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

NCT03181932

18 April 2018

Clinical Study Protocol

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

Product Name:	**AeroVanc (vancomycin hydrochloride inhalation powder), 30 mg twice daily (BID)**
Indication:	**Methicillin-resistant *Staphylococcus aureus* lung infection in patients with cystic fibrosis**
Phase:	**III**
Sponsor:	**Savara Inc.** **6836 Bee Caves Rd., Building III** **Suite 200** **Austin, TX 78746**
Date of Protocol:	**18-Apr-2018**
Savara Document Number:	**D-027**
Version:	2

Protocol Approval Signatures

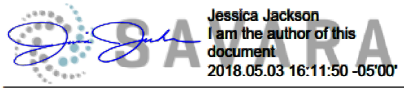
Protocol Title: A Phase III, randomized, double-blind, placebo-controlled study of AeroVanc for the treatment of persistent methicillin-resistant *Staphylococcus aureus* lung infection in cystic fibrosis patients

Protocol Number: SAV005-04

This study will be conducted in compliance with the clinical study protocol (and amendments), International Conference on Harmonization (ICH) guidelines for current Good Clinical Practice (cGCP) and applicable regulatory requirements

APPROVAL SIGNATURES

Prepared By:

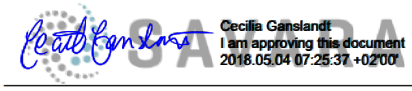


Jessica I. Jackson

Director, Clinical Operations

Savara, Inc.

Approved By:



Cecilia Ganslandt, MD

Head of Clinical Development

Savara, Inc.

Taneli Jouhikainen, MD

Chief Operating Officer

Savara, Inc.

PROTOCOL AGREEMENT
Amendment #1

I have read the protocol specified below. In my formal capacity as Investigator, my duties include ensuring the safety of the study subjects enrolled under my supervision and providing Savara with complete and timely information, as outlined in the protocol. It is understood that all information pertaining to the study will be held strictly confidential and that this confidentiality requirement applies to all study staff at this site. Furthermore, on behalf of the study staff and myself, I agree to maintain the procedures required to carry out the study in accordance with accepted GCP principles and to abide by the terms of this protocol.

Protocol Number: SAV005-04

Protocol Title: 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

Protocol Date: 18-Apr-2018

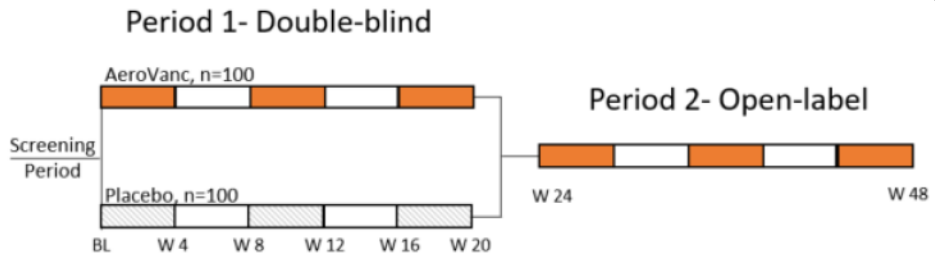
_____ _____
Investigator Signature *Date*

_____
Print Name and Title

Site # _____
PI Name _____
Site Name _____
Address _____
_____
_____
_____
Phone Number _____

SYNOPSIS

Title:	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
Study Drug:	AeroVanc (vancomycin hydrochloride inhalation powder), 30 mg BID
Number of Study Centers:	Approximately 85
Phase:	III
Number of Subjects:	200 subjects (150 subjects ≤ 21 years old, 50 subjects > 21 years old)
Coordinating Investigator:	Patrick Flume, MD
Study Design:	Randomized, multicenter, double-blind, placebo-controlled, parallel-group study to examine the safety and efficacy of AeroVanc in the treatment of persistent Methicillin resistant *Staphylococcus aureus* (MRSA) lung infection in patients diagnosed with cystic fibrosis (CF). 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 period.

	 200 subjects (150 subjects ≤ 21 years old, 50 subjects > 21 years old)
Treatment:	AeroVanc is a powder form of vancomycin, delivered using a reloadable capsule inhaler. The inhalation powder is packaged into capsules with each capsule containing 15 mg of vancomycin. The dose is AeroVanc 30 mg (2 capsules) BID. Alternatively, a subject may be randomized to receive a matching placebo, with equivalent numbers of capsules.
Study Duration:	The duration of study participation for each subject is 50-54 weeks: - Screening period, up to 42 days - Period 1, Double-blind (30 mg AeroVanc or placebo BID) for 3 cycles or 24 weeks - Period 2, Open-label (30 mg AeroVanc BID) for 3 cycles or 24 weeks
Study Population:	**Inclusion Criteria** 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 one of the following: a. Positive sweat chloride test (value ≥ 60 mEq/L), b. Genotype with 2 mutations consistent with CF (i.e., 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).

Study Population:	**Inclusion Criteria (cont)** 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 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.

	Exclusion Criteria 1. Use of anti-MRSA treatments prescribed as maintenance therapy (intravenous [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] $\geq$ 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 study 15. Female with positive pregnancy test result during Screening, pregnant (or intends to become pregnant), lactating or intends to breastfeed during 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 $\geq$ 4x upper limit of normal (ULN), of serum aspartate aminotransferase (AST) or serum alanine aminotransferase (ALT), or known cirrhosis at Screening.

	Exclusion Criteria (Cont.) 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 double-blind period (Period 1).
Primary Efficacy Endpoint:	The primary efficacy endpoint is the mean absolute change from baseline in FEV_1 percent predicted. 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 FEV_1 percent predicted after Cycle 3 will be analyzed. • The primary analysis will be based on the ITT population of all randomized subjects ≤ 21 years of age.
Secondary Efficacy Endpoints:	The following parameters will be analyzed as secondary efficacy endpoints: • 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). If a subject experiences an exacerbation and concomitant antibiotic therapy is given, the subject is considered a failure in that cycle, but the failure does not preclude success in future cycles. **Note:** A response in a cycle is defined by at least a 5 % relative improvement in FEV_1 percent predicted at the end of the respective cycle (Week 4, Week 12, and Week 20). 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. • 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.

Exploratory Efficacy Endpoints:	• 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.
Pharmacokinetics:	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.
Safety:	Safety assessments will be conducted on the safety population (those receiving at least 1 dose of drug) include 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). Potential emergence of additional pathogens in sputum will be assessed.
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 United States Food and Drug Administration (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 3-cycle study, a sample size of 75 subjects per arm will be enrolled 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.
Statistical Methods/Analysis:	All statistical testing will be two-sided and will be performed at the 0.05 significance level. Descriptive statistics will be provided by treatment group at baseline and at each critical time point. Categorical variables will be summarized by counts and by percentage of subjects in corresponding categories. Continuous variables will be summarized with means, standard deviations, medians, minimums, and maximums. The following populations will be used for efficacy analyses: - The ITT population will include all randomized subjects ≤ 21 years of age. - The Per-Protocol (PP) population will include subjects ≤ 21 years of age who adhere to all key protocol procedures, to be specified in a separate Statistical Analysis Plan (SAP).

Efficacy Analysis:	**Analysis of Primary and Secondary Endpoints** Primary and secondary efficacy analyses, for which full control of Type I error will be implemented, will be in the group of patients who are ≤ 21 years of age. The primary efficacy endpoint is the mean absolute change from baseline in FEV_1 percent predicted. 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 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 from Baseline to end of Cycle 2 will be analyzed. Similarly, if the effect after Cycle 2 is statistically significant, then the analysis of Baseline to end of Cycle 3 will be reported. The data will be analyzed using an analysis of covariance model with baseline FEV_1 percent predicted as a covariate and the stratification factors as fixed effects. For confirmation of the primary endpoint, sensitivity analyses will be conducted where missing data will be imputed in different ways. Of the secondary endpoints, 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 and the stratification factors. The number of days from randomization until the date of first exacerbation will be calculated and summarized using a Kaplan-Meier life table presentation. Subjects who do not experience a pulmonary exacerbation prior to discontinuation from the study will be censored at the date of discontinuation of the study. Changes in CFQ-R and CFRSD-CRISS score, and relative change from baseline in FEV_1 percent predicted, will all be analyzed similarly at Week 4, 12, and 20 using an analysis of covariance including baseline covariate and stratification factors. The number of successful response cycles each subject achieves over the 3 cycles of therapy (0, 1, 2 or 3) will be compared using a proportional odds model for ordered categories. Frequency of pulmonary exacerbations will be compared between the groups using a negative binomial model for count data, adjusting for each subject's length of follow-up. The randomization stratification factors will be included in the model as fixed effects. Area under the FEV_1–time profile will be analyzed using analysis of covariance including the patient's baseline FEV_1 and the stratification factors. Type I error rate will be controlled by a sequential testing procedure. For patients who are >21 years of age, the above analyses will be repeated but with an emphasis on estimation of the treatment effect, rather than statistical significance testing. No Type I error control will be used for the analyses of these subjects. No interim analyses are planned.

Safety Analysis	Extent of exposure and dosing compliance will be summarized by treatment group. Adverse events will be mapped to preferred terms and system organ classes using the Medical Dictionary for Regulatory Activities (MedDRA). The incidence of AEs (ever having) and the frequency of AEs (total number) and 95% confidence intervals will be tabulated by treatment group, system organ class, and preferred term. Serious adverse events (SAEs) will be summarized in a similar fashion. Adverse event summaries by severity and relationship to study drug will also be provided. The AE summaries will be presented for all subjects and by the two age groups. Laboratory parameters will be summarized using descriptive statistics at Baseline and at each post-Baseline visit. Changes from Baseline will also be summarized. In addition, shift tables (i.e., 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. Vital signs will be summarized using descriptive statistics at Baseline and at each post-Baseline visit. Changes from Baseline will also be summarized. Electrocardiogram parameters will be summarized using descriptive statistics at Baseline and at each post-Baseline visit where an ECG assessment was made. Changes from Baseline will also be summarized. In addition, shift tables (i.e., normal, not clinically significant [NCS], clinically significant [CS]) at Baseline versus normal, NCS, CS at each post-baseline visit in a 3-by-3 contingency table) will be provided to assess changes from Baseline.

TABLE OF CONTENTS

LISTING OF TABLES

LISTING OF FIGURES

LIST OF ABBREVIATIONS

ß-hCG	Human chorionic gonadotropin beta-subunit
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
ATS	American Thoracic Society
AUC	Area under the curve
B. cepacia	*Burkholderia cepacia*
BID	Bis in die/twice daily
BL	Baseline
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
CAT	Continuing alternating anti-Pseudomonal therapy
CF	Cystic fibrosis
CFRSD-CRISS	Cystic Fibrosis Respiratory Symptom Diary-Chronic Respiratory Symptom Score
CFTR	Cystic fibrosis transmembrane conductance regulator
CFU	Colony forming units
CFU/g	Colony forming units per gram
CI	Confidence interval
°C	Degrees Celsius
C_{max}	Maximum concentration
CNS	Central nervous system
CPMP	Committee for Proprietary Medicinal Products
CRF	Case report form
CRO	Contract research organization
CV	Coefficient of variation
DLT	Dose Limiting Toxicity
DMC	Data Monitoring Committee
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
EDC	Electronic Data Capture
e-Diary	Electronic diary
EDTA	Ethylene diaminetetra-acetic acid
ELF	Epithelial lining fluid
ET	Early termination
FDA	Food and Drug Administration
FEF	Forced expiratory flow
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GCP	Good Clinical Practice
GGT	Gamma glutamyltransferase
GI	Gastrointestinal
GLI	Global Lung Function Initiative
GLP	Good Laboratory Practices

cGMP	Current Good Manufacturing Practice
hr	Hour(s)
HBS Ag	Hepatitis B surface antigen
HCV Ab	Hepatitis C antibody
HEENT	Head, eyes, ears, nose, and throat
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HPLC	High-performance liquid chromatography
HPMC	(Hydroxypropyl)methyl cellulose
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	Intent to Treat
IUD	Intrauterine device
IV	Intravenous
IWR	Interactive Web Response
kg	Kilogram
LDH	Lactate dehydrogenase
MCH	Mean cell hemoglobin
MCHC	Mean cell hemoglobin concentration
MCV	Mean cell volume
MD	Medical Doctor
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MIC	Mean inhibitory concentration
µg	Microgram
min	Minute(s)
mITT	Modified Intent-to-Treat
mmHg	Millimeter(s) of mercury
MRSA	Methicillin resistant- *Staphylococcus aureus*
n	Number of subjects with an observation
N	Number of subjects in the dataset or population
ng	Nanogram
NOAEL	No observed adverse effect level
PA	*Pseudomonas Aeruginosa*
PEF	Peak expiratory flow
PEFR	Peak expiratory flow rate
PFRD	Peak Flow Recording Device
PFT	Pulmonary function test
PK	Pharmacokinetic(s)
PP	Per protocol
RBC	Red blood cell
REB	Research Ethics Board
s	Second(s)
S. aureus	*Staphylococcus aureus*
SAE	Serious adverse event
SAP	Statistical Analysis Plan

SD	Standard deviation
SDV	Source data verified
SOP	Standard Operating Procedure
SUSAR	Suspected unexpected serious adverse reaction
TDN	Therapeutics Development Network
TEAE	Treatment-emergent adverse event(s)
TOBI	Tobramycin inhalation solution
ULN	Upper limit of normal
US	United States
USP	US Pharmacopeial Convention
VISA	Vancomycin intermediate resistant *Staphylococcus aureus*
VRSA	Vancomycin resistant *Staphylococcus aureus*
WBC	White blood cell
WMA	World Medical Association

1 BACKGROUND

Cystic fibrosis (CF) is a genetic disease characterized, in part, by the prevalence of thick, sticky mucus produced in the lung, frequent lung infections, and a resultant decline in pulmonary function. The chronic lung infections expedite the structural damage of the lungs contributing to the premature death of the patients. In the past decade, persistent MRSA lung infection has become increasingly common in patients with CF, with a prevalence of about 26% (approx. 8,000 patients) in the United States (CFF Patient Registry, 2014). Persistent MRSA infection in patients with CF has been associated with increased use of intravenous (IV) antibiotics (Miall LS, 2001) (Elizur A, 2007), increased hospitalizations (Vanderhelst E, 2012), a faster decline of lung function (Vanderhelst E, 2012) (Dasenbrook EC M. C.-W., 2008), as well as shortened life-expectancy, (Dasenbrook EC C. W., 2010).

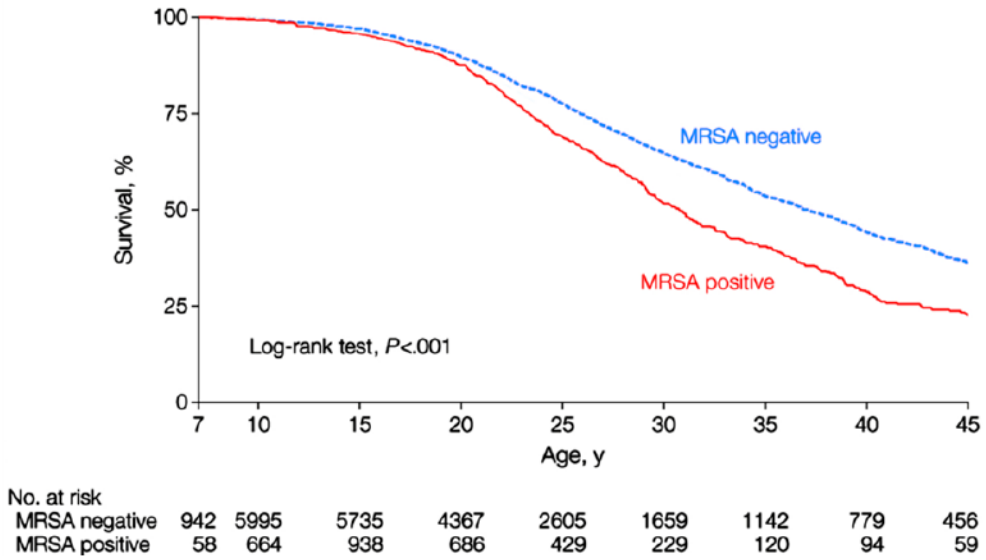


Figure 1: Survival according to MRSA infection status in CF patients (Dasenbrook, et al., 2010, reprinted with permission, Copyright © (2010) JAMA).

