the duration of representative time period. The beginning of each time period will be either the beginning of the period or the midpoint between the time of the FEV_1 measurement and the previous FEV_1 measurement. The end of each time period will be either the end of the period or the midpoint between the time of the FEV_1 measurement and the following FEV_1 measurement. Duration will be calculated as (end of time period – start of time period) as measured in days.

Area under the FEV_1–time profile will be analyzed using a Generalized Linear Model with the Area under the FEV_1–time profile for a given period as the dependent variable, and using the same rules for missing values as for the primary variable. Treatment, Baseline FEV1 percent predicted, age, Baseline FEV1 (≥60%; <60%), prior exacerbations treated with antibiotics during the previous 12 months (1-2; ≥ 3), and P. aeruginosa treatment (not treated; treated) will be the independent variables. A supportive analyses will also be provided for those who did and did not receive i.v. vancomycin during Period 1. If the model fails to run properly, age will be dropped, then Baseline FEV1 percent predicted will be dropped if necessary.

A separate by-subject listing will also be provided.

8.3. EXPLORATORY EFFICACY ENDPOINT AND ANALYSES

8.3.1. Changes from Baseline in EQ-5D-5L/EQ-5Dy Scores

EQ-5D is a standardized measure of health status developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal.[1] The EQ-5D-5L include five levels of severity in each of the existing five EQ-5D dimensions along with a 20 cm visual analog scale (VAS) to collect how good or bad the subject's health is today, with 0 - worst health you can image and 100 – best you can image.

The EQ-5D Youth (EQ-5Dy) is the youth version of the EQ-5D developed specifically for children and adolescents aged 8-15 years.

The EQ-5D-5L/EQ-5Dy will be given at each visit starting at the Baseline visit. Results will be summarized as categorical results for the 5 dimensions at each visit. Summaries will be by measure and age group (EQ-5Dy age/≤15 years, EQ-5D-5L/age ≤21 years, EQ-5D-5L/age >21 years). A shift from baseline table will be provided for Weeks 4 and 20. Additionally a by subject listing will be provided.

The VAS scores and their change from baseline will be summarized at each visit as continuous variables by measure and age group. Summary tables will also be provided by measure and other stratification factors (Baseline FEV_1 (≥60%; <60%), prior exacerbations treated with antibiotics during the previous 12 months (1-2; ≥ 3), *P. aeruginosa* treatment (not treated; treated)).

8.3.2. Change from Baseline in Body Weight

Body weight is collected at the Screening Visit, Baseline Visit, and every visit starting at Week 4. Body weight and the change from baseline will be summarized at each visit as a continuous variable by age group and other stratification factors (Baseline FEV_1 (≥60%; <60%), prior exacerbations treated with antibiotics during the previous 12 months (1-2; ≥ 3), *P. aeruginosa* treatment (not treated; treated)).

8.3.3. Minimum Inhibitory Concentration (MIC) for Vancomycin

Sputum samples are collected at the Screening Visit, Baseline Visit, and every visit starting at Week 4. Based on these sputum samples, MIC for Vancomycin will be determined. These results will be summarized at each visit as a categorical variable along with the MIC50 and MIC90 (50^{th} and 90^{th} percentile) values by age group and other stratification factors (Baseline FEV_1 (≥60%; <60%), prior exacerbations treated with antibiotics during the previous 12 months (1-2; ≥ 3), *P. aeruginosa* treatment (not treated; treated)). A summary table of the shift from Baseline to each visit will be provided.

8.3.4. MRSA Sputum Density

Methicillin resistant Staphylococcus aureus (MRSA) sputum density will be determined at all visits except Week 2 and Week 36 visits. MRSA sputum density will be summarized and listed for a subset of subjects. The MRSA sputum density summary will consist of mean, standard deviation, median, 25th percentile, 75th percentile, minimum, and maximum by age group. If multiple MRSA isolates are available at any visit then only the maximum values will be used for the descriptive statistics.

8.3.5. Emergence of Additional Pathogens

Emergence of additional pathogens during and after the study drug administration will be monitored in sputum or throat swab microbiology cultures already being collected. The presence of the following pathogens will be determined at Baseline, Week 20, and Week 44: *Pseudomonas aeruginosa*, *Achromobacter xylosoxidans*, *Aspergillus fumigatus*, *Burkholderia cepacia* complex, and *Stenotrophomonas maltophilia*.

Emergence of additional pathogens will be summarized at each scheduled visit by group and by other stratification factors (Baseline FEV_1 (≥60%; <60%), prior exacerbations

treated with antibiotics during the previous 12 months (1-2; ≥ 3), *P. aeruginosa* treatment (not treated; treated)).

8.4. OTHER EFFICACY ANALYSES

8.4.1. Pulmonary Function Tests (PFT)

All subjects will undergo standardized pulmonary function testing to determine their forced vital capacity (FVC), peak expiratory flow rate (PEFR), forced expiratory flow (FEF) between 25% and 75% of FVC (FEF_{25-75}) and FEV_1. Pulmonary Function Tests will be performed at each visit prior to the subject administering the bronchodilator pre-treatment and study drug (AeroVanc/placebo).

For all PFTs, their results and associated change from baseline will be summarized at each visit as a continuous variable by age group and by other stratification factors (Baseline FEV_1 (≥60%; <60%), prior exacerbations treated with antibiotics during the previous 12 months (1-2; ≥ 3), *P. aeruginosa* treatment (not treated; treated)).

8.4.2. Severity and Duration of Exacerbations

Exacerbations are recorded as adverse events and reported as part of the AE summaries. Additionally, summary statistics will be presented of the distribution of severity of exacerbations and duration of exacerbations (duration as determined from the AE start and end dates).

8.4.3. Time to First Use of Other Antibiotics due to Respiratory Symptoms

Time to first use of other antibiotics due to respiratory symptoms in Period 1 will be provided as a Kaplan-Meier plot by age group.

8.5. SUBGROUP ANALYSIS

All efficacy measures will be summarized at each visit by age group and other stratification factors (Baseline FEV_1 (≥60%; <60%), prior exacerbations treated with antibiotics during the previous 12 months (1-2; ≥ 3), *P. aeruginosa* treatment (not treated; treated)) using the ITT population.

With the FDA approval for Trikafta, primary and secondary efficacy measures, along with demographics will be summarized for subject who received Trikafta and those subjects who did not receive Trikafta at baseline or during Period 1. Similarly, primary and secondary efficacy variables will be summarized by use of IV vancomycin during each period.

9. ANALYSIS OF PHARMACOKINETICS

9.1. PK SAMPLING SCHEDULE

Pharmacokinetics (PK) will be studied as a sub-study of approximately 100 subjects, with trough plasma and sputum samples collected. Plasma vancomycin trough samples and sputum PK samples will be collected at the Week 2 visit.

9.2. PLASMA PK ENDPOINT

Vancomycin plasma PK trough levels at Week 2 will be summarized and listed for a subset of subject. The PK summary will consist of mean, standard deviation, geometric mean, CV, median, minimum, and maximum by age group.

9.3. SPUTUM PK ENDPOINT

Sputum PK trough values will be determined at Week 2 and Week 36 visits. These values will be summarized and listed for a subset of subjects. The sputum PK summary will consist of mean, standard deviation, geometric mean, CV, median, minimum, and maximum by age group.

9.4. PRESENTATION OF CONCENTRATION DATA

9.4.1. Handling of Missing Data

No imputation of missing PK concentrations will be done.

9.4.2. Listing and Presentation of Individual PK data

All related individual PK data will be listed.

10. SAFETY

The population used for safety analyses will be the Safety Population. Safety will be assessed on the basis of adverse event (AE) reports, clinical laboratory data (ie, hematology, serum chemistries, and urinalysis), ECG parameters, physical examinations, and vital signs. All safety measures will be summarized, unless otherwise stated.

10.1. EXTENT OF EXPOSURE

Exposure to each cycle is defined as (last dose date of the cycle – first dose date of the cycle + 1) / 7, rounded to one decimal place. For each period, the exposure of each cycle will be added together to calculate the total exposure for the period. The cumulative exposure will be the sum of periods' exposures for subjects assigned AeroVanc 30 mg BID in period 1. For Subjects assigned Placebo in Period 1, then the cumulative exposure will equal their exposure in Period 2 only. If the last dose date is not available for a cycle, such as for the end of Period 1 analysis, then the last dose date will be set to the last known dose date.

Study treatment exposure will be summarized using the Safety Population for each period and overall by Period 1 treatment. Exposure will be calculated for each Period by the summation of exposure in each cycle. Exposure will be summarized as a continuous variable. Additionally, a categorical summary will be provided with exposure broken into 4 week periods (ie, 0 - 4 weeks, >4 weeks – 8 weeks, >8 weeks – 12 weeks).

10.2. TREATMENT COMPLIANCE

Treatment compliance is defined as (actual number of capsules used / expected number of capsules used) * 100 for a period or overall and will be presented as a percentage. Actual number of capsules used in a cycle is the number of capsules dispensed (128) - number of unused capsules returned. Actual number of capsules used in a cycle is added together for each period and overall as appropriate. Expected number of capsules per cycle is defined as the minimum of (date returned – date dispensed, 28) * 4 capsules. Expected number of capsules used in a cycle is added together for each period and overall as appropriate.

Treatment compliance, actual number of capsules used and expected number of capsules used will be listed and summarized using the Safety Population for each period and overall by Period 1 treatment.

10.3. ADVERSE EVENTS

An adverse event is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related. All adverse events (AEs) will be

coded using the MedDRA version 20.0 or higher. The following listings of AEs will be provided by subjects:

- All AEs,
- Study drug-related AEs,
- Serious adverse events (SAEs)
- AEs leading to death
- AEs leading to study discontinuation

Adverse Events will be included in summary tables by Period 1 treatment and overall for each period. An overall summary table of AEs will be produced for the following categories:

- Any AE
- Severe or Life-threatening AEs
- Study drug-related AEs
- Serious AEs
- Study drug-related Serious AEs
- AEs leading to study discontinuation
- AEs leading to death

All AEs will be classified by SOC and PT. Frequency count of AEs, the number of unique subjects experiencing an AE, and percentage of unique subjects experiencing an AE will be tabulated by Period 1 treatment. Subjects who experienced more than one TEAE will be counted only once in each category. For percentages, Clopper–Pearson 95% confidence intervals will be tabulated by treatment group, system organ class, and preferred term. For the number of unique subjects reporting, if a subject reported more than one AE that was coded to the same SOC or PT, the subject will be counted only once for that specific SOC or PT.

