CLINICAL STUDY PROTOCOL

A Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase 2 Trial to Evaluate Efficacy and Safety of Lenabasum in Cystic Fibrosis

Protocol Number:	JBT101-CF-002
Study Drug:	Lenabasum
Investigational New Drug Number:	126359
EudraCT Number:	2017-003723-29
Indication:	Cystic fibrosis
Clinical Development Phase:	2
Date of Protocol:	05 NOV 2019
Version:	3.4
Name and Affiliation of Principal Investigators:	[redacted]
Responsible Medical Officer:	
Sponsor:	Corbus Pharmaceuticals, Inc. 500 River Ridge Drive, Second Floor Norwood, MA 02062 USA

Statement of Good Clinical Practice (GCP) Compliance

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, clinical research guidelines established by the Code of Federal Regulations (Title 21, CFR Parts 50, 56, and 312), and International Conference on Harmonisation of Technical Requirements of Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) Guidelines. Essential study documents have been archived in accordance with applicable regulations.

Confidentiality Statement

information is disclosed in confidence must be informed that the information is confidential and must not be disclosed by them to a third party.

PROTOCOL APPROVAL

Protocol Number: JBT101-CF-002

Protocol Title: A Multicenter, Randomized, Double-blind, Placebo-controlled Phase 2 Trial to Evaluate Efficacy and Safety of Lenabasum in Cystic Fibrosis

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

Sponsor approval:

[redacted]

PRINCIPAL INVESTIGATOR PROTOCOL AGREEMENT PAGE

PROTOCOL JBT101-CF-002

I agree:

- To assume responsibility for the proper conduct of this clinical study at this site and to conduct the study in compliance with this protocol, any future amendments, and with any other study conduct procedures provided by the sponsor.
- That I am aware of, and will comply with, the internationally recognized code of Good Clinical Practices and all other applicable regulatory requirements to obtain written and dated approval from the Ethics Committee for the study protocol, written informed consent, informed consent form updates, subject recruitment procedures (e.g., advertisements), and any other written information to be provided to the subjects, before initiating this clinical study.
- Not to implement any changes to or deviations from the protocol without prior agreement from the sponsor except to eliminate an immediate hazard to the study subjects, or when changes involve only logistical or administrative aspects of the clinical study.
- To permit direct monitoring and auditing by the sponsor or sponsor's representatives and inspection by the appropriate regulatory authorities.
- That I am thoroughly familiar with the appropriate use of the study drugs, as described in this protocol, and any other information provided by the sponsor or designee, including, but not limited to, the current Investigator's Brochure or equivalent document and approved product label (if applicable).
- To provide sufficient time and an adequate number of qualified staff and facilities for the foreseen duration of the clinical study to conduct the study properly, ethically, and safely.
- To ensure that all persons assisting in this study are adequately informed about the protocol, study drugs, and their clinical study-related duties and functions.

Principal Investigator

Signature	Date
Printed name	

1 SYNOPSIS

A Multicenter, Randomized, Double-blind, Placebo-controlled Phase 2 Trial to Evaluate Efficacy and Safety of Lenabasum in Cystic Fibrosis

INVESTIGATIONAL PRODUCT: Lenabasum

INDICATION: Cystic fibrosis

INVESTIGATIONAL SITES/LOCATIONS: Up to 100 sites in North America and Europe are planned

OBJECTIVES AND ENDPOINTS:

Primary efficacy objective	**Primary endpoint**
To evaluate the efficacy of lenabasum 20 mg twice per day (BID) compared to placebo in the treatment of cystic fibrosis (CF) by assessing the rate of pulmonary exacerbations (PEx) using primary definition of PEx	Rate of PEx using primary definition of PEx with lenabasum 20 mg BID, compared to placebo, during the treatment period
Secondary efficacy objective	**Secondary endpoints**
1. To evaluate the efficacy of lenabasum 20 mg BID compared to placebo in the treatment of CF by assessing other efficacy endpoints	a. Event rate of PEx using secondary definition of PEx with lenabasum 20 mg BID compared to placebo b. Time to first new PEx using primary definition of PEx with lenabasum 20 mg BID compared to placebo c. Time to first PEx using secondary definition of PEx with lenabasum 20 mg BID compared to placebo d. Change from baseline in CFQ-R respiratory symptom domain with lenabasum 20 mg BID compared to placebo e. Change from baseline in FEV1 % predicted with lenabasum 20 mg BID compared to placebo
2. To evaluate the efficacy of lenabasum 5 mg BID compared to placebo in the treatment of CF	a. Rate of pulmonary exacerbations (PEx) using primary definition of PEx with lenabasum 5 mg BID compared to placebo, during the treatment period b. Event rate of PEx using secondary definition of PEx with lenabasum 5 mg BID compared to placebo