Persistent MRSA lung infection in CF patients is difficult to eradicate or manage using oral or IV antibiotics, and there is no standard of care to manage the infection in CF patients (Zobell JT, 2015) despite the high need. In contrast to the established treatment of *P. aeruginosa* infection with inhaled antibiotics, there is no FDA-approved inhaled antibiotic treatment available for MRSA infection. Vancomycin is the drug of choice for the treatment of MRSA infection, but it is only available in IV form. While highly effective against gram positive bacteria, chronic use of IV vancomycin may be associated with systemic toxicity, especially renal toxicity and ototoxicity. Due to its IV use and potential for toxicity, IV vancomycin use is generally limited to hospital settings. As observed with inhaled anti-Pseudomonal drugs, there may be significant clinical advantage in delivering vancomycin directly to the site of infection in order to maximize the clinical efficacy, reduce systemic exposure and the risk of adverse effects, and to enable convenient use of the product outside of the hospital setting.

Savara has developed a high-performance inhalation powder formulation of vancomycin hydrochloride, AeroVanc, utilizing a conventional capsule inhaler. Vancomycin is a glycopeptide antibiotic effective against most gram-positive bacteria, and has been extensively used for the treatment of MRSA infections for over five decades. The proposed indication of AeroVanc is treatment of CF patients with persistent MRSA infection of the lungs. The aim of AeroVanc treatment is infection suppression in order to improve patients' respiratory symptoms, and lung function, and to prolong the time to need of other antibiotics and pulmonary exacerbation. AeroVanc was granted

Orphan Drug designation in September 2012 and Qualified Infectious Disease Product/Fast Track Designation in November 2013 by the FDA.

2 Overview of Non-Clinical Studies

The nonclinical toxicology profile for AeroVanc has been well-characterized in a series of acute and repeated dose inhalation toxicity studies in rats and dogs, as well as in the ICH/FDA prescribed safety pharmacology studies involving the cardiovascular system, pulmonary system and central nervous system (CNS). AeroVanc did not result in any adverse effects in functionality of the cardiovascular system and pulmonary system at any dose level up to 30 mg/kg in beagle dogs, and CNS at any dose level up to 100 mg/kg in Sprague-Dawley rats.

The pivotal Good Laboratory Practice (GLP) toxicology studies consisted of two 28-day inhalation toxicity studies with a 28-day recovery period in dogs and rats, and a 13-week inhalation toxicity study in rats.

Following 28 days of inhalation exposure, there were no indications of systemic toxicity noted in either the rats or dogs. Clinical pathology indices for toxicity in the major organ systems revealed comparable values between air and vehicle control animals and vancomycin-exposed rats and dogs. There were a number of microscopic changes noted along the respiratory tract and in the lungs that represented local irritative effects, adaptive changes, and normal physiological responses to the impaction of particles along the respiratory tract and deposition of particles in the lungs. A 28-day recovery period showed complete to partial reversibility of the findings, with no notable difference between the active dose groups and the vehicle control group when compared to the air control. Based on the results of these 28-day studies, the No Observed Adverse Effect Level (NOAEL) in the rats was 18.6 mg/kg/day and the NOAEL in the dogs was 11.5 mg/kg/day, both NOAEL's representing the mid dose levels used in the respective studies.

Following 13 weeks of inhalation exposure, there were no apparent indications of systemic changes noted in any tissues outside the respiratory tract. Clinical pathology indices were comparable between treated groups and respective air and vehicle control values. Administration of the vehicle (L-Leucine:Trehalose) and the test item, AeroVanc, resulted in vehicle-related and test item-related microscopic changes in the nasal cavity, upper respiratory tract and lungs of animals from the treated groups, and in the nasal cavity in the vehicle treated group. The dose-related findings in the treated groups in the nasal cavity included degeneration of the olfactory epithelial cell/increased eosinophilic droplets. The nasal cavity of the vehicle treated group showed vacuolar degeneration of the olfactory epithelium. The irritation/adaptive changes of the upper respiratory tract (carina, larynx, nasal cavity and nasopharynx) and lungs observed included changes such as squamous metaplasia of the respiratory epithelium in the carina and larynx, erosion/atrophy of the olfactory epithelium and material/exudate/cell debris in lumen of the nasal cavity and goblet cell hyperplasia of the respiratory epithelium of nasal cavity/nasopharynx, enlarged/increased alveolar histiocytes/alveolar histiocytosis (correlated with dose-dependent increases in lung weights and macroscopic finding of pale area/focus in the lungs) and goblet cell hyperplasia/metaplasia with/without cell debris/eosinophilic material in alveolar duct/bronchiolar lumen and perivascular/peribronchiolar cell infiltrate in the lungs. A higher incidence/severity of these findings was noted in the high dose group animals.

After the 4-week recovery period, the test item-related changes (degeneration of the olfactory epithelial cell/increased eosinophilic droplets) as well as the vehicle-related change (vacuolar degeneration of the olfactory epithelium) were still present in the nasal cavity of the recovery animals in the high-dose group animals, but with a lower severity, suggesting an ongoing recovery process (regeneration of the olfactory epithelium). The irritation/adaptive changes of the upper respiratory tract (carina, larynx, nasal cavity and nasopharynx) and lungs showed indications of recovery at various levels, suggesting an ongoing recovery process.

Based on the results of the 13-week study, the NOAEL was considered to be at the achieved dose level of 10.5 mg/kg/day for the rats when dosed for 91 consecutive days by nose-only inhalation.

In conclusion, the nonclinical characterization of AeroVanc powder for inhalation was successfully carried out in a series of GLP repeat dose inhalation toxicity studies in rats and dogs. In addition to determining a NOAEL in both nonclinical species, it was determined that, under the conditions of these studies, the pulmonary delivery of AeroVanc was not associated with any apparent adverse systemic findings as determined by clinical and histopathologic examinations. The changes that were noted were primarily limited to the respiratory tract and lungs and represented local irritative/adaptive changes expected following the exposure to high level of the test article.

3 Overview of Clinical Studies

3.1 Phase I

One Phase I clinical study has been conducted with AeroVanc. When administered to 18 healthy volunteers and 7 subjects with cystic fibrosis in a single escalating dose study, AeroVanc was well tolerated at the highest dose administered, 80 mg. AeroVanc showed a favorable pharmacokinetic (PK) profile, with a relatively slow pulmonary absorption phase (t_{max} of 1.33 hr–2.08 hr), followed by distribution and elimination comparable to the intravenous administration (Figure 2) The mean absolute bioavailability across all AeroVanc doses was 49% (standard deviation [SD] 8%), with no apparent difference observed between the doses. The absolute bioavailability closely corresponds with the pulmonary absorption of vancomycin, considering that vancomycin is not absorbed from the gastrointestinal (GI) tract. The mean C_{max} of AeroVanc after an 80 mg dose was 618 ng/mL, corresponding to approximately 1/5th of the dose adjusted C_{max} after a 250 mg dose of IV vancomycin. The dose linearity of AeroVanc in terms of C_{max} and area under the curve (AUC) values was excellent ($R^2 > 0.99$). In the CF cohorts, all subjects had sputum vancomycin concentrations in high excess of the mean inhibitory concentration (MIC) of vancomycin for MRSA (2 µg/mL) at 1 hr after the administration of AeroVanc with both the low and the high dose (mean of 106 µg/mL, and 261 µg/mL, respectively). At later time points, the concentrations decreased, but on average remained above the MIC values for up to 24 hours. Variability in sputum concentrations was high, as expected (SD for C_{max} 179-190%).

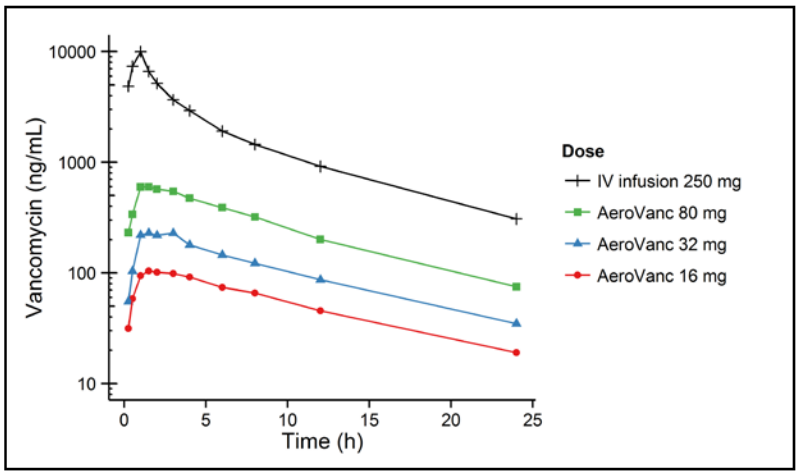


Figure 2: AeroVanc and intravenous vancomycin plasma concentration as a function of time (semi-log) after a single dose administration.

The relatively slow absorption of vancomycin after AeroVanc administration, as well as the relatively slow elimination from the sputum observed in the study are in keeping with the large molecular weight of vancomycin, the vancomycin lung concentrations observed after nebulized vancomycin administration (Shirai et al., 1995), the animal PK information (Valle, 2007), as well as the poor penetration of vancomycin to the epithelial lining fluid (ELF) from the blood observed in human studies (Cruciani et al, 1996; Lamer et al, 1993).

All the adverse events in the healthy volunteers were classified as mild, and all of the events that were considered probably drug-related involved local irritation effects and resolved spontaneously and rapidly (15 min – 60 min). Small reduction in the post-dose FEV_1 (7% – 11%) was observed in 3 subjects after the 80 mg dose. None of the subjects required bronchodilator treatment, and the changes were considered by the Data Safety Monitoring Board (DSMB) to be not clinically significant. In CF subjects, chest congestion and chest tightness were reported by 4 of the 7 subjects, and there appeared to be a slight trend towards more adverse events at the higher dose (80 mg). All reported respiratory events were mild, none of the subjects felt distressed, and the events either did not require treatment or resolved after airway clearance and/or albuterol inhalation. Based on the results, bronchodilator pre-treatment was implemented in subsequent clinical trials. Short-acting bronchodilators have been routinely used as pre-treatment in the published and unpublished studies of aerosolized IV vancomycin as well as inhaled tobramycin and aztreonam studies. Symptomatic bronchoconstriction is rare when subjects are pre-treated with a bronchodilator.

3.2 Phase II

The AeroVanc Phase II clinical study was a randomized, double-blind, placebo-controlled study of a 28-day 32 mg BID or 64 mg BID AeroVanc treatment in 87 CF subjects with persistent MRSA lung infection, conducted at 40 sites in the US. The Coordinating Investigators in the study were Dr. Elliott Dasenbrook (Case Western Reserve University, Cleveland, OH), and Dr. Patrick Flume (Medical University of South Carolina, Charleston, SC). In summary, AeroVanc reduced MRSA density in sputum and showed encouraging trends of improvement in respiratory symptoms, lung function, and prolongation of the time to need of other antibiotics, and time to pulmonary exacerbation, with best responses observed in subjects < 21 years of age. Vancomycin peak and trough concentrations in sputum were in high excess over MICs after multiple dosing in all subjects at both dose levels. The study data favors the selection of the low dose for further development, and selection of FEV_1 based endpoints as the primary endpoints for this Phase III clinical study.

3.2.1 Demographics

Demographics of the Phase II study is demonstrated in Table 1:

Table 1: Phase II Demographics and Characteristics at Baseline (BL).

Treatment	AeroVanc 32 mg Cohort 1		AeroVanc 64 mg Cohort 2		Pooled Cohorts	
	Placebo	AeroVanc	Placebo	AeroVanc	Placebo	AeroVanc
N	**20**	**20**	**23**	**24**	**43**	**44**
Age (mean)	24.6	22.4	27.8	27.8	26.3	25.3
Age (< 21/≥ 21 years)	10/10	10/10	5/18	4/20	15/28	14/30
Sex (m/f)	11/9	7/13	15/8	15/9	26/17	22/22
P. aeruginosa (+/−)	12/8	13/7	13/10	14/10	25/18	27/17
MRSA (log_{10} CFU/mL)	6.78	7.31	7.54	7.24	7.18	7.27
CFRSD-CRISS	31.6	29.1	30.4	27.6	31.0	28.3
FEV_1 percent pred. (%)	55.8	61.1	66.5	56.9	61.5	58.8

3.2.2 MRSA Density

In the Phase II clinical study, quantitative MRSA cultures from spontaneously expectorated sputum samples were used in the primary endpoint of the study. The average baseline values in both active drug cohorts, as well as the placebo cohorts were high, ranging from 6.78 to 7.54 log_{10} CFU/mL, depending on the group (Table 1). A reduction from baseline in MRSA colony forming units (CFU) was observed in both 32 mg and 64 mg dose cohorts in the ITT population (Figure 3), with means of -0.42 log_{10} CFU/mL (32 mg) and -0.60 log_{10} CFU/mL (64 mg). The reductions in the 64 mg active drug cohort and the pooled active drug cohorts were statistically significant (least squares means -0.63 versus 0.16 log_{10} CFU/mL; p=0.0145, and -0.52 versus -0.06 log_{10} CFU/mL; p=0.0312, respectively). No lasting eradications of MRSA were observed.

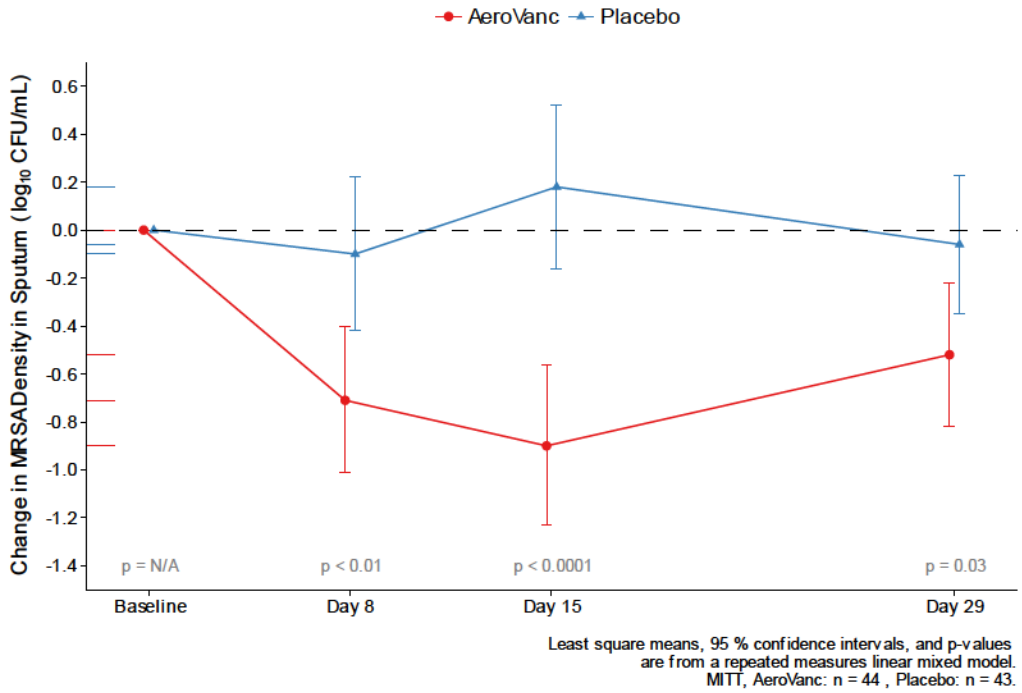


Figure 3:Change in MRSA Density in Sputum in 32 mg and 64 mg Dose Cohorts Pooled.

3.2.3 Plasma and Sputum Pharmacokinetics

Vancomycin peak and trough concentrations at Day 8 and Day 29 in sputum were in very high excess over MICs (mean C_{trough}/MIC ratio > 35) after multiple dosing in all subjects at both dose levels, with apparent dose-dependency, but no notable difference in C_{trough} between the two time points (Figure 4). The generally accepted MIC of vancomycin for MRSA is illustrated by the dotted line, at 2 µg/mL.