The following summaries of AEs will also be provided:

- AEs by SOC and PT

- AEs by SOC, PT and maximum severity
- AEs by SOC, PT and causality relationship
- Severe or Life-threatening AEs by SOC and PT
- Severe or Life-threatening treatment-related AEs by SOC and PT
- Serious AEs by SOC and PT
- Serious treatment-related AEs by SOC and PT
- AEs leading to study discontinuation by SOC and PT
- AEs leading to death by SOC and PT
- AEs by PT

For AEs presented by relationship to study treatment, the strongest relationship to study treatment(s) during the clinical trial will be presented for each subject if coded to the same SOC or PT. For AEs presented by severity, the worst severity during the clinical trial will be presented for each subject if coded to the same SOC or PT. If either relationship or severity is missing, then the strongest relationship (related) or worst severity (life-threatening) will be assigned.

10.4. LABORATORY EVALUATIONS

Blood samples for hematology and biochemistry are to be collected at screening, Baseline, on Weeks 4, 12 and 20 during Period 1, on Weeks 28, 36, and 44 of Period 2, and at the Week 48 follow-up visit. Urine for urinalysis is to be collected at screening, Baseline, on Weeks 12 and 20 of Period 1, on Weeks 24, 36 and 44 of Period 2, and at the Week 48 follow-up visit.

Descriptive statistics will be provided for each test parameter and for change from baseline by Period 1 treatment for each period. Shift tables (ie, low-normal-high at Baseline versus low-normal-high at each post-baseline visit in a 3-by-3 contingency table) will be provided to assess changes from Baseline in laboratory values by visit for each Period. Summary figures will be provided for mean change from baseline will be provided for each test parameter and each period.

Separate listings will be provided for all laboratory evaluations (hematology, biochemistry, urinalysis, and serum pregnancy results).

10.5. VITAL SIGNS

Vital signs consist of body temperature, systolic and diastolic blood pressure, pulse, pulse oxygenation (SpO_2), weight, and respirations. Vital signs are collected at Screening, on Weeks 4,8,12,16 and 20 of Period 1, on Weeks 24, 28, 36, and 44 of Period 2, and at the Week 48 follow-up visit.

Vital signs will be summarized using descriptive statistics at Baseline and at each post-Baseline visit by Period 1 treatment. Changes from Baseline will also be summarized. Summary figures will be provided for mean change from baseline for systolic and diastolic blood pressure, pulse, and respirations in each period.

Separate listings will be provided for all vital sign results.

10.6. ECG

A 12-lead ECG will be performed during the study at Screening, at Baseline, on Week 20 of Period 1, and on Week 44 of Period 2. Electrocardiogram parameters will be summarized using descriptive statistics at Baseline and at each post-Baseline visit where an ECG assessment was made by Period 1 treatment. Changes from Baseline will also be summarized. In addition, shift tables (ie, normal, abnormal not clinically significant [NCS], abnormal clinically significant [CS]) at Baseline versus normal, abnormal NCS, abnormal CS at each post-baseline visit in a 3-by-3 contingency table) will be provided to assess changes from Baseline.

Clinically significant findings, not present during the Baseline visit, should be recorded as an AE.

Separate listings will be provided for all ECG results.

10.7. PHYSICAL EXAMINATION

A complete physical examination will be performed at Screening, on Weeks 12 and 20 of Period 1, and Week 44 of Period 2. Complete physical examinations will include a minimum of a review of the subject's general appearance, head, eyes, ears, nose, and throat (HEENT), neck, heart, lungs, abdomen, extremities, skin, and general neurological system.

Symptom-oriented or brief physical examinations will be performed at Baseline, on Weeks 4, 8, and 16 of Period 1, and Weeks 24, 28, and 36 of Period 2. New abnormal physical exam findings not present during the baseline visits should be recorded as AEs.

Physical examination data is presented in a data listing only.

11. INTERIM ANALYSES

When 100% of subjects have completed Period 1 of the protocol or terminated early, the study will be unblinded. The analysis of safety and efficacy for Period 1 will be completed at that time. Given Period 2 is strictly an open-label period and only summaries will be provided, there will be no adjustment to the Period 1 p-values due to repeated testing. Following the end of Period 2 for all subjects, a full set of tables, figures, and listings will be provided.

12. CHANGE FROM ANALYSIS PLANNED IN PROTOCOL

The protocol states, with respect to in FEV1 percent predicted, "A linear regression model will be fitted using subjects with observed values for the endpoint (Week 4, 12 and 20, respectively), the covariates Baseline FEV1 percent predicted, and earlier on-treatment measurements of FEV1 percent predicted that are available (if any), and the stratification factors. Full details will be included in the SAP." In the SAP, post-baseline FEV1 percent predicted analysis using prior visit results as covariates.

While not explicitly stated in the protocol, the order of the secondary endpoints in the protocol was planned as the order of analysis. The frequency of pulmonary exacerbations is now moved from the sixth position within the secondary analyses to the first position within the secondary analyses to be the first secondary endpoint to be tested.

With the FDA approval for Trikafta, analysis of the primary and secondary efficacy measures will be performed for subjects who did not receive Trikafta at baseline or during Period 1. Summaries of the primary and secondary efficacy measures will be performed separately for subjects who received Trikafta and subjects who did not receive Trikafta at baseline or during Period 1.

Consequent to COVID-19, recruitment to the trial has been stopped prematurely and some changes to rules for handling missed visits (and resulting missing data) have been introduced. Where appropriate, the new rules for handling missing data will be applied to the primary and secondary efficacy analyses. For clarity, all changes resulting from COVID-19 issues are described in Appendix B of this document. For avoidance of doubt, the primary analyses will be based on the new rules for handling missing data (as described in Appendix B), and not necessarily as described in the original SAP text (Section 8) or in the protocol.

The definition of pulmonary exacerbations are clarified, including Updates to the definitions of exacerbations, antibiotics to be considered for an exacerbation, and the time interval required between one event in order to be considered a separate exacerbation.

Any Pulmonary Function Test that scored for reliability and repeatability with a grade of F shall not be used in analyses. In the Per Protocol analyses, results with grades of C or D will also be excluded. This was not specified in the protocol.

13. REFERENCE LIST

1. The EuroQol Group (1990). EuroQol-a new facility for the measurement of health-related quality of life. Health Policy 16(3):199-208.

14. PROGRAMMING CONSIDERATIONS

All tables, data listings, figures (TLFs), and statistical analyses will be generated using SAS® for Windows, Release 9.3 (SAS® Institute Inc., Cary, NC, USA). Computer-generated table, listing, and figure output will adhere to the following specifications.

14.1. GENERAL CONSIDERATIONS

The following items need to be clarified upfront with the sponsor and Medical Writing and modified as per study requirements.

- A separate SAS program will be created for each output.
- Each output will be stored in a separate file.
- Output files will be delivered in Word format.
- Numbering of TLFs will follow ICH E3 guidance

14.2. TABLE, LISTING, AND FIGURE FORMAT

14.2.1. General

- All TLFs will be produced in landscape format, unless otherwise specified.
- All TLFs will be produced using the Courier New font, size 8
- The data displays for all TLFs will have a minimum 1-inch margin on all 4 sides.
- Headers and footers for figures will be in Courier New font, size 8.
- Legends will be used for all figures with more than 1 variable, group, or item displayed.
- TLFs will be in black and white (no color), unless otherwise specified
- Specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, will not be used in the TLFs, unless otherwise specified. On some occasions, superscripts 1, 2, or 3 may be used (see below).
- Only standard keyboard characters will be used in the TLFs. Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will not be used. Hexadecimal-derived characters will be used, where possible, if they are appropriate to help display math symbols (e.g., μ). Certain subscripts and superscripts (e.g., cm^2, C_{max}) will be employed on a case-by-case basis.
- Mixed case will be used for all titles, footnotes, column headers, and programmer-supplied formats, as appropriate.

14.2.2. Headers

All output should have the following header at the top of each page:

Savara, Inc.	Draft/Final
Protocol SAV-005-04	Page n of N

- TLFs should be internally paginated in relation to the total length (i.e., the page number should appear sequentially as page n of N, where N is the total number of pages in the table).
- The date output was generated should appear along with the program name as a footer on each page.

14.2.3. Display Titles

- Each TLF should be identified by the designation and a numeral. (i.e., Table 14.1.1). ICH E3 numbering is strongly recommended but sponsor preferences should be obtained prior to final determination. A decimal system (x.y and x.y.z) should be used to identify TLFs with related contents. The title is centered. The analysis population should be identified on the line immediately following the title. The title and table designation are single spaced. A solid line spanning the margins will separate the display titles from the column headers. There will be 1 blank line between the last title and the solid line.

Table x.y.z
First Line of Title
Second Line of Title if Needed
ITT Analysis Population

14.2.4. Column Headers

- Column headings should be displayed immediately below the solid line described above in initial upper-case characters.
- In the case of efficacy tables, the variable (or characteristic) column will be on the far left followed by the treatment group columns and total column (if applicable). P-values may be presented under the total column or in separate p-value column (if applicable). Within-treatment comparisons may have p-values presented in a row beneath the summary statistics for that treatment.
- For numeric variables, include “unit” in column or row heading when appropriate.
- Analysis population sizes will be presented for each treatment group in the column heading as (N=xx) (or in the row headings if applicable). This is distinct from the ‘n’

used for the descriptive statistics representing the number of subjects in the analysis population.

- The order of treatments in the tables and listings will be Placebo first followed by Active, followed by a total column (if applicable).

14.2.5. Body of the Data Display

14.2.5.1. General Conventions

- Data in columns of a table or listing should be formatted as follows:
  - alphanumeric values are left-justified;
  - whole numbers (e.g., counts) are right-justified; and
  - numbers containing fractional portions are decimal aligned.

14.2.5.2. Table Conventions

- Units will be included where available
- If the categories of a parameter are ordered, then all categories between the maximum and minimum category should be presented in the table, even if n=0 for all treatment groups in a given category that is between the minimum and maximum level for that parameter. For example, the frequency distribution for symptom severity would appear as:

Severity Rating	N
severe	0
moderate	8
mild	3

Where percentages are presented in these tables, zero percentages will not be presented and so any counts of 0 will be presented as 0 and not as 0 (0%).