	c. Time to first new PEx using primary definition of PEx with lenabasum 5 mg BID compared to placebo d. Time to first PEx using secondary definition of PEx with lenabasum 5 mg BID compared to placebo e. Change from baseline in CFQ-R respiratory symptom domain with lenabasum 5 mg BID compared to placebo f. Change from baseline in FEV1 % predicted with lenabasum 5 mg BID compared to placebo
[redacted]	

[redacted]

Safety objectives	Safety endpoints
To evaluate safety of lenabasum 20 mg BID and lenabasum 5 mg BID treatment and placebo treatment	a. TEAEs b. Changes in vital signs, physical examination, blood and urine laboratory safety tests and electrocardiograms
To evaluate tolerability of lenabasum 20 mg BID and lenabasum 5 mg BID treatment	Treatment discontinuations with lenabasum treatments compared to placebo

STUDY DESIGN:

This is a multicenter, double-blind, randomized, placebo-controlled, parallel group trial of efficacy and safety of treatment of CF subjects with lenabasum 20 mg BID and lenabasum 5 mg BID.

This trial includes analyses of event rate of and time to PEx. In this study, primary definition of PEx is based on the physician decision to treat with oral, intravenous or inhaled antibiotic(s) in the presence of at least 4/12 Fuch's criteria. This definition excludes prophylactic antibiotics given at regularly scheduled times. A new PEx is a PEx that occurs ≥ 28 days from completion of antibiotic treatment of any preceding PEx. The prophylactic antibiotics taken at the scheduled time at their regular dose are not counted in this definition.

The target population is males and females with CF ≥ 12 years of age with FEV1 ≥ 40% predicted and < 100% predicted in 12 months before screening. The target population will be enriched for subjects with increased risk of a new PEx in the next 6 months. Subjects must have 2 or 3 new PEx treated with intravenous (IV) antibiotics in the 12 months before screening. Alternatively, if the subject had only 1 new PEx treated with IV antibiotics in the

last 12 months, then that subject must have ≥ 1 other new PEx treated with oral antibiotics in the last 12 months before screening; this excludes transitioning from oral to IV or IV to oral antibiotics for the same PEx. Antibiotics for the most recent PEx must be completed ≥ 28 days before Visit 1.

See Table 1 below for the eligibility criterion by number of new PEx in the 12 months before screening.

Table 1 Eligibility by Number of New PEx in 12 Months before Screening

New PEx treated with intravenous antibiotics, N	New PEx treated with oral antibiotics, N	Eligible by PEx criteria
2 or 3	No requirement	Yes
1	≥ 1	Yes
0, > 3	Not applicable	No

Assuming a screen failure rate of ~15%, ~490 subjects will be screened to identify a target of 415 eligible subjects. Assuming a ~15% drop-out rate, ~352 subjects are expected to complete the study.

Subjects will be randomized centrally to treatment assignment before dosing in a 2:1:2 ratio to 1 of 3 treatment cohorts:

1. Cohort 1: Lenabasum 20 mg BID, n = 166.
2. Cohort 2: Lenabasum 5 mg BID, n = 83.
3. Cohort 3: Placebo BID, n = 166.

Randomization will be stratified by factors that influence risk of PEx in the next 6 months or may be associated with differences in standard-of-care including treatment with CFTR-targeting treatments: number of previous PEx requiring IV antibiotics in the previous year (1 versus2 or 3), FEV1 % predicted at baseline (< 70% versus ≥ 70% predicted) and location of site (United States versus Canada, and Europe).