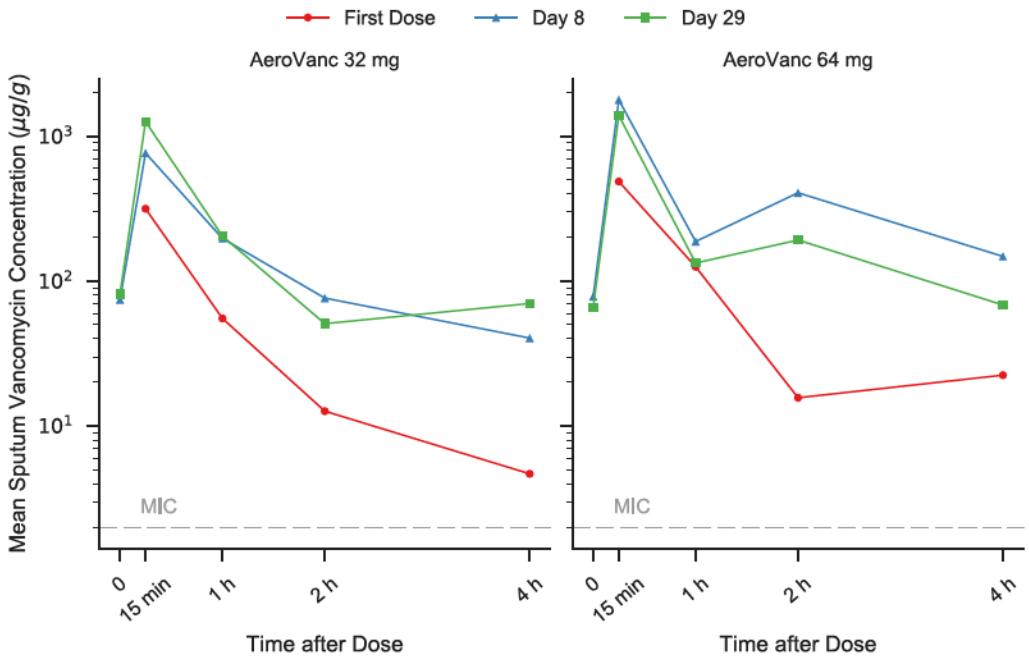


Figure 4: Mean Sputum Concentrations of Vancomycin Following AeroVanc Administration with Visits Overlaid and Separated by Treatment (Semi-log Scale).

3.2.3.1 Pharmacokinetic Analyses

Subject plasma and sputum PK samples were obtained for the measurement of vancomycin levels in a subset of 24 subjects (12 of the first adult subjects treated at each dose level). The predose samples were collected within 60 minutes prior to the start of dosing on Days 1, 8, and 29. Postdose plasma and sputum PK samples were collected 0.25, 1, 2, and 4 hours (all ±10 minutes) Postdose on Days 1, 8, and 29 (Table 2).

Table 2: Plasma PK Parameters.

Mean (CV %) Plasma PK Parameters for AeroVanc						
PK Parameter	Visit 2 (Day 1)		Visit 3 (Day 7-8)		Visit 6 (Day 28-29)	
	32 mg BID	64 mg BID	32 mg BID	64 mg BID	32 mg BID	64 mg BID
Number of Subjects	6	6	6	3	2	2
C_{max} (µg/mL)	0.283 (68.7)	0.589 (37.8)	0.315 (70.5)	0.435 (19.5)	0.266 (NC[b])	0.694 (NC[b])
C_{max}/Dose (µg/mL/mg)	0.00884 (68.7)	0.00920 (37.8)	0.00985 (70.5)	0.00679 (19.5)	0.00833 (NC[b])	0.0108 (NC[b])
T_{max}[a] (h)	1.00 (1.00-2.00)	1.00 (1.00-2.00)	1.00 (0.25-2.00)	1.00 (1.00-4.00)	1.00 (1.00-1.00)	1.5 (1.00-2.00)
C_{trough} (µg/mL)	-	-	0.146 (133)	0.0568 (46.1)[e]	0.0920 (11.4)	0.213 (NC[b])
AUC_{0-4} (h• µg/mL)	0.914 (78.7)	1.73 (33.4)	1.04 (80.2)	1.34 (21.4)	0.880 (NC[b])	2.13 (NC[b])
AUC_{0-4}/Dose (h• µg/mL/mg)	0.0286 (78.7)	0.0271 (33.4)	0.0326 (80.2)	0.0210 (21.4)	0.0275 (NC[b])	0.0333 (NC[b])
C_{max}_Acc[c]	-	-	1.13 (16.7)	0.636 (NC[b])[d]	1.22 (NC[b])	0.937 (NC[b])
AUC_Acc[c]	-	-	1.15 (22.8)	0.695 (NC[b])[d]	1.38 (NC[b])	0.991 (NC[b])

Abbreviations: Acc: accumulation ratio; AUC: area under the concentration-time curve; BID: twice daily; C_{max}: maximum concentration; C_{trough}: concentration at the end of the dosing interval; h: hour; PK: pharmacokinetic(s); T_{max}: time of maximum concentration.

[a] T_{max} was represented as Median (Range)

[b] NC = Statistics not calculated when N<3

[c] C_{max}_Acc and AUC_Acc are accumulation ratios, calculated using PK parameters (C_{max} and AUC_{0-4}) of Visit 3 or Visit 6 divided by that of Visit 2 from the same subject

[d] Number of Subjects = 3

The plasma vancomycin exposure (C_{max} and AUC_{0-4}) was generally dose-proportional for the AeroVanc 32 mg and 64 mg doses, both for single-dose and multiple-dose administration. Mean accumulation ratios of C_{max} and AUC_{0-4} ranged from 1.13 to 1.38 for the 32 mg bid group and ranged from 0.636 to 0.991 for the 64 mg bid group, indicating no notable drug accumulation in plasma over time.

The average sputum pharmacokinetic parameters following 32 mg BID and 64 mg BID AeroVanc administration are presented below in Table 3, separated by visit. The mean C_{max} and AUC_{0-4} values increased over progressive visits. The mean accumulation ratios of C_{max} and AUC_{0-4} ranged from 3.60 to 6.47 for the 32 mg BID group and ranged from 2.09 to 3.14 for the 64 mg BID group, indicating drug accumulation occurred in sputum. In general, there was a proportional increase in vancomycin exposure (C_{max} and AUC_{0-4}) with increasing dose of AeroVanc for single-dose (Visit 2, Baseline, Day 1) and multiple-dose administrations on Visit 3 (Day 8). The exposure appeared somewhat less than dose-proportional on Visit 6 (Day 29), but these estimates are less reliable because only 2 subjects were included in the estimates for each dose group.

Steady state in sputum appeared to have been reached after one week of administration, but because of the small sample size especially at the 64-mg dose after 28 days of dosing, assessment of steady state should be made with caution.

Table 3: Sputum PK Parameters.

Mean (CV %) Sputum PK Parameters for AeroVanc						
PK Parameter	Visit 2 (Day 1)		Visit 3 (Day 7-8)		Visit 6 (Day 28-29)	
	32 mg BID	64 mg BID	32 mg BID	64 mg BID	32 mg BID	64 mg BID
Number of Subjects	6	5	6	3	2	2
C_{max} (µg/g)	316 (67.5)	531 (48.4)	767 (60.7)	1790 (84.1)	1270 (NC[b])	1400 (NC[b])
C_{max}/Dose (µg/g/mg)	9.89 (67.5)	8.29 (48.4)	24.0 (60.7)	27.9 (84.1)	39.5 (NC[b])	21.8 (NC[b])
T_{max}[a] (h)	0.25 (0.25-0.25)	0.25 (0.25-0.25)	0.25 (0.25-0.25)	0.25 (0.25-0.25)	0.25 (0.25-0.25)	0.25 (0.25-0.25)
C_{trough} (µg/g)	-	-	74.5 (165)	119 (80.8)	81.4 (114)[g]	99.0 (NC[b])
C_{trough} /MIC ((µg/g)/ (µg/mL))[f]	-	-	37.3 (165)	59.3 (80.8)	40.7 (114)[g]	49.5 (NC[b])
AUC_{0-4} (h• µg/g)	194 (46.9)	284 (26.1)	647 (67.6)	1430 (91.3)	822 (NC[b])	988 (NC[b])
AUC0-4/Dose (h• µg/g/mg)	6.05 (46.9)	4.44 (26.1)	20.2 (67.6)	22.4 (91.3)	25.7 (NC[b])	15.4 (NC[b])
AUC_{0-12} (h• µg/g)[e]	-	-	1100 (80.3)	2460 (91.9)	1480 (NC[b])	1660 (NC[b])
AUC_{0-12}/MIC ((h•µg/g)/ (µg/mL))[f]	-	-	549 (80.3)	1230 (91.9)	741 (NC[b])	829 (NC[b])
$Cavg_{0-4}$[c] (µg/g)	48.4 (46.9)	71.0 (26.1)	162 (67.6)	358 (91.3)	206 (NC[b])	247 (NC[b])
C_{max}_Acc[d]	-	-	3.60 (94.6)	2.09 (NC[b])	5.96 (NC[b])	3.14 (NC[b])
AUC_Acc[d]	-	-	3.86 (82.2)	2.21 (NC[b])	6.47 (NC[b])	3.12 (NC[b])

Abbreviations: Acc: accumulation ratio; AUC: area under the concentration-time curve; BID: twice daily; Cavg: average concentration; C_{max}: maximum concentration; C_{trough}: concentration at the end of the dosing interval; h: hour; MIC: minimum inhibitory concentration; PK: pharmacokinetic(s); T_{max}: time of maximum concentration.

[a] T_{max} was represented as Median (Range)

[b] NC = Statistics not calculated when N < 3

[c] $Cavg_{0-4}$ is the average concentration of the 4-hour sampling period, calculated by $AUC_{0-4}/4$

[d] C_{max}_Acc and AUC_Acc are accumulation ratios, calculated using PK parameters (C_{max} and AUC_{0-4}) of Visit 3 or Visit 6 divided by that of Visit 2 from the same subject

[e] 12-hour concentration was imputed to the pre-dose value for the calculation of AUC_{0-12} of multiple-dose administration (Visits 3 and 6). (AUC_{0-12} value using imputed 12-hour concentration value is a reasonable estimate if steady-state can be presumed, otherwise AUC_{0-12} is underestimated, and therefore AUC/MIC is a conservative estimate)

[f] MIC = Minimum inhibitory concentration (MIC) of vancomycin for methicillin-resistant Staphylococcus aureus (MRSA) (2 µg/mL)

[g] Number of Subjects = 3

3.2.4 Safety

The Phase II clinical study demonstrated the AeroVanc 32 mg dose was well tolerated, with no notable difference from placebo in the occurrence, severity or relatedness of treatment-emergent adverse events (TEAEs). However,

the AeroVanc 64 mg dose was associated with higher severity, and relatedness of TEAEs, as well as a higher frequency of study drug discontinuations, suggesting the higher dose is not well tolerated. In subjects < 21 years of age, safety and tolerability was similar to or better than placebo at both dose levels.

The incidence of TEAEs with onset during the Treatment Period was similar between treatment groups in each cohort (range, 82.6% to 90.0%). The most common TEAE was cough, with no notable difference between the dose cohorts or between active and placebo. Signs and symptoms consistent with potential bronchoconstriction were observed slightly more often in the active treatment groups, but with no notable difference between the two dose cohorts. These events included dyspnea, chest discomfort, bronchoconstriction, and FEV_1 decrease (Table 4).

No deaths were reported during the study. Serious adverse events (SAEs) were experienced by 4 subjects and 1 subject in the AeroVanc 32 mg and 64 mg groups, respectively, and by 2 and 4 subjects in the Cohort 1 and Cohort 2 placebo groups, respectively.

The majority of all adverse events (AEs) were mild or moderate, and there was a shift from mild to moderate AEs in the 64 mg AeroVanc cohort as compared with the 32 mg AeroVanc cohort, and the placebo groups. There was no notable difference between the treatment groups in the occurrence of severe TEAEs. The incidence of treatment-related TEAEs (TEAEs considered possibly, probably, or related to study drug) was similar (21.7 % to 25.0 %) in the AeroVanc 32 mg cohort and the placebo groups, whereas it was higher (58.3 %) in the AeroVanc 64 mg group.

A total of 23 subjects discontinued study drug prior to Day 29. Three subjects discontinued in the 32 mg group, 6 subjects in the Cohort 1 placebo group, 13 subjects in the 64 mg group, and 1 subject in the Cohort 2 placebo group. The majority of subjects, 19/23, discontinued due to either a TEAE or drug intolerance. The proportion of subjects who discontinued study drug prior to day 29 due to a TEAE was 5.0 %, 25.0 %, 41.7 %, and 0 % in the AeroVanc 32 mg, Cohort 1 placebo, AeroVanc 64 mg, and Cohort 2 placebo groups, respectively (Table 5).

The results of post-hoc analyses suggested that subjects < 21 years of age treated with AeroVanc 32 mg and 64 mg experienced TEAEs at an incidence less than or similar to that of placebo subjects. In subjects ≥ 21 years of age, the observed TEAE incidence rates were higher in the AeroVanc groups compared to the corresponding placebo groups (1.56 and 1.84 for the AeroVanc 32 mg and AeroVanc 64 mg groups, respectively). No consistent or treatment-related changes in any hematology, chemistry, or urinalysis laboratory parameter values, vital signs measurement, or ECG parameter values were noted.

Table 4: Incidence of adverse events occurring in ≥2 subjects in at least one treatment group and with an onset during the treatment period.

System Organ Class Preferred Term	Cohort 1		Cohort 2		Pooled Cohorts	
	AeroVanc 32 mg (N=20)	Placebo (N=20)	AeroVanc 64 mg (N=24)	Placebo (N=23)	AeroVanc 32&64 mg (N=44)	Placebo (N=43)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Subjects reporting ≥ 1 TEAE With Onset During the Treatment Period	18 (90.0)	18 (90.0)	20 (83.3)	19 (82.6)	38 (86.4)	37 (86.0)
Cough	9 (45.0)	7 (35.0)	9 (37.5)	10 (43.5)	18 (40.9)	17 (39.5)
Respiratory tract congestion	8 (40.0)	4 (20.0)	7 (29.2)	7 (30.4)	15 (34.1)	11 (25.6)
Fatigue	5 (25.0)	4 (20.0)	8 (33.3)	3 (13.0)	13 (29.5)	7 (16.3)
Sputum increased	6 (30.0)	7 (35.0)	6 (25.0)	5 (21.7)	12 (27.3)	12 (27.9)
Paranasal sinus hypersecretion	6 (30.0)	3 (15.0)	4 (16.7)	1 (4.3)	10 (22.7)	4 (9.3)
Dyspnoea exertional	4 (20.0)	2 (10.0)	5 (20.8)	3 (13.0)	9 (20.5)	5 (11.6)
Infective pulmonary exacerbation of cystic fibrosis	3 (15.0)	5 (25.0)	5 (20.8)	2 (8.7)	8 (18.2)	7 (16.3)
Exercise tolerance decreased	5 (25.0)	1 (5.0)	2 (8.3)	2 (8.7)	7 (15.9)	3 (7.0)
Forced expiratory volume decreased	4 (20.0)	2 (10.0)	3 (12.5)	1 (4.3)	7 (15.9)	3 (7.0)
Chest discomfort	2 (10.0)	0	4 (16.7)	0	6 (13.6)	0
Sinus headache	4 (20.0)	1 (5.0)	2 (8.3)	3 (13.0)	6 (13.6)	4 (9.3)
Weight decreased	4 (20.0)	1 (5.0)	2 (8.3)	1 (4.3)	6 (13.6)	2 (4.7)
Dyspnoea	3 (15.0)	1 (5.0)	2 (8.3)	0	5 (11.4)	1 (2.3)
Increased viscosity of bronchial secretion	1 (5.0)	3 (15.0)	3 (12.5)	2 (8.7)	4 (9.1)	5 (11.6)
Decreased appetite	0	2 (10.0)	3 (12.5)	4 (17.4)	3 (6.8)	6 (14.0)
Diarrhoea	0	0	3 (12.5)	0	3 (6.8)	0
Bronchospasm	0	0	2 (8.3)	0	2 (4.5)	0
Dysgeusia	2 (10.0)	0	0	0	2 (4.5)	0
Haemoptysis	1 (5.0)	0	1 (4.2)	4 (17.4)	2 (4.5)	4 (9.3)
Oropharyngeal pain	2 (10.0)	0	0	0	2 (4.5)	0
Sputum discoloured	0	1 (5.0)	2 (8.3)	1 (4.3)	2 (4.5)	2 (4.7)
Wheezing	1 (5.0)	2 (10.0)	1 (4.2)	0	2 (4.5)	2 (4.7)

Table 5: Subject Early Discontinuations.