- If the categories are not ordered (e.g., Medical History, Reasons for Discontinuation from the Study, etc.), then only those categories for which there is at least 1 subject represented in 1 or more groups should be included.
- An Unknown or Missing category should be added to any parameter for which information is not available for 1 or more subjects.
- Unless otherwise specified, the estimated mean and median for a set of values should be printed out to 1 more significant digit than the original values, and standard deviations should be printed out to 2 more significant digits than the original values. The minimum and maximum should report the same significant digits as the original values. For example, for systolic blood pressure:

N	XX
Mean	XXX.X
Std Dev	X.XX
Median	XXX.X
Minimum	XXX
Maximum	XXX

- P-values should be output in the format: “0.xxx”, where xxx is the value rounded to 3 decimal places. Any p-value less than 0.001 will be presented as <0.001. If the p-value is returned as >0.999 then present as >0.999
- Percentage values should be printed to one decimal place, in parentheses with no spaces, one space after the count (e.g., 7 (12.8%), 13 (5.4%)). Pre-determine how to display values that round down to 0.0. A common convention is to display as '<0.1', or as appropriate with additional decimal places. Unless otherwise noted, for all percentages, the number of subjects in the analysis population for the treatment group who have an observation will be the denominator. Percentages after zero counts should not be displayed and percentages equating to 100% should be presented as 100%, without any decimal places.
- Tabular display of data for medical history, prior / concomitant medications, and all tabular displays of adverse event data should be presented by the body system, treatment class, or SOC with the highest occurrence in the active treatment group in decreasing order, assuming all terms are coded. Within the body system, drug class and SOC, medical history (by preferred term), drugs (by ATC1 code), and adverse events (by preferred term) should be displayed in decreasing order. If incidence for more than 1 term is identical, they should then be sorted alphabetically. Missing descriptive statistics or p-values which cannot be estimated should be reported as “-”.
- The percentage of subjects is normally calculated as a proportion of the number of subjects assessed in the relevant treatment group (or overall) for the analysis *population* presented. However, careful consideration is required in many instances due to the complicated nature of selecting the denominator, usually the appropriate number of subjects exposed. Describe details of this in footnotes or programming notes.

- For categorical summaries (number and percentage of subjects) where a subject can be included in more than one category, describe in a footnote or programming note if the subject should be included in the summary statistics for all relevant categories or just 1 category and the criteria for selecting the criteria.

- Where a category with a subheading (such as system organ class) has to be split over more than one page, output the subheading followed by “(cont)” at the top of each subsequent page. The overall summary statistics for the subheading should only be output on the first relevant page.

14.2.5.3. Listing Conventions

- Listings will be sorted for presentation in order of treatment groups as above, subject number, visit/collection day, and visit/collection time.
- Missing data should be represented on subject listings as either a hyphen ("-") with a corresponding footnote ("- = unknown or not evaluated"), or as "N/A", with the footnote "N/A = not applicable", whichever is appropriate.
- Dates should be printed in SAS® DATE9.format ("ddMMMyyyy": 01JUL2000). Missing portions of dates should be represented on subject listings as dashes (--JUL2000). Dates that are missing because they are not applicable for the subject are output as "N/A", unless otherwise specified.
- All observed time values must be presented using a 24-hour clock HH:MM or HH:MM:SS format (e.g., 11:26:45, or 11:26). Time will only be reported if it was measured as part of the study.
- Units will be included where available

14.2.5.4. Figure Conventions

- Unless otherwise specified, for all figures, study visits will be displayed on the X-axis and endpoint (e.g., treatment mean change from Baseline) values will be displayed on the Y-axis.

14.2.6. Footnotes

- A solid line spanning the margins will separate the body of the data display from the footnotes.
- All footnotes will be left justified with single-line spacing immediately below the solid line underneath the data display.
- Footnotes should always begin with "Note:" if an informational footnote, or 1, 2, 3, etc. if a reference footnote. Each new footnote should start on a new line where possible.
- Subject specific footnotes should be avoided, where possible.
- Footnotes will be used sparingly and must add value to the table, figure, or data listing. If more than six lines of footnotes are planned, then a cover page may be used to display footnotes, and only those essential to comprehension of the data will be repeated on each page.
- The last line of the footnote section will be a standard source line that indicates the name of the program used to produce the data display, date the program was run, and the listing source (i.e., 'Program : myprogram.sas Listing source: 16.x.y.z').

15. QUALITY CONTROL

SAS programs are developed to produce output such as analysis data populations, summary tables, data listings, figures or statistical analyses. Syneos Health SOP 3906.00 and 3907.00 or later versions provide an overview of the development of such SAS programs.

Syneos Health SOP 3908.00 or later version describes the quality control procedures that are performed for all SAS programs and output. Quality control is defined here as the operational techniques and activities undertaken to verify that the SAS programs produce the output by checking for their logic, efficiency and commenting and by review of the produced output.

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19. APPENDICES

APPENDIX A: CYSTIC FIBROSIS QUESTIONNAIRE-REVISED (CFQ-R) SCORING ALGORITHM AND SAS® CODE

General Scoring Instructions

For ease of interpretation, the questions on the CFQ-R are labeled according to the number on the questionnaire and the domain they are designed to measure. The domain label precedes the question number. For example the first question on the questionnaire is designed to measure a physical symptom and its label is "Phys1." The complete labeling for each version of the CFQ-R is presented under the section entitled "Question Labels".

The following scoring codes were written to be used with CFQ-R data that was entered into a database/spreadsheet where each question is a unique variable. The variable names should match the question labels listed in the "Question Labels" section. Values for each question range from 1 to 4. For questions with responses listed horizontally (left to right) the left response category should be assigned a value of 1, the second category should be assigned a 2, the third a 3, and the rightmost category should be assigned a 4.

Here is an example.

1. Performing vigorous activities such as running or playing sports…… . 1 2 3 4

For questions that are listed vertically (top to bottom), the top category should be assigned a value of 1, the next a 2, the third a 3, and the bottom category a 4.

Here is an example.

13. To what extent do you have difficulty walking? Scoring Values
    1. You can walk a long time without getting tired (1)
    2. You can walk a long time but you get tired (2)
    3. You cannot walk a long time because you get tired quickly (3)
    4. You avoid walking whenever possible because it's too tiring for you (4)

It is important that you assign the values according to these rules for each question. Some of the questions will be phrased in a positive direction (like Question 13 listed above) and the values may seem inappropriate. The scoring codes reverse the ordering for these positively phrased questions. Do not reverse the coding when you are entering the scores into your database/spreadsheet. We have found it to be more accurate to let the scoring procedures address the reverse coding.

Please note that question 43 (resp43) on the Teen/Adult version and question 37 (resp37) on the Parent version have one extra category (don't know) we typically assign a value of 5 to that category. This question is not included in the scoring of the respiratory scale.

Question Labels

CFQ-R Teen/Adult Version	CFQ-R Parent Version	CFQ-R Child Version
Question 1 = phys1	Question 1 = phys1	Question 1 = phys1
Question 2 = phys2	Question 2 = phys2	Question 2 = phys2
Question 3 = phys3	Question 3 = phys3	Question 3 = phys3
Question 4 = phys4	Question 4 = phys4	Question 4 = phys4
Question 5 = phys5	Question 5 = phys5	Question 5 = phys5
Question 6 = vital6	Question 6 = emot6	Question 6 = phys6
Question 7 = emot7	Question 7 = emot7	Question 7 = emot7
Question 8 = emot8	Question 8 = vital8	Question 8 = emot8
Question 9 = vital9	Question 9 = vital9	Question 9 = emot9
Question 10 = vital10	Question 10 = vital10	Question 10 = emot10
Question 11 = vital11	Question 11 = vital11	Question 11 = emot11
Question 12 = emot12	Question 12 = vital12	Question 12 = emot12
Question 13 = phys13	Question 13 = school13	Question 13 = emot13
Question 14 = eat14	Question 14 = phys14	Question 14 = emot14
Question 15 = treat15	Question 15 = phys15	Question 15 = eat15
Question 16 = treat16	Question 16 = phys16	Question 16 = treat16
Question 17 = treat17	Question 17 = eat17	Question 17 = eat17
Question 18 = health18	Question 18 = treat18	Question 18 = treat18
Question 19 = phys19	Question 19 = body19	Question 19 = eat19
Question 20 = phys20	Question 20 = body20	Question 20 = social20
Question 21 = eat21	Question 21 = body21	Question 21 = social21
Question 22 = social22	Question 22 = health22	Question 22 = social22
Question 23 = social23	Question 23 = emot23	Question 23 = social23
Question 24 = body24	Question 24 = health24	Question 24 = social24
Question 25 = body25	Question 25 = emot25	Question 25 = social25
Question 26 = body26	Question 26 = emot26	Question 26 = social26
Question 27 = social27	Question 27 = school27	Question 27 = body27
Question 28 = social28	Question 28 = school28	Question 28 = body28
Question 29 = social29	Question 29 = school29	Question 29 = body29
Question 30 = social30	Question 30 = treat30	Question 30 = treat30
Question 31 = emot31	Question 31 = treat31	Question 31 = resp31
Question 32 = health32	Question 32 = health32	Question 32 = resp32
Question 33 = emot33	Question 33 = weight33	Question 33 = resp33

CFQ-R Teen/Adult Version	CFQ-R Parent Version	CFQ-R Child Version
Question 34 = health34	Question 34 = resp34	Question 34 = resp34
Question 35 = role35	Question 35 = resp35	Question 35 = digest35
Question 36 = role36	Question 36 = resp36	
Question 37 = role37	Question 37 = resp37	
Question 38 = role38	Question 38 = resp38	
Question 39 = weight39	Question 39 = resp39	
Question 40 = resp40	Question 40 = resp40	
Question 41 = resp41	Question 41 = digest41	
Question 42 = resp42	Question 42 = digest42	
Question 43 = resp43	Question 43 = digest43	
Question 44 = resp44	Question 44 = eat44	
Question 45 = resp45		
Question 46 = resp46		
Question 47 = digest47		
Question 48 = digest48		
Question 49 = digest49		
Question 50 = eat50		