Duration and Visits

The screening period is up to 4 weeks before Visit 1. Active dosing with study drug is 28 weeks. There will be 8 scheduled study visits during active dosing with study drug, labeled Visits 1 - 8, which occur at Visit 1 and at the completion of Weeks 4, 8, 12, 16, 20, 24, and 28. For Visits 1-8, the window for each visit is ± 7 days. Subjects who complete Visit 8 on study drug will have a Safety Follow-up Visit labeled Visit 9. Visit 9 is 28 ± 7 days after Visit 8.

Subjects who discontinue early from the study drug and do not withdraw consent will be asked to return for off-treatment safety and efficacy assessments at Visit 5 and Visit 8, as applicable. Otherwise, they will return 28 ± 7 days after the last dose of study drug for a Safety Follow-up Visit that is identical to Visit 9.

All subjects who develop acute signs and symptoms of worsening lung disease will be asked to return to the site for evaluation at a Possible PEx Visit.

Unscheduled Visits may be necessary to assess the subject for safety purposes unrelated to new respiratory symptoms or a PEx.

During Visit 8 (or ET) subjects may be asked to participate in a two-year safety follow-up study. Subjects who agree to participate in the follow-up study will be consented under a separate protocol.

Efficacy Assessments

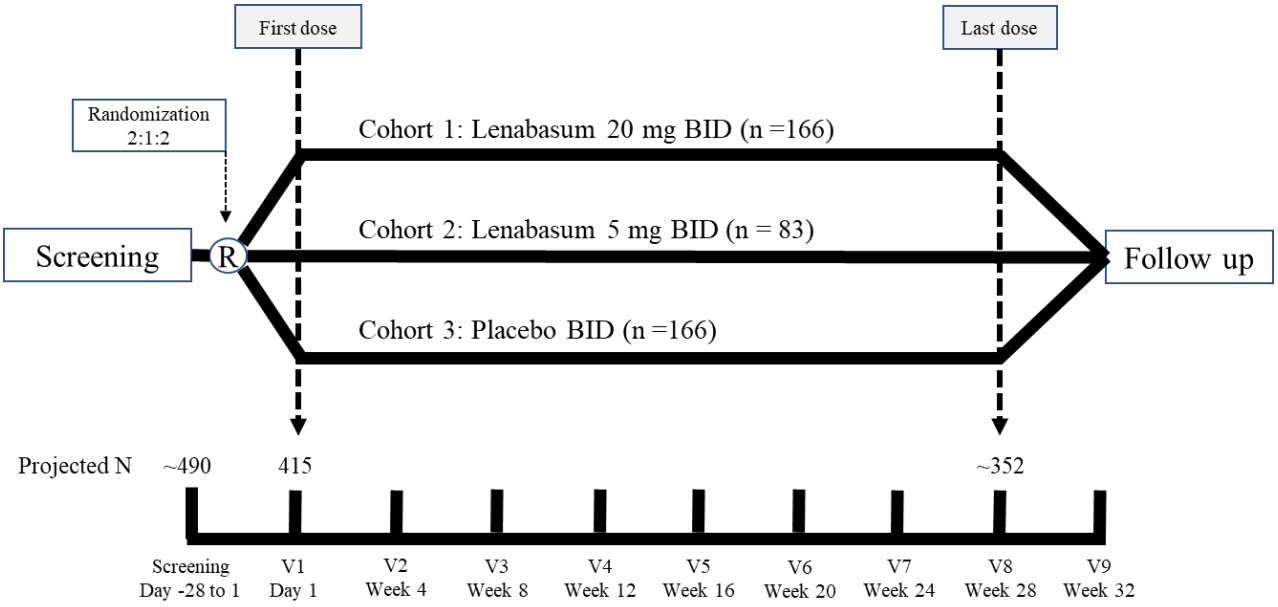
- Physician completion of antibiotic use for respiratory signs and symptoms questionnaire (AUR-Q) at all study visits (screening, Visits 1- 9, Possible PEx Visits, unscheduled visits).
- Spirometry at screening, Visits 1- 9 and Possible PEx Visits.
- CRISS questionnaires at screening, Visits 1-9 and Possible PEx Visits.
- BMI at screening, Visits 1- 9 and Possible PEx Visits.
- CFQ-R questionnaire at screening, Visit 1, Visit 5, Visit 8 and Possible PEx Visits.
- Biomarkers in blood and sputum at Visit 1, Visit 2, Visit 5, Visit 8 and Possible PEx Visits.
- Common CF pathogens in sputum at Visit 1, Visit 2, Visit 5, Visit 8 and Possible PEx Visits.