Subject Early Discontinuation							
	Cohort 1		Cohort 2		Cohorts 1&2		Total
	AeroVanc 32 mg	Placebo	AeroVanc 64 mg	Placebo	AeroVanc 32&64mg	Placebo	
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Safety Population	20 (100)	20 (100)	24 (100)	23 (100)	44 (100)	43 (100)	87 (100)
Discontinued Study Drug Prior to Day 29 (Visit 6)	3 (15.0)	6 (30.0)	13 (54.2)	1 (4.3)	16 (36.4)	7 (16.3)	23 (26.4)
Primary Reason for Discontinuation of Study Drug (All Subjects)							
Adverse Event	1 (5.0)	5 (25.0)	10 (41.7)	0	11 (25.0)	5 (11.6)	16 (18.4)
Study Drug Intolerance	0	1 (5.0)	2 (8.3)	0	2 (4.5)	1 (2.3)	3 (3.4)
Subject Withdrew Consent/Assent	1 (5.0)	0	0	0	1 (2.3)	0	1 (1.1)
Investigator Decision	1 (5.0)	0	0	0	1 (2.3)	0	1 (1.1)
Other	0	0	1 (4.2)	1 (4.3)	1 (2.3)	1 (2.3)	2 (2.3)

3.2.4.1 Serious Adverse Events

No deaths were reported during the study. Eleven subjects experienced a total of 15 Serious Adverse Events (SAEs), including 10 SAEs of infective pulmonary exacerbation of cystic fibrosis and 1 SAE each of infective exacerbation of bronchiectasis, pain, hyperglycemia, pneumonia, and pleural effusion. None of the SAEs were considered to be related to study drug. All of the SAEs required hospitalization with the exception of 1 SAE of infective pulmonary exacerbation of cystic fibrosis. All SAEs resolved (11 without sequelae). SAEs were experienced by 4 subjects and 1 subject in the AeroVanc 32 mg and 64 mg groups, respectively, and by 2 and 4 subjects in the Cohort 1 and Cohort 2 placebo groups, respectively.

3.2.5 Efficacy Results

3.2.5.1 Subjects less than 21 years of age

A *post hoc* analysis of the FEV_1 data showed that the lack of FEV_1 improvement was driven primarily by adult subjects. In contrast, encouraging improvements in FEV_1 were observed in younger subjects, as described below. These results are consistent with previous studies using inhaled tobramycin (TOBI or TOBI Podhaler®) for the treatment of *P. aeruginosa* infection in CF, where an improvement in FEV_1 is predominantly seen in younger subjects (Weers, 2015). In order to select an appropriate age cutoff for the AeroVanc subgroup analyses, guidance was sought from a large retrospective study by Dasenbrook (Dasenbrook EC M. C.-W., 2008), which showed that persistent MRSA infection in CF subjects 8–21 years of age was associated with a faster decline in lung function. As described in more detail below, clinically meaningful, but statistically non-significant, improvements were observed after AeroVanc treatment in subjects < 21 years of age in FEV_1, CFRSD-CRISS, time to need of other antibiotics, and time to exacerbation.

A mean reduction of 0.7 $\log_{10}$ CFU/mL from baseline in MRSA CFUs, the primary endpoint, was observed after 28 days of AeroVanc administration in subjects below 21 years of age (Figure 5), albeit not statistically significant due to the limited number of subjects.

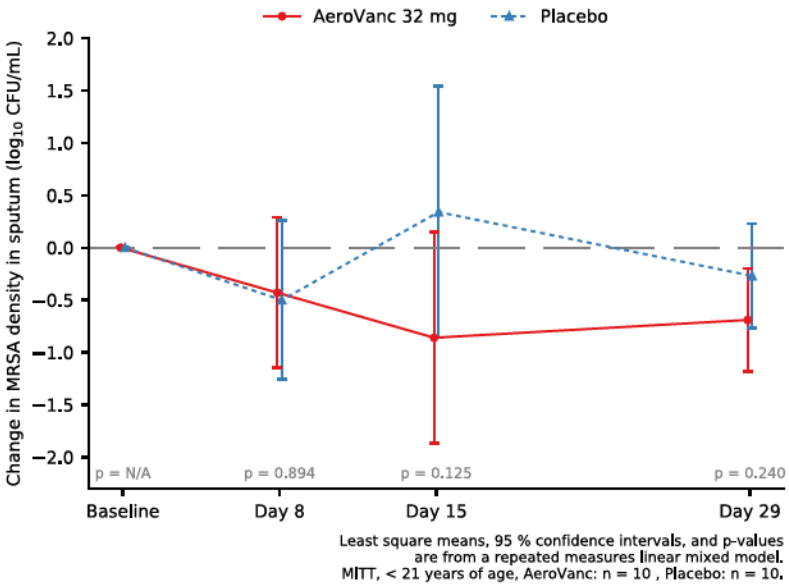


Figure 5: Change in MRSA Density in Sputum in Subjects less than 21 Years of Age.

In subjects less than 21 years old, the mean change from baseline in the daily symptom diary, CFRSD-CRISS, showed a greater reduction in CRISS that was observed consistently at all time points, as compared with placebo, but the difference was not statistically significant.

The analyses also identified encouraging improvement in FEV_1 in subjects 21 years of age or younger across all time points during the treatment period (Figure 6). The mean absolute change in FEV_1 percent predicted observed in the AeroVanc 32 mg bid arm is considered clinically meaningful, with an improvement ranging between 4 % and 6 % (or 6 % and 10 % on a relative change basis), albeit not statistically significant due to the limited number of subjects.

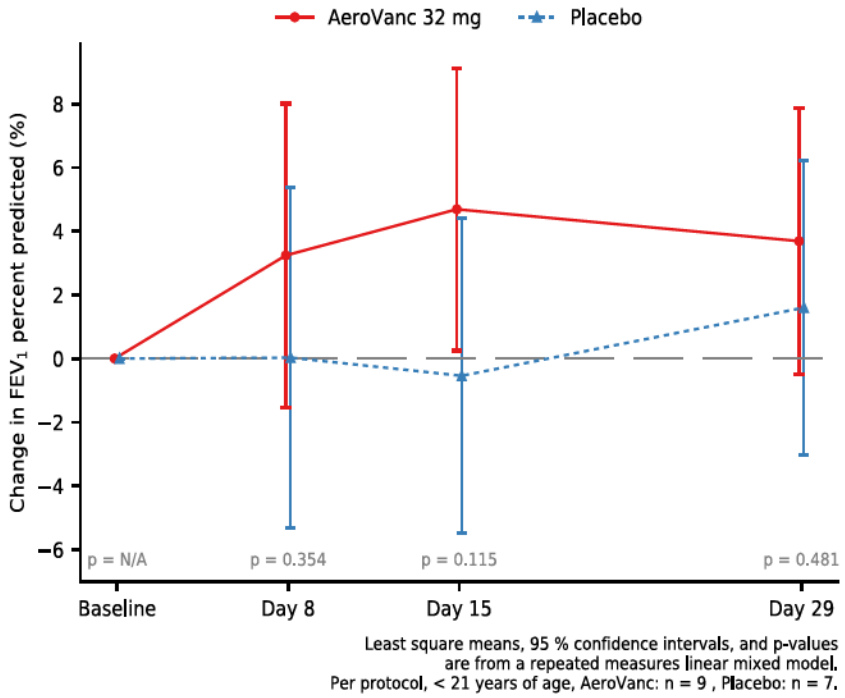


Figure 6: Absolute Change from Baseline in FEV_1 Percent Predicted in Subjects less than 21 Years of Age.

A trend of prolongation of the time to use of another antibiotic for respiratory symptoms was observed in the AeroVanc arm of the 32 mg dose cohort, as compared with placebo (Figure 7). Whereas in this single cycle study several subjects in the AeroVanc arm were prescribed other antibiotics at the scheduled one-month post-treatment visit (approximately Day 56), such treatment would not be expected to be prescribed during chronic AeroVanc treatment, or in a multiple-cycle study, because the timing would coincide with the start of a new AeroVanc treatment period.

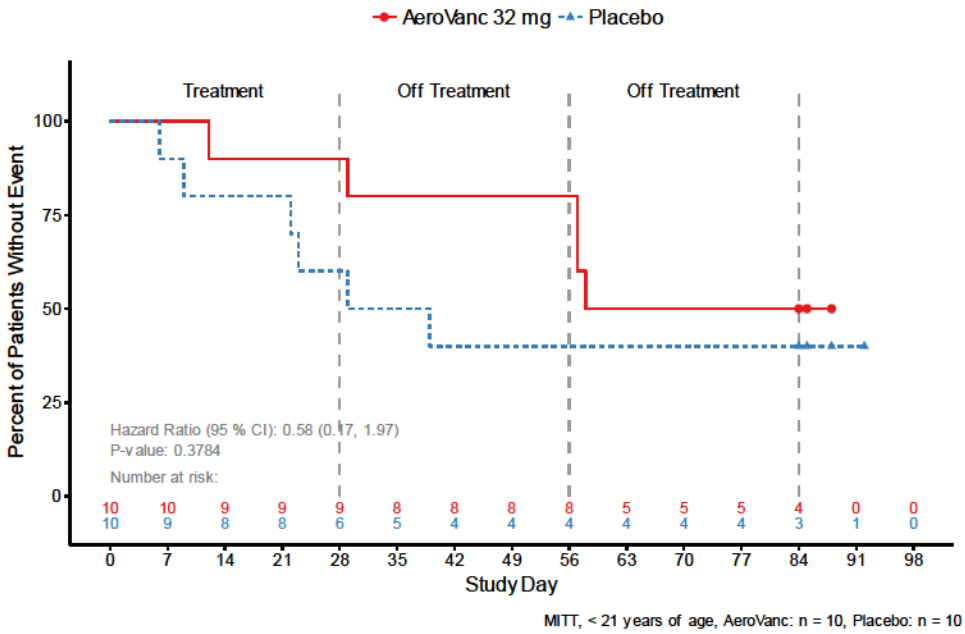


Figure 7: Time to Use of Other Antibiotics for Respiratory Infection in Subjects less than 21 Years of Age.

4 STUDY RATIONALE

In the Phase II study (SAV005-02), AeroVanc demonstrated a reduction in MRSA density in sputum along with improvement in respiratory symptoms, lung function, prolongation of the time to need of other antibiotics, and time to pulmonary exacerbation. Subjects < 21 years of age showed the best improvements across each of the endpoints when compared to the older population. The consistency of the responses across the different endpoints, as well as the magnitude of change, supports advancing the product into the next phase of development.

The study is designed as a placebo-controlled study due to the lack of a standard of care in the treatment of MRSA lung infection in subjects with CF. Based on the requirement of the FDA, the duration of the placebo-controlled period of the study will be 3 dosing cycles, each cycle being 28 days of treatment followed by 28 days of observation. A cyclic dosing regimen was chosen as it is well established for e.g. anti-pseudomonal inhalation therapy. The low dose was chosen based on the Phase II study as it was well tolerated and associated with improvements in microbiology and trends in improvement of lung function and time to antibiotic treatment, whereas the high dose was less tolerated and associated with a higher number of treatment discontinuations.

The primary and secondary efficacy endpoints will be measured and assessed during this placebo-controlled period.

In order to further evaluate the safety of AeroVanc during multiple cycles of administration, the study will include an open label extension of 3 additional cycles. During the extension, subjects will be followed for adverse events, as well as for microbiology and pulmonary function tests (PFTs). In addition to safety evaluation, the latter will be measured to assess continued efficacy of the treatment but will not be used as part of the formal efficacy evaluation.

5 STUDY OBJECTIVES

5.1 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.

5.2 Secondary Objectives

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).

6 INVESTIGATIONAL PLAN

6.1 Study Population

Subjects with a diagnosis of cystic fibrosis with confirmed persistent MRSA lung infection who meet the inclusion and exclusion criteria will be eligible for participation in this study. Two-hundred (200) subjects are expected to be enrolled in the study at approximately 85 centers in the United States (US) and Canada. Subjects will be randomized to receive AeroVanc (n=100); or placebo (n=100). It is anticipated that up to 240 subjects may need to be screened in order to enroll the targeted number of subjects.

6.2 Study Design

SAV005-04 is a 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 patients diagnosed with cystic fibrosis.

After a Screening period (up to 42 days) to confirm eligibility for study participation, 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 by 28 days of treatment followed by 28 days of observation. Subjects meeting the eligibility criteria and entering the study 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). See Figure 8 below.

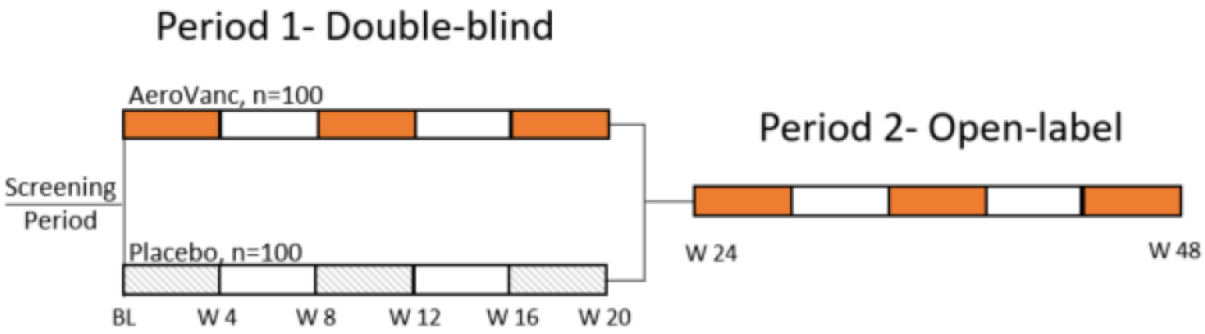


Figure 8: Study Design.

6.3 Efficacy and Safety Evaluations

Efficacy assessments will include pulmonary functions tests (PFT), pulmonary exacerbations, patient reported outcomes and sputum microbiology including MRSA density, vancomycin susceptibility, and emergence of additional pathogens. Safety assessments will include all adverse events (AEs), as well as standard hematology, biochemistry, and urine analyses, vital signs, physical examination, and electrocardiogram (ECG).

6.4 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 (i.e., 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 course of 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 course of 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.

6.5 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).

6.6 Criteria for Termination of the Study

If the Sponsor, Investigator, study monitor, or regulatory officials discover conditions arising during the study that indicate that the subject safety and/or scientific value of the study and/or quality of the study drugs have been compromised, the study should be halted, or the study center's participation should be terminated. Conditions that may warrant termination of the study include, but are not limited to, the following:

- The discovery of an unexpected, serious, or unacceptable risk to the subjects enrolled in the study;
- A decision on the part of the Sponsor to suspend or discontinue testing, evaluation, or development of the product for any reason;
- Failure of the Investigator to enroll subjects into the study at an acceptable rate;
- Failure of the Investigator to comply with pertinent governing body regulations;
- Submission of knowingly false information from the research facility to the Sponsor, study monitor, medical officer, or regulatory official; and,
- Insufficient adherence to protocol requirements.

Study termination and follow-up should be performed in compliance with applicable governing body regulations.

If an Institutional Review Board (IRB), Independent Ethics Committee (IEC), or Research Ethics Board (REB) withdraws approval for a study site due to subject safety concerns related to the investigational product, all sites will be notified and no further treatments will be given until resolution of the issue or determination by the reviewers that no undue risk exists.

If the study is terminated for safety concerns, all subjects will be followed for at least 30 days after the subject's final treatment, unless a longer follow-up period is warranted to address the safety concern. Subjects with significant safety events will be followed until resolution or stabilization of the event as stated in Section 12. Upon study termination, the Sponsor will discuss with the relevant Regulatory authorities to determine the appropriate follow up procedures and length of monitoring required to address safety concerns.

7 CONCURRENT MEDICATIONS

All subjects should be maintained on the same medications throughout the double-blind Period 1 of the study, as medically feasible, with the exception of those specified in Section 7.1.

7.1 Prohibited Medications and Treatments

Subjects must discontinue the use of IV or inhaled anti-MRSA treatments at least 28 days prior to the Baseline visit, and/or use of oral anti-MRSA treatments at least 14 days prior to the Baseline visit and should not be prescribed anti-MRSA treatments during the double-blind portion of the trial unless the subject is being treated for a pulmonary exacerbation. This may include oral or injectable antibiotics with potential activity to MRSA (e.g. vancomycin, telavancin, linezolid, tetracyclines such as doxycycline or minocycline, trimethoprim/sulfamethoxazole, MRSA-active cephalosporins (e.g. ceftaroline), clindamycin, daptomycin, gentamicin, or rifampin).

7.2 Anti-Pseudomonas Antibiotic Treatment

For subjects on a 28-day cyclical on/off anti-Pseudomonal antibiotic regimen, they 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 4-week observation periods (Week 5 through Week 8, Week 13 through Week 16, Week 21 through Week 24). Subjects on continuing alternating anti-Pseudomonal therapy (CAT) can continue their treatment during the study drug administration and Follow-up periods, but the subject's initial dose of study medication must coincide with the initial dose of aztreonam (Cayston)/ colistimethate (Colistin).