SAS Program Codes for Scoring the CFQ-R Teen/Adult Version

```
/*This scoring program requires that the data be imported into a SAS table titled
"CFQR_TA" and that the variable names in the table match those listed below.*/

Data CFQR_TA; set CFQR_TA;

/* Recoding Some Variables */

vital6      =    5-vital6;
vital10     =    5-vital10;
phys13      =    5-phys13;
treat15     =    5-treat15;
treat17     =    5-treat17;
health18    =    5-health18;
social23    =    5-social23;
social28    =    5-social28;
social30    =    5-social30;
health32    =    5-health32;
health34    =    5-health34;
role35      =    5-role35;
resp43      =    5-resp43;


/* Calculating Scores */

if nmiss (phys1, phys2, phys3, phys4, phys5, phys13, phys19, phys20) ≤ 4 then
physical = (mean (phys1, phys2, phys3, phys4, phys5, phys13, phys19, phys20)-1)/3*100;

if nmiss (role35, role36, role37, role38) ≤ 2 then
role = (mean (role35, role36, role37, role38)-1)/3*100;

if nmiss (vital6, vital9, vital10, vital11) ≤ 2 then
vitality = (mean (vital6, vital9, vital10, vital11)-1)/3*100;

if nmiss (emot7, emot8, emot12, emot31, emot33) ≤ 2 then
emotion = (mean (emot7, emot8, emot12, emot31, emot33)-1)/3*100;

if nmiss (social22, social23, social27, social28, social29, social30) ≤ 3 then
social = (mean (social22, social23, social27, social28, social29, social30)-1)/3*100;

if nmiss (body24, body25, body26) ≤ 1 then
body = (mean (body24, body25, body26)-1)/3*100;
```

```
if nmiss (eat14, eat21, eat50) ≤ 1 then
eat = (mean (eat14, eat21, eat50)-1)/3*100;

if nmiss (treat15, treat16, treat17) ≤ 1 then
treat = (mean (treat15, treat16, treat17)-1)/3*100;

if nmiss (health18, health32, health34) ≤ 1 then
health = (mean (health18, health32, health34)-1)/3*100;

if nmiss (weight39) = 0 then
weight= (mean (weight39)-1)/3*100;

if nmiss (resp40, resp41, resp42, resp44, resp45, resp46) ≤ 3 then
respirat = (mean (resp40, resp41, resp42, resp44, resp45, resp46)-1)/3*100;

if nmiss (digest47, digest48, digest49) ≤ 1 then
digest = (mean (digest47, digest48, digest49)-1)/3*100;
run;
```

SAS Program Codes for Scoring the CFQ-R Parent Version

```
/*This scoring program requires that the data be imported into a SAS table titled
"CFQR_P" and that the variable names in the table match those listed below.*/

Data CFQR_P; set CFQR_P;

/* Recoding Some Variables */

emot6 =      5- emot6;

vital10      =      5-vital10;
vital12      =      5- vital12
phys15       =      5-phys15;
treat31      =      5-treat31;
health22     =      5-health22;
health24     =      5-health24;
health32     =      5-health32;
school28     =      5-school28;
resp37 =     5- resp37;

/* Calculating Scores */

if nmiss (phys1, phys2, phys3, phys4, phys5, phys14, phys15, phys16) ≤ 4 then
```

```
physical = (mean (phys1, phys2, phys3, phys4, phys5, phys14, phys15, phys16)-1)/3*100;

if nmiss (emot6, emot7, emot23, emot25, emot26) ≤ 2 then
emotion = (mean (emot6, emot7, emot23, emot25, emot26)-1)/3*100;

if nmiss (vital8, vital9, vital10, vital11, vital12) ≤ 2 then
vitality = (mean (vital8, vital9, vital10, vital11, vital12)-1)/3*100;

if nmiss (school13, school27, school28, school29) ≤ 2 then
school = (mean (school13, school27, school28, school29)-1)/3*100;

if nmiss (eat17, eat44) = 0 then
eat = (mean(eat17, eat44)-1)/3*100;

if nmiss (body19, body20, body21) ≤ 1 then
body = (mean(body19, body20, body21)-1)/3*100;

if nmiss (treat18, treat30, treat31) ≤ 1 then
treat = (mean (treat18, treat30, treat31)-1)/3*100;

if nmiss (health22, health24, health32) ≤ 1 then
health = (mean (health22, health24, health32)-1)/3*100;

if nmiss (resp34, resp35, resp36, resp38, resp39, resp40) ≤ 3 then
respirat = (mean (resp34, resp35, resp36, resp38, resp39, resp40)-1)/3*100;

if nmiss (digest41, digest42, digest43) ≤ 1 then
digest = (mean (digest41, digest42, digest43)-1)/3*100;

if nmiss (weight33) = 0 then
weight = (mean (weight33)-1)/3*100;

run;
```

SAS Program Codes for Scoring the CFQ-R Child Version

```
/*This scoring program requires that the data be imported into a SAS table titled
"CFQR_Ch" and that the variable names in the table match those listed below.*/

Data CFQR_Ch; set CFQR_Ch;

/* Recoding Some Variables */
```

```
phys1       =     5-phys1;
phys2       =     5-phys2;
phys3       =     5-phys3;
phys4       =     5-phys4;
phys5       =     5-phys5;
emot14      =     5-emot14;
treat18     =     5-treat18;
eat19       =     5-eat19;
social20    =     5- social20;
social22    =     5- social22;
social24    =     5- social24;
social26    =     5- social26;

/* Calculating Scores */

if nmiss (phys1, phys2, phys3, phys4, phys5, phys6) ≤ 3 then
physical = (mean (phys1, phys2, phys3, phys4, phys5, phys6)-1)/3*100;

if nmiss (emot7, emot8, emot9, emot10, emot11, emot12, emot13, emot14) ≤ 4 then
emotion = (mean (emot7, emot8, emot9, emot10, emot11, emot12, emot13, emot14)-
1)/3*100;

if nmiss (social20, social21, social22, social23, social24, social25, social26) ≤ 3 then
social = (mean (social20, social21, social22, social23, social24, social25, social26)-
1)/3*100;

if nmiss (eat15, eat17, eat19) ≤ 1 then
eat = (mean(eat15, eat17, eat19)-1)/3*100;

if nmiss (body27, body28, body29) ≤ 1 then
body = (mean(body27, body28, body29)-1)/3*100;

if nmiss (treat16, treat18, treat30) ≤ 1 then
treat = (mean (treat16, treat18, treat30)-1)/3*100;

if nmiss (resp31, resp32, resp33, resp34) ≤ 2 then
respirat = (mean (resp31, resp32, resp33, resp34)-1)/3*100;

if nmiss (digest35) = 0 then
digest = (mean (digest35)-1)/3*100;

run;
```

APPENDIX B: UPDATED PRIMARY AND SECONDARY EFFICACY ANALYSIS TO ACCOUNT FOR MISSING DATA DUE TO THE COVID-19 PANDEMIC

The efficacy analyses described in Section 8 above are those planned before the occurrence of the COVID-19 pandemic in early 2020. Consequent to the outbreak of COVID-19, recruitment to the trial has been stopped prematurely and some changes to rules for handling missed visits (and resulting missing data) have been introduced. For clarity, all changes resulting from COVID-19 issues are described here. For avoidance of doubt, the primary and affected analyses will be based on the new rules for handling missing data (as described below), and not necessarily as described in the original SAP text (Section 8) or in the protocol.

Figures and listings will present actual results. No imputed data will be used. Thus no changes to the figures or listings will be made as part of Appendix B.

A subject who has a visit skipped or performed via telemedicine, a protocol deviation will be recorded as either "Week X <<insert applicable week #>> performed via telemedicine due to COVID-19 pandemic." or "Week X <<insert applicable week #>> missed due to COVID-19 pandemic." respectively. When such a protocol deviation is reported, the missing data for that visit will be considered missing due to COVID-19. Otherwise it will be treated as normally missing data.

B.1 PRIMARY EFFICACY ENDPOINT AND ANALYSIS

B.1.1 Primary Analysis of the Primary Efficacy Endpoint

The primary efficacy endpoint is the absolute change from baseline in FEV_1 percent predicted. The primary analysis will be based on the ITT population of ≤ 21 years of age using all observed data, with a PFT scoring grade of A, B, C, or D, at Weeks 4, 12, and 20.

For any subjects who have one or more missing FEV_1 result(s) (whether that be because they withdrew early from the trial, or for any other reason **not** relating to the COVID-19 pandemic), their missing FEV_1 will be imputed using the least favorable group visit median change from baseline. This imputation can occur for more than one visit (if necessary); in such cases, the "least favorable group" will be determined on a visit-by-visit basis (i.e. the "least favorable" group could be different at weeks 4, 12 and 20).

For any subject who has one or more missing FEV_1 result(s) due to the COVID-19 pandemic, data will be left missing in the ADaM dataset. After the COVID-19 unrelated missing data is imputed as specified above, multiple imputation will be applied using Markov Chain Monte Carlo methods, assuming these data to be missing at random. A total of 500 datasets will be created. Each dataset will be analyzed using the MMRM model listed below with the results used to determine the final results.

For each imputed dataset, absolute change from baseline in FEV_1 percent predicted will be analyzed using same MMRM model as described in Section 8.1.1 above. The results of each dataset will then be combined into a single result using PROC MIANALYZE.

The absolute change from baseline in FEV_1 percent predicted will be tested sequentially at Week 4 (end of Cycle 1), Week 12 (end of Cycle 2), and at Week 20 (end of Cycle 3). If a statistically significant difference is observed in favor of AeroVanc compared to placebo after Cycle 1, then the mean change in the FEV_1 percent predicted during Cycle 2 will be tested. Similarly, if the effect after Cycle 2 is statistically significant, then the analysis of Baseline to end of Cycle 3 will be tested.

As a supportive analysis three Analysis of Covariance (ANCOVA) models (one at each of weeks 4, 12 and 20) with the absolute change from baseline in FEV_1 percent predicted for a given visit as the dependent variable will be performed. Treatment, Baseline FEV_1 percent predicted, age, Baseline FEV1 (≥60%; <60%), prior exacerbations treated with antibiotics during the previous 12 months (1-2; ≥ 3) and *P. aeruginosa* treatment (not treated; treated) will be used as independent variables. If an ANCOVA model fails to run properly, the variable Baseline FEV_1 percent predicted will be dropped. The same missing value multiple imputation strategies as for the primary analysis (i.e. missing for COVID-19 related or non-related reasons) will be used to allow clearer comparisons between analysis strategies.

All analyses will be performed for Period 1 only.

Summarization and listing of the change from baseline in FEV_1 percent predicted will be provided as detailed in Section 8.1.1 above.

B.1.1.1 Sensitivity Analysis of the Primary Efficacy Endpoint

For confirmation of the primary endpoint, sensitivity analyses will be performed where COVID-19 unrelated missing data will be imputed using worst reasonable case analysis, best reasonable case analysis, and tipping point analysis as described in Section 6.3. COVID-19 related missing data will be imputed using the same multiple imputation method describe in B.1.1 above.

An additional sensitivity analysis will be performed using the Per-Protocol Population in place of the ITT and including results with a PFT scoring grade of A or B.

Given the FDA approval of Trikafta, sensitivity analyses will be performed by Trikafta use during the study.

Sensitivity analyses will be performed to assess the effect of actual stratification as based on eCRF data instead of strata reported at time of randomization. These analyses will be repeated for all primary supportive analyses.

All sensitivity analyses will be performed using the same analysis methodology and, unless otherwise specified, the same imputations methods as the primary analysis (B.1.1 above).