[redacted]

Safety Assessments

- Adverse events (AEs) including serious adverse events (SAEs) at screening and Visits 1-9, Possible PEx Visits, and Unscheduled Visits.
- Vital signs consisting of systolic and diastolic blood pressure (BP), pulse rate (P), respiratory rate (R), body temperature (T), weight, height, and oxygen (O_2) saturation at screening and Visits 1-9, Possible PEx Visits, and Unscheduled Visits. Body mass index (BMI) will be calculated centrally.
- Laboratory safety tests from blood and urine at screening and Visits 1-9 and as indicated during Possible PEx Visits and Unscheduled Visits.
- ECGs will be completed by subjects at Visit 1 before and 3 ± 0.5 hours after administration of the first study drug dose, and pre-dose at Visit 5 and at Visit 8.
- Physical examination

STUDY SCHEMATIC



R = randomization; V = Visit; N = number of subjects; BID = twice daily

SUBJECTS (PLANNED): 415 subjects

PATIENT POPULATION:

Target population for this study is subjects ≥ 12 years of age with known diagnosis of CF, with history of prior PEx in the last 12 months, but otherwise stable without any antibiotic use within 28 days of Visit 1 (prophylactic antibiotic use is allowed).

STUDY PRODUCTS, DOSE AND MODE OF ADMINISTRATION:

Study drugs are formulated as powder-in-capsules of lenabasum 20 mg, lenabasum 5 mg and placebo.

- Lenabasum: The preparation of lenabasum that will be used in this study is a ≥ 97% pure synthetic preparation of a dimethylheptyl derivative of tetrahydrocannabinol-11-oic acid.
- Placebo: Microcrystalline cellulose (no active ingredient).

Lenabasum and placebo capsules are identical in terms of appearance. Both are packaged in the same type container closures with the same number of capsules.

Subjects will self-administer the study drug orally. The first dose of study drug will be administered at the site at Visit 1, and subjects will be observed for TEAEs for at least 30 minutes following dosing.

DURATION OF TREATMENT: 28 weeks

DISCONTINUATION FROM TREATMENT:

Removal of Subjects from Therapy or Assessments:

An individual subject will have study drug permanently discontinued if any of the following occur in the subject in question:

- Withdrawal of consent
- Pregnancy
- Any serious TEAE probably or definitely-related to lenabasum
- Any life-threatening AE

Unless consent is withdrawn or the subject is lost to follow-up, subjects who have study drug permanently discontinued prematurely will be asked to return for Visit 5 (if they have not already had Visit 5) and Visit 8, for all assessments scheduled at those visits. If they decline, they will be asked to return for a Safety Follow-up Visit 28 ± 7 days after the last dose of study drug, which is identical to Visit 9 assessments.

Premature Termination or Suspension of the Study:

This study may be suspended or prematurely terminated if there is sufficient reasonable cause. If any of the following events occur in a subject during enrollment, study entry and randomization of new subjects into the study will be suspended until review of the event in question occurs by the Data Monitoring Committee (DMC):

- Death in any subject probably or definitely-related to lenabasum.
- A life-threatening clinical event probably or definitely-related to lenabasum.
- Determination of unexpected, significant, or unacceptable risk to subjects that contradicts dosing of additional subjects in the opinion of the Chief Medical Officer of Corbus Pharmaceuticals, Inc. (Corbus).
- Any new information about the execution of the trial, that in the opinion of Chief Medical Officer of Corbus contraindicates further study entry and randomization of new subjects, such as unsatisfactory enrollment with respect to quantity or quality, insufficient adherence to protocol requirements, data that are not sufficiently complete and/or evaluable, falsification of records, or determination of futility.