8 STUDY TREATMENT

8.1 AeroVanc Formulation

Vancomycin hydrochloride powder for inhalation is a white to off-white dry powder formulation of the active pharmaceutical ingredient (API) vancomycin hydrochloride, developed by Savara Pharmaceuticals. As shown in Table 6, in addition to the active ingredient, vancomycin hydrochloride powder for inhalation contains the excipient l-leucine. Water for injection is used as a processing aid in the manufacturing process and is present in the finished drug product. Each clear, (Hydroxypropyl)methyl cellulose (HPMC), size 3 capsule contains a dry powder of 15 mg of vancomycin and 2 mg of l-leucine. The Phase III study label claim is lowered from 16 mg (Phase II dose) to 15 mg per capsule. This change reflects improvements in analytical methods and does not represent a change in the formulation or actual quantity of vancomycin in the capsule. In other words, despite a change in label claim, the actual content of vancomycin in the capsule will be comparable between the Phase II and Phase III batches.

Table 6: Formulation of AeroVanc.

Ingredient	Purpose/Role
Vancomycin Hydrochloride USP	Active pharmaceutical ingredient
L-Leucine USP	Dispersion and stability enhancement
Purified Water USP	Manufacturing processing aid

8.2 Placebo Formulation

Matching Placebo is a dry powder formulation containing inactive excipients, l-leucine, and trehalose. Table 7 indicates the ingredients of Placebo.

Table 7: Formulation of Placebo.

Ingredient	Purpose/Role
Trehalose Dihydrate NF	Bulking agent
L-Leucine USP	Dispersion and stability enhancement
Purified Water USP	Manufacturing processing aid

8.3 Packaging and Labeling

AeroVanc will be supplied as size 3, clear capsule filled with dry powder vancomycin or matching placebo. Study drug is supplied in a 4-week clinical kit. Each clinical kit contains 4 weekly boxes containing 8 daily dosing cards. Each daily dosing card will contain 4 capsules. Two (2) capsules will be used for the morning dose and 2 capsules for the evening dose.

Labeling: Each 4-week clinical kit, and contents within the kit (i.e., weekly boxes and dosing cards), will be labeled with product name, the protocol number, the name of the Sponsor and address, and directions for the use and storage (4-week clinical and weekly kit) and the required applicable regulatory agency warning statements ("Caution: New Drug - Limited by Federal Law to Investigational Use.").

8.4 Supply of Study Drug at the Site

The Sponsor (or designee) will ship Study Drug to the investigational sites prior to enrollment of the first subject. The initial study drug shipment will be shipped after site activation (i.e., all required regulatory documentation, including ethic's approval, and an executed trial contract) has been received by the Sponsor. Subsequent study drug shipments will be made as necessary based upon subject recruitment.

AeroVanc will be shipped to the clinical site in an insulated container controlled to 2-8°C. Each shipment will be equipped with a TempTale 4 USB recorder. Instructions on how to stop temperature recording, download data and email data will be provided with each shipment.

8.5 Dosage/Dosage Regimen

The inhalation powder is packaged into capsules, each capsule containing 15 mg of vancomycin. The dose in this study is 30 mg (2 capsules) BID (at least 6 hours apart). Alternatively, a subject may be randomized to receive a matching placebo, with equivalent numbers of capsules.

8.6 Dispensing

During the Baseline visit, the subject will be dispensed a 4-week kit containing 4 weekly boxes. Each box will contain 8 daily dosing cards (7 + 1 extra). Each daily dosing card contains 4 capsules, 2 capsules for the morning dose and 2 capsules for the evening dose. During subsequent visits, a resupply of study drug will be dispensed the day of the visit and as indicated in the schedule of events.

8.7 Method of Assigning Subjects to Treatment Groups

Upon the completion of the Screening period (up to 42 days) to confirm inclusion/exclusion criteria, eligible subjects will be randomized to receive either AeroVanc 30 mg BID, or placebo BID (1:1 active to placebo) by inhalation for three 4-weekly cycles. A central randomization scheme will be produced with four stratification factors 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). Randomization will be carried out via Interactive Web Response (IWR).

8.8 Blinding and Unblinding of Study Medication

This study includes a double-blind period and an open-label period. Upon completion of the double-blind period, subjects will proceed on to the open-label period. The subjects, clinic staff, and Sponsor will not know the assigned treatment during the double-blind period. In the case of a medical emergency, when knowledge of the treatment assignment is essential to the welfare of the subject, the Investigator or designee may request unblinding of that subject. Whenever feasible, the Sponsor should be consulted in advance of breaking the blind for any subject. In any case, the Sponsor must be notified of the unblinding, and the Investigator or designee will document the reason(s) necessary to break the blind for any subject. Subjects will be discontinued from the study if the blind is broken.

8.9 Inhaler Device

The AeroVanc inhaler (Monodose RS01 Model 7 standard inhaler) is a unit dose, dry powder inhaler device that utilizes size 3 capsules and is manufactured by Plastiape S.p.A. A Canadian and US Drug Master File (DMF) has been filed. Five (4 + 1 extra {weekly}) inhalers will be provided within each 4-week clinical kit and labeled with study number, name of Sponsor and address and a warning statement, "Caution: New Device - Limited by Federal Law to Investigational Use." The AeroVanc inhaler should be stored under the same conditions as the drug supplies (i.e. refrigerated prior to dispensing and ambient room temperature conditions after dispensing).

For detailed instructions of use, see Appendix 6.

8.10 Administration Instructions

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.

8.11 Storage

Study drug should be stored by the study site at controlled refrigerated temperature, 2ºC to 8ºC prior to dispensing. If the temperature of study drug storage in the clinic/pharmacy exceeds or falls below this range, this should be reported to the Sponsor or designee prior to dispensing study drug. The Subjects will be instructed to store the medication in original packaging (aluminum foil blister packs and protected from light) at room temperature according to the instructions outlined in the Instructions for Use of AeroVanc Inhaler listed in Appendix 6.

8.12 Study Drug Accountability

An accurate and current accounting of the dispensing and return of study drug for each subject will be maintained on an ongoing basis by a member of the study site staff. The number of study drug dispensed and returned by the subject will be recorded on the Investigational Drug Accountability Record. The study monitor will verify these documents throughout the course of the study.

8.13 Treatment Compliance

Two capsules will be inhaled twice daily as per the Schedule of Events. Subjects are required to bring all used and unused blisters, capsules, and inhalers back to the research center for accountability. If a subject misses a scheduled dose (morning or evening) and has at least 6 hours until the next scheduled dose, the missed dose should be taken as soon as possible. Otherwise, the subject should wait for the next scheduled dose and not increase the number of capsules to make up for the missed dose.

8.14 Dose Adjustment

No dose adjustment of AeroVanc is allowed.

8.15 Accountability

The Investigator is required to maintain adequate records of the disposition of the investigational agent, including dates, quantity, and use by subjects throughout the study (Code of Federal Regulations, Title 21, Part 312.57). Records will be kept on product accountability and inventory forms. All product, whether used or unused, will be documented on drug accountability forms. Accountability of the investigational agent will be verified by the study monitor during on-site monitoring visits.

If the investigation is terminated, suspended, discontinued, or completed upon instruction from Savara, the Investigator shall return all used and unused supplies (blisters, capsules, and inhalers) to Savara's clinical return vendor. The shipment must contain final drug accountability forms, which complete the accountability of the entire study and reconcile any discrepancies.

9 STUDY PROCEDURES AND GUIDELINES

A Schedule of Events representing the required testing procedures to be performed for the duration of the study is diagrammed in Appendix 1.

Prior to conducting any study-related activities, written informed consent and the country specific personal information and data privacy authorization must be signed and dated by the subject or subject's legal representative. If appropriate, assent must also be obtained prior to conducting any study-related activities.

9.1 Clinical Assessments

9.1.1 Concomitant Medications

All medications taken in the 6 months prior to Baseline, as well as all concurrent therapies during the study, will be documented throughout the course of the study. Dose, route, unit frequency of administration, and indication for administration and dates of medication will be captured.

9.1.2 Demographics

Demographic information (date of birth, sex, race and ethnicity) will be recorded at the Screening visit.

9.1.3 Medical History

Relevant medical history, including history of current disease, other pertinent respiratory history, and information regarding underlying diseases will be recorded at the Screening visit and confirmed during the Baseline visit.

9.1.4 Physical Examination

A complete physical examination will be performed by either the Investigator or a Sub-Investigator as indicated on the Schedule of Events. 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 time points noted in the Schedule of Events and as clinically indicated. New abnormal physical exam findings not present during the baseline visits should be recorded as AEs and followed during subsequent visits.

9.1.5 Vital Signs

Body temperature, blood pressure, pulse, SpO_2 and respirations will be performed after resting for 5 minutes as indicated in the Schedule of Events.

9.1.6 12-lead Electrocardiogram (ECG)

A 12-lead ECG will be performed during the study as indicated on the Schedule of Events. All ECGs will be transmitted to the CRO from the laptop (CPS/BEAMS). The tracings will be processed and a confirmed ECG (over-read by a centralized Cardiologist) will be returned to the site, generally within 2 business days. A summary of the readings will be provided to the site for their records. It will be the responsibility of the Investigator or a Sub-Investigator to review the tracings for safety. Clinically significant findings, not present during the Baseline visit, should be recorded as an AE.

9.1.7 CFRSD-CRISS

The Cystic Fibrosis Respiratory Symptom Diary – Chronic Respiratory Infection Symptom Score (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 assessments should be completed weekly by the subject at home at bedtime. The CFRSD-CRISS will be administered using an e-Diary (hand held device) that will be provided to each subject.

9.1.8 CFQ-R

The Cystic Fibrosis Questionnaire-Revised (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, Emotional Functioning, and Social Functioning. The CRQ-R will be administered using an e-Diary that will be provided to each subject every two weeks.

9.1.9 EQ-5D-5L & EQ-5Dy

The EuroQol-5D (EQ-5D) is a more general questionnaire which is widely used to measure health outcome in terms of mobility, self-care, usual activities, pain/discomfort, anxiety/depression. The 5-level instrument (EQ-5D-5L) which uses a 5-point scale (no problems, slight problems, moderate problems, severe problems, and extreme problems) will be used in the local language. For subjects 15 years or younger the EQ-5D Youth (EQ-5Dy) will be used. This instrument will be used to measure overall self-rated health status. The questionnaire will be conducted in the clinic during the visit.

9.1.10 Pulmonary Function Tests (PFT)

All subjects will undergo standardized pulmonary function testing as indicated in the Schedule of Events 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 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 3 acceptable and reproducible efforts for PFTs will be recorded on the subject's CRFs and a copy of the spirometry reports will be retained with the subject's source documents.

Pre-dose PFTs will be performed at all visits prior to the subject administering the bronchodilator pre-treatment and study drug (AeroVanc/placebo). The Baseline PFT must be performed and meet inclusion criteria, prior to being randomized to study medication, after which administration of bronchodilator and study drug will be done as described below.

The sequence of events on the days of study drug administration will be performed as follows:

- Subjects will perform their morning airway clearance at home in a normal fashion (eg, administering a short-acting bronchodilator, followed by hypertonic saline, vest, Pulmozyme®, and potentially a long-acting bronchodilator/corticosteroid inhalation). As a reminder, all subjects should be maintained on the same medications throughout the entire study period, as medically feasible, with the exception of those specified in Section 7.1.
- Subjects will then come to the clinic during the morning. The subjects are not allowed to use albuterol (or other short-acting bronchodilator) for 2 hours prior to PFTs. The subjects will have PFTs performed first, then a self-administered pre-treatment with a short-acting bronchodilator no less than 10 minutes and up to 45 minutes prior to the self-administration of study drug (AeroVanc or Placebo) under supervision.
- The subjects should follow this exact same procedure at all treatment visits, and thereby, they should not take their morning study drug until they have come to the clinic, completed PFTs, then pre-treated with a short-acting bronchodilator, followed by study drug administration.

9.1.11 Sputum Microbiology

A sputum sample will be collected and cultured for MRSA as per the time points outlined in the Schedule of Events. Assessment of sputum samples will include identification and quantification of MRSA and susceptibility to vancomycin (MIC) at all timepoints, and susceptibility to a standard panel of antibiotics at Baseline, Week 20 and Week 44. . Assessments will be conducted during the study by an experienced centralized microbiology laboratory according to the Central Laboratory Manual.

Subjects able to spontaneously expectorate sputum samples at Screening should do so throughout the study. If a subject becomes unable to spontaneously expectorate sputum samples during a subsequent visit, the subject should continue to attempt to provide samples in future visits. Subjects who are unable to expectorate a sputum sample will have throat swabs taken.

Subjects not able to spontaneously expectorate sputum samples at Screening will have throat swabs taken instead. The inability to collect sputum (after the Screening visit) will not be considered a protocol deviation.

Subjects with a negative culture (sputum or throat swab) at Screening will have the opportunity to provide a second sample during the Screening period to confirm a positive culture.

9.1.12 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*.

9.1.13 Time to Antibiotic Use and Exacerbation Assessment

If a subject is treated with antibiotics for a pulmonary infection, the Investigator will record reasons for treatment initiation in the CRF and assess whether there is a pulmonary exacerbation. At the discretion of the Investigator, the subject will have the option to continue study drug during treatment of the pulmonary exacerbation unless the pulmonary infection is treated with IV vancomycin, in which case study drug should be discontinued during IV treatment and may be resumed thereafter without adjusting the dosing cycles. Subjects will be allowed to remain on study after the pulmonary infection is resolved.

9.2 Clinical Laboratory Measurements

All laboratory tests will be performed by a central laboratory.

9.2.1 Hematology and Blood Chemistry Profiles

Blood will be obtained and sent to the central laboratory for evaluation. Any tests determined as abnormal and clinically significant but not present at baseline should be recorded as an AE.

The hematology and clinical chemistry laboratory analyses will be performed at a central laboratory and as per the Appendix 1, Schedule of Events. Reference ranges will be supplied and used by the Investigator to assess the laboratory data for clinical significance and pathological changes.

The incidence of clinically significant laboratory values, as well as clinically significant shifts in laboratory values, should be reported as an AE in the subject's CRF (see also Section 12 for reporting of AEs related to laboratory abnormalities). The Investigator will assess any clinically significant values relevant to the subject population to determine if termination of the study drug is required.

Note: In the event of abnormal laboratory tests, follow-up laboratory tests may be conducted. Any clinically significant abnormalities noted in laboratory tests should be discussed with the Sponsor or designee. Creatinine clearance for kidney function assessment at Screening will be determined by Cockroft-Gault calculation in adults or Schwartz equation in children.

9.2.2 Pregnancy Test

A serum pregnancy test will be obtained from female subjects who are of childbearing age prior to their participation in the study, as indicated in Appendix 1, Schedule of Events.

9.2.3 Urinalysis

Urine will be obtained as indicated in Appendix 1, Schedule of Events, processed and mailed to the central laboratory for evaluation.

9.3 Pharmacokinetic Measurements

Subject plasma and sputum sample will be obtained for the measurement of vancomycin concentration in patients who participate in the PK sub-study. The pre-dose pharmacokinetic samples will be collected within 60 minutes prior to the start of dosing at the times indicated in the schedule of events.

Pharmacokinetic blood samples will be collected in evacuated tubes and processed within 1 hour of sample collection and kept frozen at -70 °C until shipment. Pharmacokinetic sputum samples will be collected in specimen collection cups and kept frozen at -20 °C until shipment. Subjects will be asked to attempt to produce a sample at the times noted in Appendix I, Schedule of Events. If a subject makes an attempt but is unable to produce a sample within the specified window, the failed attempt will not be considered a protocol deviation. If no blood is collected due to bad accessibility of veins, no other venipuncture will be made at that visit. The lack of blood collection, if it was attempted, will not be counted as a protocol deviation.

9.4 Unscheduled Visit(s)

Visits occurring outside of the scheduled visits listed in Appendix I, Schedule of Events should complete the procedures noted under Week 44/Early Termination visit, to assess a potential exacerbation or other clinical event after study treatment administration.

Assessments to be completed for an unscheduled visit, for any other reason, will be at the Investigator's discretion.

10 PRECAUTION

10.1 Pregnancy

Although pregnancy is not considered an AE, the Investigator (or his or her designee) is responsible for recording in the subject's source document any pregnancy during or within 30 days after completing study treatment. Any subject (or subject's partner) who becomes pregnant during the study should be followed through delivery or termination of the pregnancy. In addition, subjects who become pregnant during the study must discontinue study drug administration immediately.

In pregnancies that progress to term, any congenital abnormalities/birth defects in the offspring of a subject who received study medication should be reported as an SAE. The outcome of the pregnancy and the presence or absence of a congenital abnormality will be documented by completion of a Pregnancy Questionnaire and a Pregnancy Outcome Form in accordance with GCP and ICH guidelines and Standard Operating Procedures (SOPs).

Female subjects should also notify the Investigator if they become pregnant within 30 days after last dose of study medication. Male subjects should notify the Investigator if a female partner becomes pregnant within 30 days after last dose of study medication. The Sponsor must be notified of all pregnancies reported to the Investigators.