B.2 SECONDARY EFFICACY ENDPOINT(S) AND ANALYSES

B.2.1 Frequency of pulmonary exacerbations

Pulmonary exacerbations can be determined by the clinician during a telemedicine contact. Therefore, missing data cannot be strictly associated with COVID-19. Analysis of the frequency of pulmonary exacerbations will be performed as described in Section 8.2.1 above.

B.2.2 Time to first pulmonary exacerbation

Pulmonary exacerbations can be determined by the clinician during a telemedicine contact. Therefore, missing data cannot be strictly associated with COVID-19. Analysis of time to first pulmonary exacerbation will be performed as described in Section 8.2.2 above.

B.2.3 Number of successful response cycles a subject achieves over Period 1

Analysis of number of successful cycles a subject achieves across Period 1 will be performed as described in Section 8.2.6 above.

B.2.4 Relative change from Baseline in FEV1 percent predicted at Weeks 4, 12, and 20

Relative change from Baseline in FEV_1 percent predicted is defined as (Visit FEV_1 percent predicted – Baseline FEV_1 percent predicted)/Baseline FEV_1 percent predicted. Relative change from Baseline in FEV_1 percent predicted will be analyzed using the same methods as the primary efficacy analysis, including the same rules for missing values (See B.1.1 above). Summary tables will also be provided by age group and other stratification factors (Baseline FEV_1 (≥60%; <60%), prior exacerbations treated with antibiotics during the previous 12 months (1-2; ≥ 3), *P. aeruginosa* treatment (not treated; treated)).

Secondary analysis will be performed using subjects ≤21 years old. Subjects >21 years old, subjects using Trikafta, and subjects not using Trikafta will be analyzed separately as supportive analyses. An additional supportive analysis using eCRF-identified strata in place of strata identified at randomization will also be provided.

A sensitivity analysis of relative change from Baseline in FEV1 percent predicted will also be performed as originally planned (Section 8.2.4 above).

A separate by-subject listing will also be provided.

B.2.5 Change from Baseline in the Cystic Fibrosis Questionnaire-Revised (CFQ-R) scores at Weeks 4, 12, and 20

The CFQ-R is able to be collected by a handheld device. The CFQ-R data is electronically captured and an office visit is not required for the questionnaire to be completed. Therefore, missing data cannot be strictly associated with COVID-19. Analysis of the change from baseline in CFQ-R will be performed as described in Section 8.2.3 above.

B.2.6 Chronic Respiratory Symptom Score (CFRSD-CRISS) scores at Weeks 4, 12, and 20

The CFRSD-CRISS is able to be collected by a handheld device. The CFQ-R data is electronically captured and an office visit is not required for the questionnaire to be completed. Therefore, missing data cannot be strictly associated with COVID-19. Analysis of the CFRSD-CRISS will be performed as described in Section 8.2.4 above.

B.2.7 Area under the FEV1-time profile

Area under the FEV_1–time profile will be calculated for each subject over the course of each period. The area will be the sum of each FEV_1 multiplied by the duration of representative time period. The beginning of each time period will be either the beginning of the period or the midpoint between the time of the FEV_1 measurement and the previous FEV_1 measurement. The end of each time period will be either the end of the period or the midpoint between the time of the FEV_1 measurement and the following FEV_1 measurement. Duration will be calculated as (end of time period – start of time period) as measured in days.

Area under the FEV_1–time profile will be analyzed using a Generalized Linear Model with the Area under the FEV_1–time profile for a given period as the dependent variable, and using the same rules and methods for missing values as for the primary variable (Section B.1.1 above). Treatment, Baseline FEV1 percent predicted, age, Baseline FEV1 (≥60%; <60%), prior exacerbations treated with antibiotics during the previous 12 months (1-2; ≥ 3), and P. aeruginosa treatment (not treated; treated) will be the independent variables. If the model fails to run properly, age will be dropped, then Baseline FEV1 percent predicted will be dropped if necessary.

Summary tables will also be provided by period and age group, and by other stratification factors (Baseline FEV1 (≥60%; <60%), prior exacerbations treated with antibiotics during the previous 12 months (1-2; ≥ 3), *P. aeruginosa* treatment (not treated; treated)).

Secondary analysis will be performed using subjects ≤21 years old. Subjects >21 years old, subjects using Trikafta, and subjects not using Trikafta will be analyzed separately as supportive analyses. An additional supportive analysis using eCRF-identified strata in place of strata identified at randomization will also be provided.

B.2.8 Exploratory and Other Efficacy Analyses

No changes to any exploratory or other efficacy analyses will be made. All summaries and analyses will be provided based on available data, as described in Sections 8.3 and 8.4 above.

B.3 PRIMARY AND SECONDARY EFFICACY TABLES

Tables 14.1.*x*, 14.3.*x*, 14.4.*x*, and exploratory and other efficacy tables are unaffected by the COVID-19 pandemic. These tables will be provided as stated in Section 16 above. Similarly, figures and listings present actual results without any imputations. Figures and listings will remain unchanged.

Table Number	Table Title	Population	New or Updated Analysis
14.2.1.1.1	Analysis of Mean Absolute Change from Baseline in FEV_1 Percent Predicted at Weeks 4, 12, and 20 Subjects ≤ 21 Years	ITT Population	Updated Analysis
14.2.1.1.1.1	Analysis of Mean Absolute Change from Baseline in FEV_1 Percent Predicted at Weeks 4, 12, and 20 using Strata as Reported in Database Subjects ≤ 21 Years	ITT Population	Updated Analysis
14.2.1.1.1.2	Analysis of Mean Absolute Change from Baseline in FEV_1 Percent Predicted at Weeks 4, 12, and 20 Original Planned Analysis Subjects ≤ 21 Years	ITT Population	New (Original 14.2.1.1.1)
14.2.1.1.2	Analysis of Mean Absolute Change from Baseline in FEV_1 Percent Predicted at Weeks 4, 12, and 20 Subjects > 21 Years	ITT Population	Updated Analysis

Table Number	Table Title	Population	New or Updated Analysis
14.2.1.1.3	Analysis of Imputed Mean Absolute Change from Baseline in FEV_1 Percent Predicted at Weeks 4, 12, and 20 Worst Reasonable Case Analysis Subjects ≤ 21 Years	ITT Population	Updated Analysis
14.2.1.1.3.1	Analysis of Imputed Mean Absolute Change from Baseline in FEV1 Percent Predicted at Weeks 4, 12, and 20 Worst Reasonable Case Analysis using Strata as Reported in Database Subjects ≤ 21 Years	ITT Population	Updated Analysis
14.2.1.1.4	Analysis of Imputed Mean Absolute Change from Baseline in FEV_1 Percent Predicted at Weeks 4, 12, and 20 Best Reasonable Case Analysis Subjects ≤ 21 Years	ITT Population	Updated Analysis
14.2.1.1.4.1	Analysis of Imputed Mean Absolute Change from Baseline in FEV1 Percent Predicted at Weeks 4, 12, and 20 Best Reasonable Case Analysis using Strata as Reported in Database Subjects ≤ 21 Years	ITT Population	Updated Analysis
14.2.1.1.5	Analysis of Imputed Mean Absolute Change from Baseline in FEV_1 Percent Predicted at Weeks 4, 12, and 20 Tipping Point Analysis Subjects ≤ 21 Years	ITT Population	Updated Analysis
14.2.1.1.5.1	Analysis of Imputed Mean Absolute Change from Baseline in FEV1 Percent Predicted at Weeks 4, 12, and 20 Tipping Point Analysis using Strata as Reported in Database Subjects ≤ 21 Years	ITT Population	Updated Analysis
14.2.1.1.6	Analysis of Mean Absolute Change from Baseline in FEV_1 Percent Predicted Weeks 4, 12, and 20 Subjects ≤ 21 Years	Per-Protocol Population	Updated Analysis

Table Number	Table Title	Population	New or Updated Analysis
14.2.1.1.6.1	Analysis of Mean Absolute Change from Baseline in FEV1 Percent Predicted Weeks 4, 12, and 20 using Strata as Reported in Database Subjects ≤ 21 Years	Per-Protocol Population	Updated Analysis
14.2.1.1.7	Analysis of Mean Absolute Change from Baseline in FEV1 Percent Predicted at Weeks 4, 12, and 20 Subjects ≤ 21 Years with no Trikafta use at Baseline or During Period 1	ITT Population	Updated Analysis
14.2.1.1.8	Analysis of Mean Absolute Change from Baseline in FEV1 Percent Predicted at Weeks 4, 12, and 20 Subjects > 21 Years with no Trikafta use at Baseline or During Period 1	ITT Population	Updated Analysis
14.2.1.1.9	Analysis of Mean Absolute Change from Baseline in FEV1 Percent Predicted at Weeks 4, 12, and 20 by i.v. Vancomycin use during Period 1 Subjects ≤ 21 Years	ITT Population	
14.2.1.1.10	Analysis of Mean Absolute Change from Baseline in FEV1 Percent Predicted at Weeks 4, 12, and 20 by i.v. Vancomycin use during Period 1 Subjects > 21 Years	ITT Population	
14.2.1.2.1	Summary of Mean Absolute Change from Baseline in FEV_1 Percent Predicted at Weeks 4, 12, and 20 by Baseline FEV_1 Subjects ≤ 21 Years	ITT Population	
14.2.1.2.2	Summary of Mean Absolute Change from Baseline in FEV_1 Percent Predicted at Weeks 4, 12, and 20 by Baseline FEV_1 Subjects > 21 Years	ITT Population	
14.2.1.3.1	Summary of Mean Absolute Change from Baseline in FEV_1 Percent Predicted at Weeks 4, 12, and 20 by Prior Exacerbations Treated with Antibiotics During the Previous 12 Months Subjects ≤ 21 Years	ITT Population	