Administration of study drug may continue during the time of review in subjects who are already receiving study drug, based on the judgment of the Chief Medical Officer of Corbus.

An expedited and cumulative review of safety data and the circumstances of the event(s) in question will be conducted by the DMC, with additional external expertise as needed, to make recommendations to Corbus whether screening, randomization, and/or dosing can resume or should be discontinued, whether the protocol should be modified, or whether the study should be discontinued permanently. Upon consideration of a cumulative review of safety and other data, the study can be discontinued permanently by Corbus.

Written notification, documenting the reason for study suspension or termination, will be provided by Corbus to the investigators and the respective country regulatory authorities. If the study is suspended or prematurely terminated, the investigators will promptly inform the reviewing Independent Ethics Committee/Institutional Review Board (hereafter referred to as the Ethics Committee or EC) at each site and will provide the reason(s) for the suspension or termination. Review and approval by the reviewing EC at each site is required for resumption of the study in the event the study is interrupted.

STATISTICAL ANALYSES:

The Statistical Analysis Plan (SAP) will be completed before database locking and unblinding.

The study is expected to enroll approximately 415 subjects, with ~166 subjects each in the lenabasum 20 mg BID and placebo BID cohorts and ~83 subjects in the lenabasum 5 mg BID cohort (accounting for an approximate 15% dropout rate). The study provides 80% power to detect a significant difference between the lenabasum 20 mg BID dose and placebo in the primary endpoint (PEx event rate) at a two-sided alpha of 0.05. This is based on an event rate ratio of 0.65 when the the event rate in the control group is 0.80 (a 35% event rate reduction in the lenabasum group).

This also provides 90% power to detect a significant difference between lenabasum 20 mg BID and placebo BID in the secondary endpoint, time to first PEx. This is based on an estimate of the probability of an event (PEx) in the placebo group of 0.60, an estimated hazard ratio of 0.60 (risk reduction 0.40), and the probability of an event in the lenabasum group of 0.36.

There will be four analysis populations. The modified intent to treat (mITT) population will consist of all randomized subjects who received study drug. These will be categorized by planned treatment. This population will be used for the primary analysis. The safety set (SS) will consist of all subjects who received study drug. This population will be categorized by actual treatment.

The per protocol set (PPS) will consist of the mITT population minus subjects with major protocol deviations. Major protocol violations are defined as those that may have a substantial effect on the efficacy assessment and will be determined before database lock. The PPS will be used in sensitivity analyses.

[redacted]

[redacted]

All data will be provided in data listings sorted by treatment groups, subject number, and visit. Summary data will be presented in tabular format by treatment group. Categorical data will be summarized by the number and percentage of subjects in each category. Continuous data will be summarized by descriptive statistics including subject number (n), mean, standard deviation (SD), median, and range. All percentages will be rounded to 1 decimal place. Differences between treatment groups will be calculated as active – placebo. The baseline measure will be defined as the last non-missing measure before initiation of study drug at Visit 1.

Efficacy comparisons will be made between each dose of lenabasum and placebo. The event rate of new PEx will be compared between the lenabasum and placebo groups using a Poisson regression model. A sensitivity analysis will be performed using a negative binomial regression model.

For time to first PEx, a Cox-proportional hazards (regression) model will be used for comparing the covariate-adjusted difference in event time distributions between the active and placebo groups. Covariates in the model will include all stratification variables. A log rank test will also be performed as a sensitivity analysis.

Continuous variable endpoints such as change in CRISS, change in CFQ-R domain scores, change in FEV1 % predicted, change in FEV1 mL, change in FVC % predicted, change in FVC mL, and change in BMI will be analyzed using a mixed model for repeated measures (MMRM). The MMRM model will include stratification factors, visit, treatment, and treatment-by-visit interaction as fixed effects and baseline as a covariate.

The treatment comparisons for the proportion of subjects who improve by predefined criteria (for CRISS, CFQ-R, and FEV1 % predicted) will be performed using a Cochran-Mantel-Haenszel test.