11 SAFETY EVALUATIONS

In this study, safety will be evaluated through AE monitoring, clinical evaluations (i.e., vital signs, physical examinations, ECGs), and laboratory tests (i.e., hematology, serum chemistries, and urinalysis) from the signing of informed consent until the last study visit.

Definitions and reporting procedures provided in this protocol comply with current ICH E6 and other applicable international and local regulatory requirements. The Medical Monitor assigned by the Sponsor will promptly review all information relevant to the safety of AeroVanc. The Investigator will carefully monitor each subject throughout the study for AEs and will be followed until adequately resolved. Medical queries should be addressed to the Medical Monitor.

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12 ADVERSE EVENT REPORTING AND DOCUMENTATION

12.1 Adverse Events

At each visit, all AEs that are observed, elicited by the Investigator, or reported by the subject will be recorded in the appropriate section of the CRF and evaluated by the Investigator. Minimum information required for each AE includes description of the event, duration (start and end dates), severity, assessment of seriousness, and causal relationship to study drug.

An adverse event (AE) is any unfavorable or unintended sign, symptom, or disease temporally associated with the use of study treatment, whether or not considered related to the study treatment. Clinical changes prior to the first dose of study drug will not be considered adverse events but will be included in the subject's medical history. All AEs must be recorded in the source documents and on the Adverse Event CRF, regardless whether the event is considered related to study medication.

This definition includes an exacerbation of pre-existing medical conditions or events, historical condition not present prior to study treatment, which reappear following study treatment, intercurrent illnesses, hypersensitivity reactions, drug interaction, or the significant worsening of the disease under investigation that is not recorded elsewhere in the CRF. Anticipated day-to-day fluctuations of pre-existing conditions that do not represent a clinically significant exacerbation or worsening need not be considered AEs.

For all AEs, the Investigator must pursue and obtain information adequate both to determine the nature and outcome of the adverse event and to assess whether it meets the criteria for classification as a serious adverse event (SAE) requiring immediate notification of the Medical Monitor. Follow-up of clinically significant AEs of at least a grade 3 (see Section 12.2 for definition), even after the date of therapy discontinuation, is required until resolution or stabilization is judged acceptable by the Investigator.

The Investigator or Sub-Investigator must interpret all laboratory findings and sign and date the laboratory report to confirm their review. Any grade 3 or higher laboratory abnormalities that are either serious or unexpected should be promptly reported to the Sponsor's Medical Monitor. Any clinically significant laboratory abnormality will be recorded as an adverse event on the CRF, including the diagnosis, if any, associated with the lab abnormality. The AE should be recorded as the underlying abnormality or diagnosis (eg, renal insufficiency), if one is determined, as opposed to the observed deviation in the laboratory result (eg, elevated creatinine).

In addition to recording clinically significant laboratory abnormalities, changes to clinical signs and symptoms will also be assessed at baseline and at all planned and unplanned study visits at which other clinical assessments are to be carried out.

Additional tests and other evaluations required to establish the significance or etiology of a clinically significant abnormal result or to monitor the course of an AE are to be obtained when clinically indicated. In particular, if a clinically significant abnormal result is observed that is not resolved by the final study visit, repeated tests should be performed and follow up continued until resolution or stabilization of the AE.

For all AEs resulting in discontinuation of the study drug, the event must be assessed by the safety committee to determine if the event meets the definition of a dose limiting toxicity (DLT). The committee will assess the event type, temporal relationship of the event to dosing, and severity of the event.

12.2 Severity

Severity will be graded utilizing Table 8 below.

Table 8: AE Severity Grading.

Severity (Toxicity Grade)	Description
Mild (1)	Transient or mild discomfort; no limitation in activity; no medical intervention or therapy required. The subject may be aware of the sign or symptom but tolerates it reasonably well.
Moderate (2)	Mild to moderate limitation in activity, no or minimal medical intervention/therapy required.
Severe (3)	Marked limitation in activity, medical intervention/therapy required, hospitalizations possible.
Life-threatening (4)	The subject is at risk of death due to the adverse experience as it occurred. This does not refer to an experience that hypothetically might have caused death if it were more severe.

12.3 Relationship to Study Treatment

The relationship or association of the AE to a study treatment, which includes procurement procedures, should be specified by the Investigator using the following definitions:

Table 9: Relatedness.

Relatedness	Description

Unrelated	Clinical event with an incompatible time relationship to study drug administration, and that could be explained by underlying disease or other drugs or chemicals or is incontrovertibly not related to the study drug.
Unlikely	Clinical event whose time relationship to study drug administration makes a causal connection improbable, but that could plausibly be explained by underlying disease or other drugs or chemicals.
Possible	Clinical event with a reasonable time relationship to study drug administration, but that could also be explained by concurrent disease or other drugs or chemicals.
Probable	Clinical event with a reasonable time relationship to study drug administration and is unlikely to be attributed to concurrent disease or other drugs or chemicals.
Related	Clinical event with plausible time relationship to study drug administration, and that cannot be explained by concurrent disease or other drugs or chemicals

12.4 Serious Adverse Events (SAE)

An SAE is defined as any AE occurring at any dose that results in any of the following outcomes:

1. **Is fatal:** applies if the subject's death is a direct outcome of an AE.

2. **Is life threatening:** applies if the subject, in the view of the Investigator, is at substantial risk of dying from the AE as it occurs. It does not apply if the AE could hypothetically have caused death had it been more severe.

3. **Requires or prolongs in-patient hospitalization:** applies if the AE requires at least a 24-hour in-patient hospitalization or, if in the opinion of the Investigator, prolongs an existing hospitalization. A hospitalization for an elective procedure or a routinely scheduled treatment is not an SAE by this criterion because a "procedure" or a "treatment" is not an untoward medical occurrence. An emergency room visit of less than 24 hours by itself does not constitute a SAE.

4. **Results in permanent or significant disability/incapacity:** applies if the "disability" caused by the reported AE results in a substantial disruption of the subject's ability to carry out normal life functions.

5. **Is a congenital anomaly/birth defect:** applies if a subject exposed to a medicinal (investigational) product gives birth to a child with congenital anomaly or birth defect.

Medical and scientific judgment should be exercised in determining seriousness in other situations, such as important medical events that may not be immediately life- threatening, result in death, or hospitalization, but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These events should be considered serious and subject to reporting procedures specified below.

Other important medical events may also be considered an SAE when, based on appropriate medical judgment, they jeopardize the subject or require intervention to prevent one of the outcomes listed.

12.4.1 Serious Adverse Event Reporting

Within 24 hours of becoming aware of any SAE (regardless of its relationship to investigational product) that occurs during the clinical study, the study personnel at the site must complete the SAE Report Form (even if all information regarding the SAE is unknown or incomplete), and fax or email it to the Safety Officer listed below. Should you not be able to contact the Safety Officer, you must reach out to the Sponsor Medical Monitor. This ensures timely reporting of applicable reports to all Regulatory Authorities. The form must be signed by the Principal Investigator or designee, and if not available, the unsigned report should be faxed or emailed for initial processing and resubmitted after the Investigator's signature has been obtained. After submission, the study personnel should await a confirmation of receipt from the Safety Officer and/or the Sponsor; if not received the report must be resubmitted.

Safety Officer	Sponsor-Medical Monitor	Sponsor-Clinical Operations
Fax: 1-800-352-8133 INCDrugSafety@increasearch.com	Cecilia Ganslandt, M.D Slotsmarken 17, 2.tv. DK-2970 Horsholm, Denmark Cell: +46 705 797075 Cecilia.Ganslandt@savarapharma.com	Jessica Jackson Director of Clinical Operations 6836 Bee Caves Rd, Building III, Suite 200 Austin, Texas 78746, USA Cell: 832-231-6283 jessica.jackson@savarapharma.com

The initial written report should be followed by full written summary detailing relevant aspects of the SAE in question using the provided SAE report form. Where applicable, information from relevant hospital case records and autopsy reports should be obtained. The SAE should also be recorded on the AE page of the subject's CRF. The Safety Officer and Medical Monitor will review the SAE documentation received for accuracy and completeness and follow-up with the Investigator to obtain missing information, if required.

If an AE does not meet the regulatory definition of "serious" but is considered by the Investigator to be related to the study medication and of such clinical concern as to influence the overall assessment of safety, it must be reported as defined for an SAE.

All AEs and SAEs will be followed until the event has resolved, the event has reached a new baseline, and for a minimum of 30 days after the last dose of study drug, or until the end of the study. Follow-up SAE information should be submitted as new information becomes available by using the follow-up SAE report form and faxing/emailing this form to the Safety Officer and Medical Monitor or designee. If the follow-up information changes the Investigator's assessment of seriousness or causality or relationship to the study drug, this change should be noted on the follow-up SAE form. The initial and any follow-up SAE reports should be placed in the subject's file. Upon receiving any updates, the Investigator must review and retain the updates and immediately submit a copy of this information to the IRB/IEC/REB. The Investigator should also comply with IRB/IEC/REB procedures for reporting any other safety information.

In addition, if the Investigator learns of an SAE occurring after the last follow-up visit, but within 30 days after the last administration of the study treatment, he/she should report the event within 24 hours to the contact persons for drug safety as described above.

12.5 Suspected Unexpected Serious Adverse Reactions (SUSARs)

The FDA and/or other applicable Regulatory Authorities and all participating Investigators will be notified by a written Investigational New Drug Application (IND) safety report and/or other applicable regulatory report (eg, expedited case report) of any suspected adverse reaction that is both serious and unexpected (i.e. a SUSAR), no later than 15 calendar days from the "date learned" of the event. In addition, all applicable regulatory bodies will be notified within 7 calendar days of any unexpected fatal or life-threatening suspected adverse reaction.

An untoward and unintended response to a non-study drug is, by definition, **not** a SUSAR.

13 DISCONTINUATION AND WITHDRAWAL OF SUBJECTS

13.1 Early Discontinuation and Withdrawal of Study and Study Drug

A subject may be discontinued from study or study treatment at any time if the subject, the Investigator, or the Sponsor feels that it is not in the subject's best interest to continue. The following is a list of possible reasons for study treatment discontinuation:

- Subject withdrawal of consent (or assent)
- Subject is not compliant with study procedures
- Exacerbation (use of antimicrobial medication to treat respiratory symptoms) - after completion of antimicrobial treatment study drug may be restarted at the discretion of the Investigator.
- Adverse event that in the opinion of the Investigator would be in the best interest of the subject to discontinue study treatment
- Protocol violation requiring discontinuation of study treatment
- Lost to follow-up
- Sponsor request for early termination of study
- Positive pregnancy test (females)

Subjects who are discontinued from study treatment before completing the entire duration of the Treatment Period should continue clinic visits according to the study schedule in Appendix I, Schedule of Event for Period 1; this includes the reporting of any AEs, including SAEs. Subjects who discontinue study medication in Period 1 will not be allowed to proceed to Period 2.

Subjects who discontinue study treatment, and who are not willing to continue clinic visits (eg, withdrawal of consent) should be encouraged to complete the Week 48/ End of Study (EOS) assessments as identified in the Schedule of Events.

The date the subject discontinues study treatment, the primary reason for study treatment discontinuation, study termination, and/or termination of participation (eg, withdrawal of consent), will be captured within the CRF.

When subjects withdraw consent from study participation, it must be recorded on the CRF whether the withdrawal of consent applies to specific aspects of the study such as discontinuation of study treatment, participation in study visits, contact by study personnel, or access to information about potential SAEs. If specific consent has not been withdrawn, study personnel should contact the subject (or a previously approved designee such as a caregiver, partner, or family member) at the scheduled Follow-up visit to inquire about health status.

13.2 Replacement of Subjects

Subjects who withdraw from the study treatment will not be replaced.

14 PROTOCOL VIOLATIONS

A protocol violation occurs when the subject or Investigator fails to adhere to significant protocol requirements affecting the inclusion, exclusion, subject safety, or primary endpoint criteria. Protocol violations for this study include, but are not limited to, the following:

- Failure to meet inclusion/exclusion criteria

- Use of a prohibited concomitant medication
- Failure to conduct protocol required procedures
- Non-compliant with study drug regimen
- Failure to comply with Good Clinical Practice (GCP) guidelines.

The Sponsor will determine if a protocol violation will result in withdrawal of a subject.

When a protocol violation occurs, it will be discussed with the Investigator and a Protocol Violation Form detailing the violation will be generated. This form will be signed by a Sponsor representative and the Investigator. A copy of the form will be filed in the site's regulatory binder and Sponsor's files. The Ethics Committee should be informed of the violation.

15 DATA SAFETY MONITORING

Safety oversight for this trial will be conducted by the Cystic Fibrosis Foundation Therapeutics (CFFT) Data and Safety Monitoring Board (DSMB). A subcommittee of the DSMB, a Data Monitoring Committee (DMC), will serve as the review board for this trial. The DMC will consist of at least 2 physicians experienced in treating CF, and a biostatistician with expertise in clinical trial safety monitoring. The DMC members will all be independent to Savara and to the clinical investigators.

Specifically, the DMC is responsible for:

- Reviewing clinical trial design (including relevant data from prior clinical trials and Investigator Brochures regarding the drug being studied);
- Reviewing SAEs and toxicity data;
- Examining unblinded accumulated outcome and safety data in order to make recommendations concerning continuation, termination or modification of the trial, based on the effects of the interventions under study. Termination or modification will only be for necessary safety reasons;
- Reviewing clinical trial design modifications proposed by the Therapeutics Development Network (TDN) or Sponsor and any future amendments prior to implementation;
- Reviewing the general progress of the clinical trial with regard to accrual/withdrawals or drop-out rates, protocol violations and/or deviations, and trial conduct

16 STATISTICAL METHODS AND CONSIDERATIONS

Prior to the analysis of the final study data, a detailed Statistical Analysis Plan (SAP) will be written describing all analyses that will be performed. The SAP will contain any modifications or clarifications to the analysis plan described below that may be necessary.

16.1 Data Sets Analyzed

All statistical testing will be two-sided and will be performed at the 0.05 significance level. Descriptive statistics will be provided by treatment group at baseline and at each critical time point. Categorical variables will be summarized by counts and by percentage of subjects in corresponding categories. Continuous variables will be summarized with means, standard deviations, medians, minimums, and maximums.

The following populations will be used for efficacy analyses:

- Intent-to-Treat (ITT) population will include all randomized subjects $\leq$ 21 years of age.

- The Per-Protocol (PP) population will include ITT subjects who adhere to all key protocol procedures, to be specified in a separate Statistical Analysis Plan (SAP).

Primary efficacy analyses, for which full control of Type I error will be implemented, will be in the group of patients who are ≤ 21 years of age.

Supporting analyses in patients who are > 21 years of age will be presented, with emphasis on estimation of the treatment effect, rather than statistical significance testing.

16.2 Demographic and Baseline Characteristics

The estimated response rate and its confidence interval will be estimated and assessed by the following *a priori* subgroups:

- Age group (6–21 years old and > 21)
- Baseline FEV_1 (≥60%; <60%)
- Prior exacerbations treated with antibiotics during the previous 12 months (1-2; ≥ 3)
- *P. aeruginosa* treatment (not treated; treated)

16.3 Analysis of Primary Endpoint

The primary efficacy endpoint is the mean absolute change from Baseline in FEV_1 percent predicted in patients who are ≤ 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 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 from Baseline to end of Cycle 2 will be analyzed. Similarly, if the effect after Cycle 2 is statistically significant, then the analysis of Baseline to end of Cycle 3 will be reported. The data will be analyzed using an analysis of covariance model with baseline FEV_1 percent predicted as a covariate and the stratification factors as fixed effects.

A linear regression model will be fitted using subjects with observed values for the endpoint (Week 4, 12 and 20, respectively), the covariates Baseline FEV_1 percent predicted, and earlier on-treatment measurements of FEV_1 percent predicted that are available (if any), and the stratification factors. Full details will be included in the SAP.

For confirmation of the primary endpoint, a sensitivity analysis 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 median for the placebo group and subjects in the placebo group with a missing FEV_1 percent predicted will be assigned the 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 median for the AeroVanc group and subjects in the placebo group with a missing FEV_1 percent predicted will be assigned the median for the placebo group.
- **Tipping point analysis**: In the event that statistical significance in favour of AeroVanc is determined from the primary analysis, subjects in either group with a missing FEV_1 percent predicted will be assigned successively more extreme values to find the point at which statistical significance is lost (i.e. the 2-sided P-value becomes greater than 0.05).

16.4 Analysis of Secondary Endpoints

Of the secondary endpoints, 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, and the

stratification factors. The number of days from randomization until the date of first exacerbation will be calculated and summarized using a Kaplan-Meier life table presentation. Subjects who do not experience an exacerbation prior to discontinuation from the study will be censored at the date of discontinuation from the study.