Table Number	Table Title	Population	New or Updated Analysis
14.2.1.3.2	Summary of Mean Absolute Change from Baseline in FEV_1 Percent Predicted at Weeks 4, 12, and 20 by Prior Exacerbations Treated with Antibiotics During the Previous 12 Months Subjects > 21 Years	ITT Population	
14.2.1.4.1	Summary of Mean Absolute Change from Baseline in FEV_1 Percent Predicted at Weeks 4, 12, and 20 by P. Aeruginosa Treatment Subjects ≤ 21 Years	ITT Population	
14.2.1.4.2	Summary of Mean Absolute Change from Baseline in FEV_1 Percent Predicted at Weeks 4, 12, and 20 by P. Aeruginosa Treatment Subjects > 21 Years	ITT Population	
14.2.2.1.1	Analysis of Frequency of Pulmonary Exacerbation During Period 1 Subjects ≤ 21 Years	ITT Population	
14.2.2.1.1.1	Analysis of Frequency of Pulmonary Exacerbation During Period 1 using Strata as Reported in Database Subjects ≤ 21 Years	ITT Population	
14.2.2.1.2	Analysis of Frequency of Pulmonary Exacerbation During Period 1 Subjects > 21 Years	ITT Population	
14.2.2.1.3	Analysis of Frequency of Pulmonary Exacerbation During Period 1 Subjects ≤ 21 Years	Per-Protocol Population	
14.2.2.1.4	Analysis of Frequency of Pulmonary Exacerbation During Period 1 Subjects ≤ 21 Years with no Trikafta use at Baseline or During Period 1	ITT Population	
14.2.2.1.5	Analysis of Frequency of Pulmonary Exacerbation During Period 1 Subjects > 21 Years with no Trikafta use at Baseline or During Period 1	ITT Population	

Table Number	Table Title	Population	New or Updated Analysis
14.2.2.1.6	Analysis of Frequency of Pulmonary Exacerbation During Period 1 by i.v. Vancomycin use during Period 1 Subjects <= 21 Years	ITT Population	
14.2.2.1.7	Analysis of Frequency of Pulmonary Exacerbation During Period 1 by i.v. Vancomycin use during Period 1 Subjects > 21 Years	ITT Population	
14.2.2.2.1	Summary of Frequency of Pulmonary Exacerbation by Period Subjects ≤ 21 Years	ITT Population	
14.2.2.2.2	Summary of Frequency of Pulmonary Exacerbation by Period Subjects > 21 Years	ITT Population	
14.2.2.3.1	Summary of Frequency of Pulmonary Exacerbation by Period and Trikafta use at Baseline or During Period 1 Subjects ≤ 21 Years	ITT Population	
14.2.2.3.2	Summary of Frequency of Pulmonary Exacerbation by Period and Trikafta use at Baseline or During Period 1 Subjects > 21 Years	ITT Population	
14.2.2.4.1	Summary of Frequency of Pulmonary Exacerbation by Period and Baseline FEV_1 Subjects ≤ 21 Years	ITT Population	
14.2.2.4.2	Summary of Frequency of Pulmonary Exacerbation by Period and Baseline FEV_1 Subjects > 21 Years	ITT Population	
14.2.2.5.1	Summary of Frequency of Pulmonary Exacerbation by Period and Prior Exacerbations Treated with Antibiotics During the Previous 12 Months Subjects ≤ 21 Years	ITT Population	
14.2.2.5.2	Summary of Frequency of Pulmonary Exacerbation by Period and Prior Exacerbations Treated with Antibiotics During the Previous 12 Months Subjects > 21 Years	ITT Population	

Table Number	Table Title	Population	New or Updated Analysis
14.2.2.6.1	Summary of Frequency of Pulmonary Exacerbation by Period and P. Aeruginosa Treatment Subjects ≤ 21 Years	ITT Population	
14.2.2.6.2	Summary of Frequency of Pulmonary Exacerbation by Period and P. Aeruginosa Treatment Subjects > 21 Years	ITT Population	
14.2.3.1.1	Analysis of Time to First Pulmonary Exacerbation During Period 1 Subjects ≤ 21 Years	ITT Population	
14.2.3.1.1.1	Analysis of Time to First Pulmonary Exacerbation During Period 1 using Strata as Reported in Database Subjects ≤ 21 Years	ITT Population	
14.2.3.1.2	Analysis of Time to First Pulmonary Exacerbation During Period 1 Subjects > 21 Years	ITT Population	
14.2.3.1.3	Analysis of Time to First Pulmonary Exacerbation During Period 1 Subjects ≤ 21 Years	Per-Protocol Population	
14.2.3.1.4	Analysis of Time to First Pulmonary Exacerbation During Period 1 Subjects ≤ 21 Years with no Trikafta use at Baseline or During Period 1	ITT Population	
14.2.3.1.5	Analysis of Time to First Pulmonary Exacerbation During Period 1 Subjects > 21 Years with no Trikafta use at Baseline or During Period 1	ITT Population	
14.2.3.1.6	Analysis of Time to First Pulmonary Exacerbation During Period 1 by i.v. Vancomycin use during Period 1 Subjects ≤ 21 Years	ITT Population	
14.2.3.1.7	Analysis of Time to First Pulmonary Exacerbation During Period 1 by i.v. Vancomycin use during Period 1 Subjects > 21 Years	ITT Population	
14.2.3.1.8	Kaplan-Meier Life Table for Time to First Pulmonary Exacerbation During Period 1 Subjects ≤ 21 Years	ITT Population	

Table Number	Table Title	Population	New or Updated Analysis
14.2.3.1.9	Kaplan-Meier Life Table for Time to First Pulmonary Exacerbation During Period 1 Subjects > 21 Years	ITT Population	
14.2.3.2.1	Summary of Time to First Pulmonary Exacerbation During Period 1 Subjects ≤ 21 Years	ITT Population	
14.2.3.2.2	Summary of Time to First Pulmonary Exacerbation During Period 1 Subjects > 21 Years	ITT Population	
14.2.3.3.1	Summary of Time to First Pulmonary Exacerbation During Period 1 by Trikafta use at Baseline or During Period 1 Subjects ≤ 21 Years	ITT Population	
14.2.3.3.2	Summary of Time to First Pulmonary Exacerbation During Period 1 by Trikafta use at Baseline or During Period 1 Subjects > 21 Years	ITT Population	
14.2.3.4.1	Summary of Time to First Pulmonary Exacerbation During Period 1 by Baseline FEV_1 Subjects ≤ 21 Years	ITT Population	
14.2.3.4.2	Summary of Time to First Pulmonary Exacerbation During Period 1 by Baseline FEV_1 Subjects > 21 Years	ITT Population	
14.2.3.5.1	Summary of Time to First Pulmonary Exacerbation During Period 1 by Prior Exacerbations Treated with Antibiotics During the Previous 12 Months Subjects ≤ 21 Years	ITT Population	
14.2.3.5.2	Summary of Time to First Pulmonary Exacerbation During Period 1 by Prior Exacerbations Treated with Antibiotics During the Previous 12 Months Subjects > 21 Years	ITT Population	
14.2.3.6.1	Summary of Time to First Pulmonary Exacerbation During Period 1 by P. Aeruginosa Treatment Subjects ≤ 21 Years	ITT Population	

Table Number	Table Title	Population	New or Updated Analysis
14.2.3.6.2	Summary of Time to First Pulmonary Exacerbation During Period 1 by P. Aeruginosa Treatment Subjects > 21 Years	ITT Population	
14.2.4.1.1	Analysis of Number of Successful Response Cycles During Period 1 Subjects ≤ 21 Years	ITT Population	
14.2.4.1.1.1	Analysis of Number of Successful Response Cycles During Period 1 using Strata as Reported in Database Subjects ≤ 21 Years	ITT Population	
14.2.4.1.1.2	Analysis of Number of Successful Response Cycles During Period 1 Original Planned Analysis Subjects ≤ 21 Years	ITT Population	
14.2.4.1.2	Analysis of Number of Successful Response Cycles During Period 1 Subjects > 21 Years	ITT Population	
14.2.4.1.3	Analysis of Number of Successful Response Cycles During Period 1 Subjects ≤ 21 Years	Per-Protocol Population	
14.2.4.1.4	Analysis of Number of Successful Response Cycles During Period 1 Subjects ≤ 21 Years with no Trikafta use at Baseline or During Period 1	ITT Population	
14.2.4.1.5	Analysis of Number of Successful Response Cycles During Period 1 Subjects > 21 Years with no Trikafta use at Baseline or During Period 1	ITT Population	
14.2.4.2.1	Summary of Number of Successful Response Cycles During Period 1 by Baseline FEV_1 Subjects ≤ 21 Years	ITT Population	
14.2.4.1.6	Analysis of Number of Successful Response Cycles During Period 1 by i.v. Vancomycin use during Period 1 Subjects ≤ 21 Years	ITT Population	
14.2.4.1.7	Analysis of Number of Successful Response Cycles During Period 1 by i.v. Vancomycin use during Period 1 Subjects > 21 Years	ITT Population	

Table Number	Table Title	Population	New or Updated Analysis
14.2.4.2.2	Summary of Number of Successful Response Cycles During Period 1 by Baseline FEV_1 Subjects > 21 Years	ITT Population	
14.2.4.3.1	Summary of Number of Successful Response Cycles During Period 1 by Prior Exacerbations Treated with Antibiotics During the Previous 12 Months Subjects ≤ 21 Years	ITT Population	
14.2.4.3.2	Summary of Number of Successful Response Cycles During Period 1 by Prior Exacerbations Treated with Antibiotics During the Previous 12 Months Subjects > 21 Years	ITT Population	
14.2.4.4.1	Summary of Number of Successful Response Cycles During Period 1 by P. Aeruginosa Treatment Subjects ≤ 21 Years	ITT Population	
14.2.4.4.2	Summary of Number of Successful Response Cycles During Period 1 by P. Aeruginosa Treatment Subjects > 21 Years	ITT Population	
14.2.5.1.1	Analysis of Relative Change from Baseline in FEV_1 Percent Predicted at Week 4, 12, and Week 20 Subjects ≤ 21 Years	ITT Population	Updated Analysis
14.2.5.1.1.1	Analysis of Relative Change from Baseline in FEV1 Percent Predicted at Week 4, 12, and Week 20 using Strata as Reported in Database Subjects ≤ 21 Years	ITT Population	Updated Analysis
14.2.5.1.1.2	Analysis of Relative Change from Baseline in FEV_1 Percent Predicted at Week 4, 12, and Week 20 Original Planned Analysis Subjects ≤ 21 Years	ITT Population	New (Original 14.2.5.1.1)
14.2.5.1.2	Analysis of Relative Change from Baseline in FEV_1 Percent Predicted at Week 4, 12, and Week 20 Subjects > 21 Years	ITT Population	Updated Analysis

Table Number	Table Title	Population	New or Updated Analysis
14.2.5.1.3	Analysis of Relative Change from Baseline in FEV_1 Percent Predicted at Week 4, 12, and Week 20 Subjects ≤ 21 Years	Per-Protocol Population	Updated Analysis
14.2.5.1.4	Analysis of Relative Change from Baseline in FEV_1 Percent Predicted at Week 4, 12, and Week 20 Subjects ≤ 21 Years with no Trikafta use at Baseline or During Period 1	ITT Population	Updated Analysis
14.2.5.1.5	Analysis of Relative Change from Baseline in FEV_1 Percent Predicted at Week 4, 12, and Week 20 Subjects > 21 Years with no Trikafta use at Baseline or During Period 1	ITT Population	Updated Analysis
14.2.5.1.6	Analysis of Relative Change from Baseline in FEV_1 Percent Predicted at Week 4, 12, and Week 20 by i.v. Vancomycin use during Period 1 Subjects ≤ 21 Years	ITT Population	
14.2.5.1.7	Analysis of Relative Change from Baseline in FEV_1 Percent Predicted at Week 4, 12, and Week 20 by i.v. Vancomycin use during Period 1 Subjects > 21 Years	ITT Population	
14.2.5.2.1	Summary of Relative Change from Baseline in FEV_1 Percent Predicted at Weeks 4, 12, and 20 by Baseline FEV_1 Subjects ≤ 21 Years	ITT Population	
14.2.5.2.2	Summary of Relative Change from Baseline in FEV_1 Percent Predicted at Weeks 4, 12, and 20 by Baseline FEV_1 Subjects > 21 Years	ITT Population	
14.2.5.3.1	Summary of Relative Change from Baseline in FEV_1 Percent Predicted at Weeks 4, 12, and 20 by Prior Exacerbations Treated with Antibiotics During the Previous 12 Months Subjects ≤ 21 Years	ITT Population	

Table Number	Table Title	Population	New or Updated Analysis
14.2.5.3.2	Summary of Relative Change from Baseline in FEV_1 Percent Predicted at Weeks 4, 12, and 20 by Prior Exacerbations Treated with Antibiotics During the Previous 12 Months Subjects > 21 Years	ITT Population	
14.2.5.4.1	Summary of Relative Change from Baseline in FEV_1 Percent Predicted at Weeks 4, 12, and 20 by P. Aeruginosa Treatment Subjects ≤ 21 Years	ITT Population	
14.2.5.4.2	Summary of Relative Change from Baseline in FEV_1 Percent Predicted at Weeks 4, 12, and 20 by P. Aeruginosa Treatment Subjects > 21 Years	ITT Population	
14.2.6.1.1	Analysis of Change from Baseline in the Respiratory Symptoms Domain of the Cystic Fibrosis Questionnaire-Revised (CFQ-R) Parent Scaled Scores and Teen/Adult Scaled Scores at Weeks 4, 12, and 20 Subjects ≤ 21 Years	ITT Population	
14.2.6.1.1.1	Analysis of Change from Baseline in the Respiratory Symptoms Domain of the Cystic Fibrosis Questionnaire-Revised (CFQ-R) Parent Scaled Scores and Teen/Adult Scaled Scores at Weeks 4, 12, and 20 using Strata as Reported in Database Subjects ≤ 21 Years	ITT Population	
14.2.6.1.2	Analysis of Change from Baseline in the Respiratory Symptoms Domain of the Cystic Fibrosis Questionnaire-Revised (CFQ-R) Parent Scaled Scores at Weeks 4, 12, and 20 Subjects ≤ 13 Years	ITT Population	
14.2.6.1.3	Analysis of Change from Baseline in the Respiratory Symptoms Domain of the Cystic Fibrosis Questionnaire-Revised (CFQ-R) Teen/Adult Scaled Scores at Weeks 4, 12, and 20 13 Years < Subjects ≤ 21 Years	ITT Population	

Table Number	Table Title	Population	New or Updated Analysis
14.2.6.1.4	Analysis of Change from Baseline in the Respiratory Symptoms Domain of the Cystic Fibrosis Questionnaire-Revised (CFQ-R) Teen/Adult Scaled Scores at Weeks 4, 12, and 20 Subjects > 21 Years	ITT Population	
14.2.6.1.5	Analysis of Change from Baseline in the Respiratory Symptoms Domain of the Cystic Fibrosis Questionnaire-Revised (CFQ-R) Parent Scaled Scores and Teen/Adult Scaled Scores at Weeks 4, 12, and 20 Subjects ≤ 21 Years	Per-Protocol Population	
14.2.6.1.6	Analysis of Change from Baseline in the Respiratory Symptoms Domain of the Cystic Fibrosis Questionnaire-Revised (CFQ-R) Parent Scaled Scores at Weeks 4, 12, and 20 Subjects ≤ 13 Years	Per-Protocol Population	
14.2.6.1.7	Analysis of Change from Baseline in the Respiratory Symptoms Domain of the Cystic Fibrosis Questionnaire-Revised (CFQ-R) Teen/Adult Scaled Scores at Weeks 4, 12, and 20 13 Years < Subjects ≤ 21 Years	Per-Protocol Population	
14.2.6.1.8	Analysis of Change from Baseline in the Respiratory Symptoms Domain of the Cystic Fibrosis Questionnaire-Revised (CFQ-R) Parent Scaled Scores and Teen/Adult Scaled Scores at Weeks 4, 12, and 20 Subjects ≤ 21 Years with no Trikafta use at Baseline or During Period 1	ITT Population	
14.2.6.1.9	Analysis of Change from Baseline in the Respiratory Symptoms Domain of the Cystic Fibrosis Questionnaire-Revised (CFQ-R) Parent Scaled Scores at Weeks 4, 12, and 20 Subjects ≤ 13 Years with no Trikafta use at Baseline or During Period 1	ITT Population	

Table Number	Table Title	Population	New or Updated Analysis
14.2.6.1.10	Analysis of Change from Baseline in the Respiratory Symptoms Domain of the Cystic Fibrosis Questionnaire-Revised (CFQ-R) Teen/Adult Scaled Scores at Weeks 4, 12, and 20 13 Years < Subjects ≤ 21 Years with no Trikafta use at Baseline or During Period 1	ITT Population	
14.2.6.1.11	Analysis of Change from Baseline in the Respiratory Symptoms Domain of the Cystic Fibrosis Questionnaire-Revised (CFQ-R) Teen/Adult Scaled Scores at Weeks 4, 12, and 20 Subjects > 21 Years with no Trikafta use at Baseline or During Period 1	ITT Population	
14.2.6.1.12	Analysis of Change from Baseline in the Respiratory Symptoms Domain of the Cystic Fibrosis Questionnaire-Revised (CFQ-R) Teen/Adult Scaled Scores at Weeks 4, 12, and 20 by i.v. Vancomycin use during Period 1 Subjects ≤ 13 Years	ITT Population	
14.2.6.1.13	Analysis of Change from Baseline in the Respiratory Symptoms Domain of the Cystic Fibrosis Questionnaire-Revised (CFQ-R) Teen/Adult Scaled Scores at Weeks 4, 12, and 20 by i.v. Vancomycin use during Period 1 13 Years < Subjects ≤ 21 Years	ITT Population	
14.6.1.14	Analysis of Change from Baseline in the Respiratory Symptoms Domain of the Cystic Fibrosis Questionnaire-Revised (CFQ-R) Teen/Adult Scaled Scores at Weeks 4, 12, and 20 by i.v. Vancomycin use during Period 1 Subjects > 21 Years	ITT Population	
14.2.6.2.1	Analysis of Change from Baseline in the Cystic Fibrosis Questionnaire-Revised (CFQ-R) Parent Scaled Scores and Teen/Adult Scaled Scores at Weeks 4, 12, and 20 Subjects ≤ 21 Years	ITT Population	

Table Number	Table Title	Population	New or Updated Analysis
14.2.6.2.2	Analysis of Change from Baseline in the Cystic Fibrosis Questionnaire-Revised (CFQ-R) Parent Scaled Scores at Weeks 4, 12, and 20 Subjects ≤ 13 Years	ITT Population	
14.2.6.2.3	Analysis of Change from Baseline in the Cystic Fibrosis Questionnaire-Revised (CFQ-R) Teen/Adult Scaled Scores at Weeks 4, 12, and 20 13 Years < Subjects ≤ 21 Years	ITT Population	
14.2.6.2.4	Analysis of Change from Baseline in the Cystic Fibrosis Questionnaire-Revised (CFQ-R) Teen/Adult Scaled Scores at Weeks 4, 12, and 20 Subjects > 21 Years	TT Population	
14.2.6.3.1	Analysis of Change from Baseline in the Cystic Fibrosis Questionnaire-Revised (CFQ-R) Parent Scaled Scores and Teen/Adult Scaled Scores at Weeks 4, 12, and 20 Subjects ≤ 21 Years with no Trikafta use at Baseline or During Period 1	ITT Population	
14.2.6.3.2	Analysis of Change from Baseline in the Cystic Fibrosis Questionnaire-Revised (CFQ-R) Parent Scaled Scores at Weeks 4, 12, and 20 Subjects ≤ 13 Years with no Trikafta use at Baseline or During Period 1	ITT Population	
14.2.6.3.3	Analysis of Change from Baseline in the Cystic Fibrosis Questionnaire-Revised (CFQ-R) Teen/Adult Scaled Scores at Weeks 4, 12, and 20 13 Years < Subjects ≤ 21 Years with no Trikafta use at Baseline or During Period 1	ITT Population	
14.2.6.3.4	Analysis of Change from Baseline in the Cystic Fibrosis Questionnaire-Revised (CFQ-R) Teen/Adult Scaled Scores at Weeks 4, 12, and 20 Subjects > 21 Years with no Trikafta use at Baseline or During Period 1	TT Population	

Table Number	Table Title	Population	New or Updated Analysis
14.2.6.4.1	Summary of Actual and of Change from Baseline in the Cystic Fibrosis Questionnaire-Revised (CFQ-R) Parent Scaled Scores by Period Subjects ≤ 13 Years	ITT Population	
14.2.6.4.2	Summary of Actual and of Change from Baseline in the Cystic Fibrosis Questionnaire-Revised (CFQ-R) Teen/Adult Scaled Scores by Period 13 Years < Subjects ≤ 21 Years	ITT Population	
14.2.6.4.3	Summary of Actual and of Change from Baseline in the Cystic Fibrosis Questionnaire-Revised (CFQ-R) Teen/Adult Scaled Scores by Period Subjects > 21 Years	TT Population	
14.2.6.5.1	Summary of Actual and of Change from Baseline in the Cystic Fibrosis Questionnaire-Revised (CFQ-R) Parent Scaled Scores by Period and Trikafta use at Baseline or During Period 1 Subjects ≤ 13 Years	ITT Population	
14.2.6.5.2	Summary of Actual and of Change from Baseline in the Cystic Fibrosis Questionnaire-Revised (CFQ-R) Teen/Adult Scaled Scores by Period and Trikafta use at Baseline or During Period 1 13 Years < Subjects ≤ 21 Years	ITT Population	
14.2.6.5.3	Summary of Actual and of Change from Baseline in the Cystic Fibrosis Questionnaire-Revised (CFQ-R) Teen/Adult Scaled Scores by Period and Trikafta use at Baseline or During Period 1 Subjects > 21 Years	TT Population	
14.2.6.6.1	Summary of Actual and of Change from Baseline in the Cystic Fibrosis Questionnaire-Revised (CFQ-R) Parent Scaled Scores by Period and Baseline FEV1 Subjects ≤ 13 Years	ITT Population	