The changes in CFQ-R and CFRSD-CRISS score, relative change from baseline in FEV_1 percent predicted, will all be analyzed similarly at Week 4, 12 and 20 using analysis of covariance including baseline covariate and stratification factors.

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 patients across the 4 levels of response (0, 1, 2, or 3 successful treatment cycles). A response in a cycle is defined by at least a 5 % relative improvement in FEV_1 percent predicted at the end of each cycle (Week 4, Week 12, and Week 20). 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 receives concomitant non-maintenance antibiotic therapy for pulmonary infection (e.g. for pulmonary exacerbation), the subject is considered a failure in that cycle but the failure does not preclude success in future cycles. An appropriate proportional odds model for ordered categories will be used to analyze these data.

Frequency of pulmonary exacerbations will be compared between the groups using a negative binomial model for count data, adjusting for each subject's length of follow-up. The randomization stratification factors will be included in the model as fixed effects.

Area under the FEV_1–time profile will be analyzed using analysis of covariance including the subject's baseline FEV_1 and the stratification factors.

16.5 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:
        - time to first pulmonary exacerbation
        - change in CFQ-R at 4 weeks, then 12 weeks, then 20 weeks
        - change in CFRSD-CRISS score at 4 weeks, then 12 weeks, then 20 weeks
        - relative change from baseline in FEV_1 percent predicted at 4 weeks, then 12 weeks, then 20 weeks.
        - number of successful response cycles.
        - frequency of pulmonary exacerbations.
        - AUC of FEV_1-time profile.

The statistical decision rule for moving to each analysis will be based on the sequence listed above and meeting a threshold of $P < 0.05$ at each stage. 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. 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.

16.6 Safety Analysis

A single set of safety analyses will be produced including all patients (those ≤ 21 years old and those >21 years old, combined). Selected analyses will be repeated for the two groups separately (subject ≤ 21 years old and subjects >21 years old, respectively).

Extent of exposure and dosing compliance will be summarized by treatment group. Adverse events will be mapped to preferred terms and system organ classes using the Medical Dictionary for Regulatory Activities (MedDRA). The incidence of AEs (ever having) and the frequency of AEs (total number) and 95% confidence intervals will be tabulated by treatment group, system organ class, and preferred term. Serious adverse events (SAEs) will be summarized in a similar fashion. Adverse event summaries by severity and relationship to study drug will also be provided. The AE summaries will be presented for all subjects and by the two age groups.

Laboratory parameters will be summarized using descriptive statistics at Baseline and at each post-baseline visit. Changes from Baseline will also be summarized. In addition, shift tables (i.e., 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.

Vital signs will be summarized using descriptive statistics at Baseline and at each post-Baseline visit. Changes from Baseline will also be summarized.

Electrocardiogram parameters will be summarized using descriptive statistics at Baseline and at each post-baseline visit where an ECG assessment was made. Changes from Baseline will also be summarized. In addition, shift tables (i.e., normal, not clinically significant [NCS], clinically significant [CS]) at Baseline versus normal, NCS, CS at each post-baseline visit in a 3-by-3 contingency table) will be provided to assess changes from Baseline.

16.7 Interim Analysis

No interim analysis will be conducted.

16.8 Sample Size and Randomization

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 subjects per arm in the over 21-year age group will be included.

17 DATA COLLECTION, RETENTION AND MONITORING

17.1 Data Collection Instruments

The Investigator will prepare and maintain adequate and accurate source documents designed to record all observations and other pertinent data for each subject treated with the study drug.

Study personnel at each site will enter data from source documents corresponding to a subject's visit into the protocol-specific Case Report Form (CRF when the information corresponding to that visit is available). Subjects will not be identified by name in the study database or on any study documents to be collected by the Sponsor (or designee), but will be identified by a site number, subject number and initials.

If a correction is required for an eCRF, the time and date stamps track the person entering or updating eCRF data and creates an electronic audit trail. The Investigator is responsible for all information collected on subjects enrolled in this study. All data collected during this study must be reviewed and verified for completeness and accuracy by the Investigator, via electronic signature. A copy of the CRF will remain at the Investigator's site at the completion of the study.

17.2 Data Management Procedures

The data will be entered into a validated database. The Data Management group will be responsible for data processing, in accordance with procedural documentation. Database lock will occur once quality assurance procedures have been completed.

All procedures for the handling and analysis of data will be conducted using good computing practices meeting FDA guidelines, following the Data Management Plan, and staying within the delegated Standard Operating Procedures (SOPs), for handling and analysis of data for clinical trials.

17.3 Data Quality Control and Reporting

After data have been entered into the study database, a system of computerized data validation checks will be implemented and applied to the database on a regular basis. Queries are entered, tracked, and resolved through the EDC system directly. The study database will be updated in accordance with the resolved queries. All changes to the study database will be documented.

17.4 Archival of Data

The database is safeguarded against unauthorized access by established security procedures; appropriate backup copies of the database and related software files will be maintained. Databases are backed up by the database administrator in conjunction with any updates or changes to the database.

At critical junctures of the protocol, data for analysis is locked and cleaned per established procedures.

17.5 Availability and Retention of Investigational Records

The Investigator must make study data accessible to the monitor, other authorized representatives of the Sponsor (or designee), IRB/IEC, and Regulatory Agency (eg, FDA) inspectors upon request. A file for each subject must be maintained that includes the signed Informed Consent, HIPAA Authorization and Assent Form and copies of all source documentation related to that subject. The Investigator must ensure the reliability and availability of source documents from which the information on the CRF was derived.

All study documents (subject files, signed informed consent forms, copies of CRFs, Study File Notebook, etc.) must be kept secured for a period of 2 years following marketing of the investigational product or for 2 years after centers have been notified that the IND has been discontinued. There may be other circumstances for which the Sponsor is

required to maintain study records and, therefore, the Sponsor should be contacted prior to removing study records for any reason.

17.6 Monitoring

Monitoring visits will be conducted by representatives of the Sponsor according to the U.S. CFR Title 21 Parts 50, 56, and 312 and ICH Guidelines for GCP (E6). By signing this protocol, the Investigator grants permission to the Sponsor (or designee), and appropriate regulatory authorities to conduct on-site monitoring and/or auditing of all appropriate study documentation.

17.7 Subject Confidentiality

In order to maintain subject confidentiality, only a site number, subject number and subject initials will identify all study subjects on CRFs and other documentation submitted to the Sponsor. Additional subject confidentiality issues are covered in the Clinical Study Agreement.

18 ADMINISTRATIVE, ETHICAL, REGULATORY CONSIDERATIONS

The study will be conducted according to the Declaration of Helsinki, Protection of Human Volunteers (21 CFR 50), Institutional Review Boards (21 CFR 56), and Obligations of Clinical Investigators (21 CFR 312).

To maintain confidentiality, all laboratory specimens, evaluation forms, reports and other records will be identified by a coded number and initials only. All study records will be kept in a locked room with limited access. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by the FDA. The Investigator must also comply with all applicable privacy regulations (eg, Health Insurance Portability and Accountability Act of 1996, EU Data Protection Directive 95/46/EC).

18.1 Protocol Amendments

Any amendment to the protocol will be approved by the Sponsor. Protocol amendments cannot be implemented without prior written IRB/IEC approval except as necessary to eliminate immediate safety hazards to subjects. A protocol amendment intended to eliminate an apparent immediate hazard to subjects may be implemented immediately, provided the IRBs are notified.

18.2 Institutional Review Boards and Independent Ethics Committees

The protocol and consent form will be reviewed and approved by the IRB/IEC of each participating center prior to study initiation. Serious adverse events will be reported to the IRB/IEC in accordance with the standard operating procedures and policies of the IRB/IEC, and the Investigator will keep the IRB/IEC informed as to the progress of the study. The Investigator will obtain assurance of IRB/IEC compliance with regulations.

Any documents that the IRB/IEC may need to fulfill its responsibilities (such as protocol, protocol amendments, Investigator's Brochure, consent forms, information concerning subject recruitment, payment or compensation procedures, or other pertinent information) will be submitted to the IRB/IEC. The IRB/IECs written approval of the study protocol and the informed consent form will be in the possession of the Investigator before the study is initiated. The IRB/IECs approval statement will be transmitted by the Investigator to the Sponsor or designee prior to the shipment of study supplies to the site. This approval must refer to the study by exact protocol title and number and should identify the documents reviewed and the date of review.

Protocol and/or informed consent modifications or changes may not be initiated without prior written IRB/IEC approval except when necessary to eliminate immediate hazards to the subjects or when the change(s) involves only logistical or administrative aspects of the study. Such modifications will be submitted to the IRB/IEC and written verification that the modification was submitted and subsequently approved should be obtained.

The IRB/IEC must be informed of revisions to other documents originally submitted for review; serious and/or unexpected adverse experiences occurring during the study in accordance with the standard operating procedures and policies of the IRB; new information that may affect adversely the safety of the subjects of the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

18.3 Informed Consent Form

Informed consent will be obtained in accordance with the Declaration of Helsinki, ICH GCP, US Code of Federal Regulations for Protection of Human Subjects (21 CFR 50.25[a, b], CFR 50.27, and CFR Part 56, Subpart A), the Health Insurance Portability and Accountability Act (HIPAA, if applicable), and local regulations.

The Investigator will prepare the informed consent form, assent and HIPAA authorization and provide the documents to the Sponsor or designee for approval prior to submission to the IRB/IEC. The consent form generated by the Investigator must be acceptable to the Sponsor and be approved by the IRB/IEC. The written consent document will embody the elements of informed consent as described in the International Conference on Harmonization and will also comply with local regulations. The Investigator will send an IRB/IEC-approved copy of the Informed Consent Form to the Sponsor (or designee) for the study file.

A properly executed, written, informed consent will be obtained from each subject prior to entering the subject into the trial. Information should be given in both oral and written form and subjects (or their legal representatives) must be given ample opportunity to inquire about details of the study. If appropriate and required by the local IRB/IEC, assent from the subject will also be obtained. If a subject is unable to sign the informed consent form (ICF) and the HIPAA authorization, a legal representative may sign for the subject. A copy of the signed consent form (and assent) will be given to the subject or legal representative of the subject and the original will be maintained with the subject's records.

18.4 Publications

The preparation and submittal for publication of manuscripts containing the study results shall be in accordance with a process determined by mutual written agreement among the study Sponsor and participating institutions. The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, the Health Insurance Portability and Accountability Act of 1996.

It is the Sponsor's intent to eventually publish the results of this study. The Sponsor will separately agree with the Coordinating Investigator and the Principal Investigators on a publication strategy, which will include the names of the authors of the publication(s). The Sponsor must review and approve any manuscripts or abstracts prepared for submission to scientific journals or for professional meetings. Data from individual study centers shall not be published separately.

18.5 Investigator Responsibilities

By signing the Agreement of Investigator form, the Investigator agrees to:

1. Conduct the study in accordance with the protocol and only make changes after notifying the Sponsor (or designee), except when to protect the safety, rights or welfare of subjects.
2. Personally conduct or supervise the study (or investigation).
3. Ensure that the requirements relating to obtaining informed consent and IRB review and approval meet federal guidelines, as stated in § 21 CFR, parts 50 and 56.
4. Report to the Sponsor or designee any AEs that occur in the course of the study, in accordance with §21 CFR 312.64.

5. Ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.
6. Maintain adequate and accurate records in accordance with §21 CFR 312.57 and to make those records available for inspection with the Sponsor (or designee).
7. Ensure that an IRB that complies with the requirements of §21 CFR part 56 will be responsible for initial and continuing review and approval of the clinical study.
8. Promptly report to the IRB and the Sponsor (or designee) all changes in the research activity and all unanticipated problems involving risks to subjects or others (to include amendments and IND safety reports).
9. Seek IRB approval before any changes are made in the research study, except when necessary to eliminate hazards to the patients/subjects.
10. Comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements listed in § 21 CFR part 312.

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APPENDIX 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	X		X
Height	X	X	X	X	X	X		X		X	X	X	X
Weight and vitals	X	X	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 microbiological testing	X	X		X	X	X	X	X	X	X		X	
Obtain throat swab for microbiological testing [3]	X	X		X	X	X	X	X	X	X		X	
Obtain sputum for PK sample			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 no less than 10 minutes and up to 45 minutes 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] Collected only when sputum cannot be collected

[4]Subjects will be administered study drug during the clinic visit after completion of all study procedures

[5]CFQ-R conducted every two weeks and CFRSD conducted weekly on ePRO diary. EQ-5D-5L/y conducted during the clinic visit

APPENDIX 2. Blood Volume Calculation

Assessment	Sample volume (mL)	Number of samples	*Estimated total volume (mL)*
CBC (hematology)	3	9	***27***
Blood Chemistry	2.5	4	***10***
Serum Pregnancy	4	5*	***20***
Pharmacokinetics Sample	6	1	***6***
Estimated Total (mL)			***63***

*Includes Blood Chemistry collection.

APPENDIX 3. CYSTIC FIBROSIS RESPIRATORY SYMPTOM DIARY (CFRSD©) SELF-REPORT – WEEKLY VERSION 2.0

(Only the first 8 questions will be completed by subjects in this study to provide the CFRSD-CRISS.)

Cystic Fibrosis Respiratory Symptom Diary – (CFRSD©)

Self-Report – Version 2.0

7-Day Recall

University Of Washington

Seattle Quality of Life Group and Department of Medicine

This work has been supported with a grant from the Cystic Fibrosis Foundation

Cystic Fibrosis: Your Weekly Experience

Instructions:

- Complete this diary between 5:00 P.M. and when you go to bed.
- Think carefully about your experience with cystic fibrosis, **specifically during the last 7 days**, before responding to each question.
- ***Please complete all of the questions in one sitting if possible.***

What is today's date? *(write-in your answer)*:	_____, _____ 20____ MONTH DAY YEAR
What is the current time? *(write-in your answer, and circle "AM" (before noon) or "PM" (after noon)*:	_____:_____ o' clock AM PM

During the last 7 days…

1. How difficult was it to breathe? *(Check one)*

- Not difficult ☐
- A little difficult ☐
- Somewhat difficult ☐
- A good deal difficult ☐
- A great deal difficult ☐

During the last 7 days…

2. How feverish did you feel (have a temperature)? *(Check one)*

- Not feverish ☐
- A little feverish ☐
- Somewhat feverish ☐
- A good deal feverish ☐
- A great deal feverish ☐

During the last 7 days…

3. How tired did you feel? *(Check one)*

- Not tired ☐
- A little tired ☐
- Somewhat tired ☐
- A good deal tired ☐
- A great deal tired ☐

During the last 7 days…

4. How bad were your chills or sweats? *(Check one)*

- No chills or sweats ☐
- Slightly Bad ☐
- Moderately Bad ☐
- Very Bad ☐
- Extremely Bad ☐

Please continue to the next page.

During the last 7 days…

5. How bad was your cough? *(Check one)*

- No cough ☐
- Slightly Bad ☐
- Moderately Bad ☐
- Very Bad ☐
- Extremely Bad ☐

During the last 7 days…

6. How much mucus did you cough up? *(Check one)*

- No mucus ☐
- A little mucus ☐
- Some mucus ☐
- A good deal of mucus ☐
- A great deal of mucus ☐

During the last 7 days…

7. How much tightness in the chest did you have? *(Check one)*

- No tightness ☐
- A little tightness ☐
- Some tightness ☐
- A good deal of tightness ☐
- A great deal of tightness ☐

During the last 7 days…

8. How bad was your wheezing? *(Check one)*

- No wheezing ☐
- Slightly Bad ☐
- Moderately Bad ☐
- Very Bad ☐
- Extremely Bad ☐

Please continue to the next page.

During the last 7 days…

9. How difficult was it to sleep? *(Check one)*

- Not difficult ☐
- A little difficult ☐
- Somewhat difficult ☐
- A good deal difficult ☐
- A great deal difficult ☐

During the last 7 days…

10. How worried were you about your cystic fibrosis? *(Check one)*

- Not worried ☐
- A little worried ☐
- Somewhat worried ☐
- A good deal worried ☐
- A great deal worried ☐

During the last 7 days…

11. How cranky did you feel? *(Check one)*

- Not cranky ☐
- A little cranky ☐
- Somewhat cranky ☐
- A good deal cranky ☐
- A great deal cranky ☐

During the last 7 days…

12. How sad or depressed did you feel? *(Check one)*

- Not sad or depressed ☐
- A little sad or depressed ☐
- Somewhat sad or depressed ☐
- A good deal sad or depressed ☐
- A great deal sad or depressed ☐

Please continue to the next page.