Table Number	Table Title	Population	New or Updated Analysis
14.2.6.6.2	Summary of Actual and of Change from Baseline in the Cystic Fibrosis Questionnaire-Revised (CFQ-R) Teen/Adult Scaled Scores by Period and Baseline FEV1 13 Years < Subjects ≤ 21 Years	ITT Population	
14.2.6.6.3	Summary of Actual and of Change from Baseline in the Cystic Fibrosis Questionnaire-Revised (CFQ-R) Teen/Adult Scaled Scores by Period and Baseline FEV1 Subjects > 21 Years	TT Population	
14.2.6.7.1	Summary of Actual and of Change from Baseline in the Cystic Fibrosis Questionnaire-Revised (CFQ-R) Parent Scaled Scores by Period and Prior Exacerbations Treated with Antibiotics during the Previous 12 Months Subjects ≤ 13 Years	ITT Population	
14.2.6.7.2	Summary of Actual and of Change from Baseline in the Cystic Fibrosis Questionnaire-Revised (CFQ-R) Teen/Adult Scaled Scores by Prior Exacerbations Treated with Antibiotics during the Previous 12 Months 13 Years < Subjects ≤ 21 Years	ITT Population	
14.2.6.7.3	Summary of Actual and of Change from Baseline in the Cystic Fibrosis Questionnaire-Revised (CFQ-R) Teen/Adult Scaled Scores by Period and Prior Exacerbations Treated with Antibiotics during the Previous 12 Months Subjects > 21 Years	TT Population	
14.2.6.8.1	Summary of Actual and of Change from Baseline in the Cystic Fibrosis Questionnaire-Revised (CFQ-R) Parent Scaled Scores by Period and P. aeruginosa Treatment Subjects ≤ 13 Years	ITT Population	

Table Number	Table Title	Population	New or Updated Analysis
14.2.6.8.2	Summary of Actual and of Change from Baseline in the Cystic Fibrosis Questionnaire-Revised (CFQ-R) Teen/Adult Scaled Scores by Period and P. aeruginosa Treatment 13 Years < Subjects ≤ 21 Years	ITT Population	
14.2.6.8.3	Summary of Actual and of Change from Baseline in the Cystic Fibrosis Questionnaire-Revised (CFQ-R) Teen/Adult Scaled Scores by Period and P. aeruginosa Treatment Subjects > 21 Years	TT Population	
14.2.7.1.1	Analysis of Change from Baseline in Chronic Respiratory Symptom Score (CFRSD-CRISS) Scores at Weeks 4, 12, and 20 Subjects ≤ 21 Years	ITT Population	
14.2.7.1.1.1	Analysis of Change from Baseline in Chronic Respiratory Symptom Score (CFRSD-CRISS) Scores at Weeks 4, 12, and 20 using Strata as Reported in Database Subjects ≤ 21 Years	ITT Population	
14.2.7.1.2	Analysis of Change from Baseline in Chronic Respiratory Symptom Score (CFRSD-CRISS) Scores at Weeks 4, 12, and 20 Subjects > 21 Years	ITT Population	
14.2.7.1.3	Analysis of Change from Baseline in Chronic Respiratory Symptom Score (CFRSD-CRISS) Scores at Weeks 4, 12, and 20 Subjects ≤ 21 Years	Per-Protocol Population	
14.2.7.1.4	Analysis of Change from Baseline in Chronic Respiratory Symptom Score (CFRSD-CRISS) Scores at Weeks 4, 12, and 20 Subjects ≤ 21 Years with no Trikafta use at Baseline or During Period 1	ITT Population	
14.2.7.1.5	Analysis of Change from Baseline in Chronic Respiratory Symptom Score (CFRSD-CRISS) Scores at Weeks 4, 12, and 20 Subjects > 21 Years with no Trikafta use at Baseline or During Period 1	ITT Population	

Table Number	Table Title	Population	New or Updated Analysis
14.2.7.1.6	Analysis of Change from Baseline in Chronic Respiratory Symptom Score (CFRSD-CRISS) Scores at Weeks 4, 12, and 20 by i.v. Vancomycin use during Period 1 Subjects ≤ 21 Years	ITT Population	
14.2.7.1.7	Analysis of Change from Baseline in Chronic Respiratory Symptom Score (CFRSD-CRISS) Scores at Weeks 4, 12, and 20 by i.v. Vancomycin use during Period 1 Subjects> 21 Years	ITT Population	
14.2.7.2.1	Summary of Actual and Change from Baseline in Chronic Respiratory Symptom Score (CFRSD-CRISS) Scores by Period Subjects ≤ 21 Years	ITT Population	
14.2.7.2.2	Summary of Actual and Change from Baseline in Chronic Respiratory Symptom Score (CFRSD-CRISS) Scores by Period Subjects > 21 Years	ITT Population	
14.2.7.3.1	Summary of Actual and Change from Baseline in Chronic Respiratory Symptom Score (CFRSD-CRISS) Scores by Period and Trikafta use at Baseline or During Period 1 Subjects ≤ 21 Years	ITT Population	
14.2.7.3.2	Summary of Actual and Change from Baseline in Chronic Respiratory Symptom Score (CFRSD-CRISS) Scores by Period and Trikafta use at Baseline or During Period 1 Subjects > 21 Years	ITT Population	
14.2.7.4.1	Summary of Actual and Change from Baseline in Chronic Respiratory Symptom Score (CFRSD-CRISS) Scores by Period and Baseline FEV_1 Subjects ≤ 21 Years	ITT Population	
14.2.7.4.2	Summary of Actual and Change from Baseline in Chronic Respiratory Symptom Score (CFRSD-CRISS) Scores by Period and Baseline FEV_1 Subjects > 21 Years	ITT Population	

Table Number	Table Title	Population	New or Updated Analysis
14.2.7.5.1	Summary of Actual and Change from Baseline in Chronic Respiratory Symptom Score (CFRSD-CRISS) Scores by Period and Prior Exacerbations Treated with Antibiotics During the Previous 12 Months Subjects ≤ 21 Years	ITT Population	
14.2.7.5.2	Summary of Actual and Change from Baseline in Chronic Respiratory Symptom Score (CFRSD-CRISS) Scores by Period and Prior Exacerbations Treated with Antibiotics During the Previous 12 Months Subjects > 21 Years	ITT Population	
14.2.7.6.1	Summary of Actual and Change from Baseline in Chronic Respiratory Symptom Score (CFRSD-CRISS) Scores by Period and P. Aeruginosa Treatment Subjects ≤ 21 Years	ITT Population	
14.2.7.6.2	Summary of Actual and Change from Baseline in Chronic Respiratory Symptom Score (CFRSD-CRISS) Scores by Period and P. Aeruginosa Treatment Subjects > 21 Years	ITT Population	
14.2.8.1.1	Analysis of Area Under the FEV1–time Profile Subjects ≤ 21 Years	ITT Population	Updated Analysis
14.2.8.1.1.1	Analysis of Area Under the FEV1–time Profile using Strata as Reported in Database Subjects ≤ 21 Years	ITT Population	Updated Analysis
14.2.8.1.1.2	Analysis of Area Under the FEV1–time Profile Original Planned Analysis Subjects ≤ 21 Years	ITT Population	New (Original 14.2.8.1.1)
14.2.8.1.2	Analysis of Area Under the FEV1–time Profile Subjects > 21 Years	ITT Population	Updated Analysis
14.2.8.1.3	Analysis of Area Under the FEV1–time Profile Subjects ≤ 21 Years	Per-Protocol Population	Updated Analysis

Table Number	Table Title	Population	New or Updated Analysis
14.2.8.1.4	Analysis of Area Under the FEV1–time Profile Subjects ≤ 21 Years with no Trikafta use at Baseline or During Period 1	ITT Population	Updated Analysis
14.2.8.1.5	Analysis of Area Under the FEV1–time Profile Subjects > 21 Years with no Trikafta use at Baseline or During Period 1	ITT Population	Updated Analysis
14.2.8.1.6	Analysis of Area Under the FEV1–time Profile by i.v. Vancomycin use during Period 1 Subjects ≤ 21 Years	ITT Population	
14.2.8.1.7	Analysis of Area Under the FEV1–time Profile by i.v. Vancomycin use during Period 1 Subjects > 21 Years	ITT Population	
14.2.8.2.1	Summary of Area Under the FEV1–time Profile by Period Subjects ≤ 21 Years	ITT Population	
14.2.8.2.2	Summary of Area Under the FEV1–time Profile by Period Subjects > 21 Years	ITT Population	
14.2.8.3.1	Summary of Area Under the FEV1–time Profile by Period and Trikafta use at Baseline or During Period 1 Subjects ≤ 21 Years	ITT Population	
14.2.8.3.2	Summary of Area Under the FEV1–time Profile by Period and Trikafta use at Baseline or During Period 1 Subjects > 21 Years	ITT Population	
14.2.8.4.1	Summary of Area Under the FEV1–time Profile by Period and Baseline FEV_1 Subjects ≤ 21 Years	ITT Population	
14.2.8.4.2	Summary of Area Under the FEV1–time Profile by Period and Baseline FEV_1 Subjects > 21 Years	ITT Population	

Table Number	Table Title	Population	New or Updated Analysis
14.2.8.5.1	Summary of Area Under the FEV1–time Profile by Period and Prior Exacerbations Treated with Antibiotics During the Previous 12 Months Subjects ≤ 21 Years	ITT Population	
14.2.8.5.2	Summary of Area Under the FEV1–time Profile by Period and Prior Exacerbations Treated with Antibiotics During the Previous 12 Months Subjects > 21 Years	ITT Population	
14.2.8.6.1	Summary of Area Under the FEV1–time Profile by Period and P. Aeruginosa Treatment Subjects ≤ 21 Years	ITT Population	
14.2.8.6.2	Summary of Area Under the FEV1–time Profile by Period and P. Aeruginosa Treatment Subjects > 21 Years	ITT Population	

Note: New or Updated Analysis column indicates a table as either New (new table number and title) or Updated Analysis (Same table title, number and design, but a change in analysis due to the COVID-19 epidemic). If there is no change in a table or the presented analysis, this column is left blank.