During the last 7 days…

13. How frustrated did you feel? *(Check one)*

- Not frustrated ☐
- A little frustrated ☐
- Somewhat frustrated ☐
- A good deal frustrated ☐
- A great deal frustrated ☐

During the last 7 days…

14. How much time did you spend sitting or lying down? *(Check one)*

- Hardly any of the time ☐
- Some of the time ☐
- Most of the time ☐
- All of the time ☐

During the last 7 days…

15. Did you reduce your usual activities? *(Check one)*

- Yes ☐
- No ☐

During the last 7 days…

16. Did you miss work or school? *(Check one)*

- Yes ☐
- No ☐
- Does not apply, I did not have work or school in the last 7 days ☐

APPENDIX 4. Cystic Fibrosis questionnaire - revised (CFQ-R) Self-Report – Two Week Recall; version 2

TEEN/ADULT VERSION FOR AGES 14 THROUGH ADULTHOOD

During the past two weeks, to what extent have you had difficulty:	A lot of difficulty	Some difficulty	A little difficulty	No difficulty
1. Performing vigorous activities such as running or playing sports	☐	☐	☐	☐
2. Walking as fast as others	☐	☐	☐	☐
3. Carrying or lifting heavy things such as books, groceries, or school bags	☐	☐	☐	☐
4. Climbing one flight of stairs	☐	☐	☐	☐
5. Climbing stairs as fast as others	☐	☐	☐	☐

***During the past two weeks**, indicate how often:*	Always	Often	Sometimes	Never
6. You felt well	☐	☐	☐	☐
7. You felt worried	☐	☐	☐	☐
8. You felt useless	☐	☐	☐	☐
9. You felt tired	☐	☐	☐	☐
10. You felt energetic	☐	☐	☐	☐
11. You felt exhausted	☐	☐	☐	☐
12. You felt sad	☐	☐	☐	☐

Please circle the number indicating your answer. Please choose only one answer for each question.

*Thinking about the state of your health over the last **two weeks**:*

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

14. How do you feel about eating?
    1. Just thinking about food makes you feel sick
    2. You never enjoy eating
    3. You are sometimes able to enjoy eating
    4. You are always able to enjoy eating

15. To what extent do your treatments make your daily life more difficult?
    1. Not at all
    2. A little
    3. Moderately
    4. A lot

16. How much time do you currently spend each day on your treatments?
    1. A lot
    2. Some
    3. A little
    4. Not very much

17. How difficult is it for you to do your treatments (including medications) each day?
    1. Not at all
    2. A little
    3. Moderately
    4. Very

18. How do you think your health is now?

1. Excellent
2. Good
3. Fair
4. Poor

Please select a box indicating your answer.

*Thinking about your health during the past **two weeks**, indicate the extent to which each sentence is true or false for you.*	Very true	Somewhat true	Somewhat false	Very false
19. I have trouble recovering after physical effort	☐	☐	☐	☐
20. I have to limit vigorous activities such as running or playing sports	☐	☐	☐	☐
21. I have to force myself to eat	☐	☐	☐	☐
22. I have to stay at home more than I want to	☐	☐	☐	☐
23. I feel comfortable discussing my illness with others	☐	☐	☐	☐
24. I think I am too thin	☐	☐	☐	☐
25. I think I look different from others my age	☐	☐	☐	☐
26. I feel bad about my physical appearance	☐	☐	☐	☐
27. People are afraid that I may be contagious	☐	☐	☐	☐
28. I get together with my friends a lot	☐	☐	☐	☐
29. I think my coughing bothers others	☐	☐	☐	☐
30. I feel comfortable going out at night	☐	☐	☐	☐
31. I often feel lonely	☐	☐	☐	☐
32. I feel healthy	☐	☐	☐	☐
33. It is difficult to make plans for the future (for example, going to college, getting married, advancing in a job, etc.)	☐	☐	☐	☐
34. I lead a normal life	☐	☐	☐	☐

Questions 35 through 38 are about school, work, or other daily tasks.

35. To what extent did you have trouble keeping up with your schoolwork, professional work, or other daily activities during the past **two weeks**?

1. You have had no trouble keeping up
2. You have managed to keep up but it's been difficult
3. You have been behind
4. You have not been able to do these activities at all

36. How often were you absent from school, work, or unable to complete daily activities during the last two weeks because of your illness or treatments?

☐ Always ☐ Often ☐ Sometimes ☐ Never

37. How often does CF get in the way of meeting your school, work, or personal goals

☐ Always ☐ Often ☐ Sometimes ☐ Never

38. How often does CF interfere with getting out of the house to run errands such as shopping or going to the bank?

☐ Always ☐ Often ☐ Sometimes ☐ Never

Indicate how you have been feeling during the past two weeks.	A great deal	Somewhat	A little	Not at all
39. Have you had trouble gaining weight?	☐	☐	☐	☐
40. Have you been congested?	☐	☐	☐	☐
41. Have you been coughing during the day?	☐	☐	☐	☐
42. Have you had to cough up mucus?	☐	☐	☐	☐ Go to Question 44

43. Has your mucus been mostly: ☐ Clear ☐ Clear to yellow ☐ Yellowish-green ☐ Green with traces of blood ☐ Don't know

How often during the past two weeks:	Always	Often	Sometimes	Never
44. Have you been wheezing?	☐	☐	☐	☐
45. Have you had trouble breathing?	☐	☐	☐	☐
46. Have you woken up during the night because you were coughing?	☐	☐	☐	☐
47. Have you had problems with gas?	☐	☐	☐	☐
48. Have you had diarrhea?	☐	☐	☐	☐
49. Have you had abdominal pain?	☐	☐	☐	☐
50. Have you had eating problems?	☐	☐	☐	☐

PARENT VERSION FOR CHILDREN AGES 6-13 (PARENTS REPORTING ON THE CHILD'S HRQOL)

To what extent has your child had difficulty:	**A lot of difficulty**	**Some difficulty**	**A little difficulty**	**No difficulty**
1. Performing vigorous activities such as running or playing sports	☐	☐	☐	☐
2. Walking as fast as others	☐	☐	☐	☐
3. Climbing stairs as fast as others	☐	☐	☐	☐
4. Carrying or lifting heavy objects such as books, a school bag, or backpack	☐	☐	☐	☐
5. Climbing several flights of stairs	☐	☐	☐	☐

Please check the box matching your response.

During the past two weeks, indicate how often your child:	**Always**	**Often**	**Sometimes**	**Never**
6. Seemed happy	☐	☐	☐	☐
7. Seemed worried	☐	☐	☐	☐
8. Seemed tired	☐	☐	☐	☐
9. Seemed short-tempered	☐	☐	☐	☐
10. Seemed well	☐	☐	☐	☐
11. Seemed grouchy	☐	☐	☐	☐
12. Seemed energetic	☐	☐	☐	☐
13. Was absent or late for school or other activities because of his/her illness or treatments	☐	☐	☐	☐

Please circle the number indicating your answer. Please choose only one answer for each question.

*Thinking about the state of your child's health over the past **two weeks**, indicate:*

14. The extent to which your child participated in sports and other physical activities, such as gym class
1. Has not participated in physical activities
2. Has participated less than usual in sports
3. Has participated as much as usual but with some difficulty
4. Has been able to participate in physical activities without any difficulty

15. The extent to which your child has difficulty walking
1. He or she can walk a long time without getting tired
2. He or she can walk a long time but gets tired
3. He or she cannot walk a long time, because he or she gets tired quickly
4. He or she avoids walking whenever possible, because it's too tiring for him or her

	Very true	Somewhat true	Somewhat false	Very false
16. My child has trouble recovering after physical effort	☐	☐	☐	☐
17. Mealtimes are a struggle	☐	☐	☐	☐
18. My child's treatments get in the way of his/her activities	☐	☐	☐	☐
19. My child feels small compared to other kids the same age	☐	☐	☐	☐
20. My child feels physically different from other kids the same age	☐	☐	☐	☐
21. My child thinks that he/she is too thin	☐	☐	☐	☐
22. My child feels healthy	☐	☐	☐	☐
23. My child tends to be withdrawn	☐	☐	☐	☐
24. My child leads a normal life	☐	☐	☐	☐
25. My child has less fun than usual	☐	☐	☐	☐
26. My child has trouble getting along with others	☐	☐	☐	☐
27. My child has trouble concentrating	☐	☐	☐	☐
28. My child is able to keep up with his/her school work or summer activities (e.g. camp)	☐	☐	☐	☐
29. My child is not doing as well as usual in school or summer activities (e.g. camp)	☐	☐	☐	☐
30. My child spends a lot of time on his/her treatments everyday	☐	☐	☐	☐

Please circle the number indicating your answer. Please choose only one answer for each question.

31. How difficult is it for your child to do his/her treatments (including medications) each day?
1. Not at all
2. A little
3. Moderately
4. Very

32. How do you think your child's health is now?
1. Excellent
2. Good
3. Fair
4. Poor

Please indicate how your child has been feeling during the past two weeks.	A great deal	Somewhat	A little	Not at all
33. My child had trouble gaining weight	☐	☐	☐	☐
34. My child was congested	☐	☐	☐	☐
35. My child coughed during the day	☐	☐	☐	☐
36. My child had to cough up mucus	☐	☐	☐	☐ ↓ **Go to Question 38**

37. My child's mucus has been mostly: ☐ Clear ☐ Clear to yellow ☐ Yellowish-green ☐ Green with traces of blood ☐ Don't know

During the past two weeks:	Always	Often	Sometimes	Never
38. My child wheezed	☐	☐	☐	☐
39. My child had trouble breathing	☐	☐	☐	☐
40. My child woke up during the night because he/she was coughing	☐	☐	☐	☐
41. My child had gas	☐	☐	☐	☐
42. My child had diarrhea	☐	☐	☐	☐
43. My child had abdominal pain	☐	☐	☐	☐
44. My child has had eating problems	☐	☐	☐	☐

APPENDIX 5. EQ-5D-5L & EQ-5Dy

add copy of questionnaires

Under each heading, please tick the **ONE** box that best describes your health **TODAY**

MOBILITY

I have no problems in walking about	❑
I have slight problems in walking about	❑
I have moderate problems in walking about	❑
I have severe problems in walking about	❑
I am unable to walk about	❑

SELF-CARE

I have no problems washing or dressing myself	❑
I have slight problems washing or dressing myself	❑
I have moderate problems washing or dressing myself	❑
I have severe problems washing or dressing myself	❑
I am unable to wash or dress myself	❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities	❑
I have slight problems doing my usual activities	❑
I have moderate problems doing my usual activities	❑
I have severe problems doing my usual activities	❑
I am unable to do my usual activities	❑

PAIN / DISCOMFORT

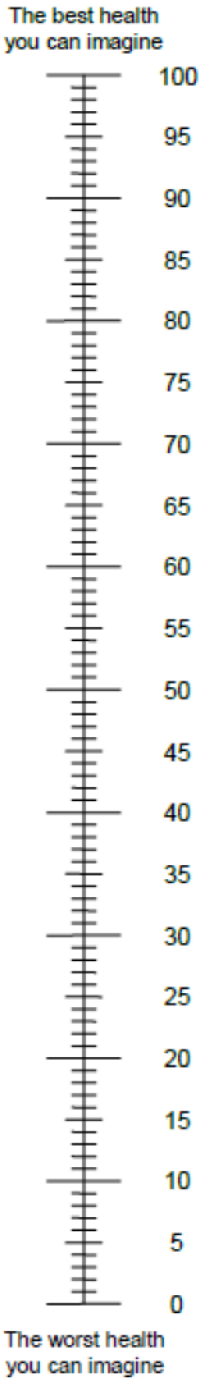
I have no pain or discomfort	❑
I have slight pain or discomfort	❑
I have moderate pain or discomfort	❑
I have severe pain or discomfort	❑
I have extreme pain or discomfort	❑

ANXIETY / DEPRESSION

I am not anxious or depressed	❑
I am slightly anxious or depressed	❑
I am moderately anxious or depressed	❑
I am severely anxious or depressed	❑
I am extremely anxious or depressed	❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



APPENDIX 6. Instructions for Use of AeroVanc Inhaler

INSTRUCTIONS FOR USE OF AEROVANC INHALER

Please read the following instructions carefully to learn how to use and care for your AeroVanc inhaler.

- Only use the AeroVanc inhaler provided. Do not use AeroVanc or Placebo capsules with any other inhaler, and do not use the AeroVanc inhaler to take any other capsule medicine.
- **Do not swallow the capsules.** The powder in the capsules is for you to inhale.

The AeroVanc inhaler enables you to inhale the product contained in an AeroVanc or Placebo capsule.

AeroVanc and Placebo capsules are supplied in aluminum foil peelable laminated blisters. Each blister strip contains 4 capsules in a 2 x 2 configuration separated by a perforation into morning and evening doses. There are 7 blister strips plus 1 spare blister strip in each weekly box. Four weekly boxes, 4 AeroVanc inhalers plus 1 spare inhaler, these instructions for use, a quick start sheet, and a returns bag are included in each 28-day clinical kit.

How to use your inhaler

1. Pull off the cap.

2. Open the inhaler:

Hold the base of the inhaler firmly and twist the mouthpiece in the direction of the arrow. This opens the inhaler.

3. Prepare the capsule:

Immediately before use, with dry hands, carefully tear and remove the end of the blister strip. Peel open the foil blister from one of the halves only, taking care to only expose one of the two capsules from that half. Remove one capsule. Do not open by pushing the capsule through the foil since this can damage the capsule.

4. Insert the capsule:

Place the capsule into the capsule chamber.

Never place a capsule directly into the mouthpiece.

5. Close the inhaler:

Close the inhaler until you hear a “click”.

6. Pierce the capsule:

Hold the inhaler upright with the mouthpiece pointing up.

Pierce the capsule by firmly pressing together both side buttons at the same time. **Do this only once.**

You should hear a “click” as the capsule is being pierced.

7. Release the side buttons fully.

8. Breathe out:

Before placing the mouthpiece in your mouth, breathe out fully.

Do not blow into the mouthpiece.

9. Inhale the medicine:

To breathe the medicine deeply into your airways:

- Hold the inhaler in a horizontal orientation. The side buttons should be facing left and right. Do not press the side buttons.
- Place the mouthpiece in your mouth and close your lips firmly around the mouthpiece.
- Breathe in quickly and deeply.

As you breathe in through the inhaler, the capsule spins around in the chamber and you should hear a whirring noise. If you do not hear a whirring noise, the capsule may be stuck in the capsule chamber. If this happens:

- Open the inhaler and carefully loosen the capsule by tapping the base of the inhaler. Close the inhaler. Do not press the side buttons again.
- Inhale the medicine again by repeating Steps 8 and 9.

You may experience a slight taste as the medicine goes into your lungs. This is normal.

Occasionally, very small pieces of the capsule can get past the screen and enter your mouth. If this happens, you may be able to feel these pieces on your tongue. It is not harmful if these pieces are swallowed or inhaled. The chances of the capsule shattering will be increased if the capsule is accidentally pierced more than once (Step 6).

10. Hold your breath:

After you have inhaled the medicine:

- Hold your breath for at least 5-10 seconds or as long as you comfortably can while taking the inhaler out of your mouth.
- Then breathe out.
- Open the inhaler to see if any powder is left in the capsule.

If there is powder left in the capsule:

- Close the inhaler.
- Repeat Steps 8, 9 and 10.

Most people are able to empty the capsule with one or two inhalations.

Additional information:

Some people may occasionally cough briefly soon after inhaling the medicine. If you do, don't worry. As long as the capsule is empty, you have received enough of your medicine.

11. After you have finished taking the study drug:

Open the mouthpiece again and remove the empty capsule by tipping it out of the capsule chamber. Put the empty capsule in the plastic waste bag provided for return to the clinical site.

Repeat Steps 3 to 11 with the second of the two capsules in that half of the blister strip.

Close the inhaler and replace the cap.

Do not store the capsules in the AeroVanc inhaler.

REMEMBER:

- Do not swallow AeroVanc or Placebo capsules.
- Only use the AeroVanc inhaler provided.
- AeroVanc and Placebo capsules must always be stored in the sealed foil blister, and only removed immediately before use.
- Never place an AeroVanc or Placebo capsule directly into the mouthpiece of the AeroVanc inhaler.
- Do not press the side buttons more than once.
- Never blow into the mouthpiece of the AeroVanc inhaler.
- Always release the push buttons before inhalation.
- Do not clean the AeroVanc inhaler.
- Never take the AeroVanc inhaler apart.
- Do not store the capsules in the AeroVanc inhaler.
- Always keep the AeroVanc inhaler and AeroVanc and Placebo capsules in a dry place.