Data from subjects who discontinue study drug but do not discontinue the study and return for off-treatment Visit 5 and 8, as applicable, will be included as data for that cohort. Thus, both on-treatment assessment of PEx and assessments of PEx after treatment discontinuation (for subjects who discontinued dosing early) will be included in primary analyses.

No formal statistical testing will be performed to compare the safety in different cohorts.

[redacted]

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LIST OF IN-TEXT FIGURES

3 LIST OF ABBREVIATIONS AND GLOSSARY OF TERMS

3.1 List of Abbreviations

Abbreviation	Definition
AE	Adverse event
ARCI-M	Addiction research center inventory-marijuana
AUC	Area under the curve
AUR-Q	Antibiotic Use for Respiratory Signs and Symptoms questionnaire
BID	Twice per day
BP	Blood pressure
CB	Cannabinoid
CB1	Cannabinoid type 1 receptor
CB2	Cannabinoid type 2 receptor
CBC	Complete blood count
CF	Cystic fibrosis
CFF-TDN	Cystic Fibrosis Foundation Therapeutics Development Network
CFQ-R	Cystic Fibrosis Questionnaire – Revised
CFR	Code of federal regulations
CFTR	Cystic fibrosis transmembrane conductance regulator
C_{max}	Concentration maximum
Corbus	Corbus Pharmaceuticals, Inc. and its designees
CRF	Case report form
Cox	Cox proportional hazard
CRISS	Cystic Fibrosis Respiratory Symptom Diary - Chronic Respiratory Infection Symptom Score
CRP	C-reactive protein
CTCAE	Common Terminology Criteria for Adverse Events
DAE	Discontinuation adverse event
DEA	Drug Enforcement Agency
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EC	Ethics committee
EDC	Electronic data capture
EMA	European Medicines Agency
ESR	Erythrocyte sedimentation rate
EU	European Union
FDA	Food and Drug Administration
FEV1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GCP	Good Clinical Practice
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IL	Interleukin
IMPD	Investigational Medicinal Product Dossier
IND	Investigational New Drug Application
ITT	Intent to treat

Abbreviation	Definition
IV	Intravenous
IWRS	Interactive web-based response system
MDRD	Modification of Diet in Renal Disease
mITT	Modified intent to treat
MMRM	Mixed model repeated measures
NCI	National Cancer Institute
NOAEL	No observed adverse effect level
P	Pulse rate
PEx	Pulmonary exacerbation(s)
PG	Prostaglandin
PK	Pharmacokinetic(s)
PKAS	Pharmacokinetic analysis set
PPS	Per protocol set
QD	Once per day
QTc	Corrected QT
R	Respiratory rate
SAE	Serious adverse event
SID	Subject identification number
SPMs	Specialized Pro-resolving lipid Mediators
Sponsor	Corbus Pharmaceuticals, Inc.
SS	Safety Set
SUSAR	Suspected Unexpected Serious Adverse Reaction
T	Temperature
TEAE	Treatment emergent adverse event
THC	Tetrahydrocannabinol
TID	Three times per day
TLR	Toll-like receptors
TNFα	Tumor necrosis factor α
US	United States
WOCBP	Woman of childbearing potential

3.2 Glossary of Terms

Ethics Committee (EC)

Term used throughout when referring to Institutional Review Board or Independent Ethics Committee or Research Ethics Board, whose composition, functions, and operations will be in accordance with the detailed description in the ICH Guideline for Good Clinical Practice.

Study drug

A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial.

Subject Identification Number (SID)

A unique number identifying a treatment to a subject, per the study randomization.

Suspected Unexpected Serious Adverse Reaction (SUSAR)

An adverse event that (a) meets the definition of a serious adverse event, (b) the nature or severity of which is not consistent with study drug information in the Investigator's Brochure, and (c) there is reason to conclude that the study drug caused the event.

4 ETHICAL CONDUCT OF THE STUDY AND REGULATORY REQUIREMENTS

4.1 Ethical Conduct of the Study

This study will be conducted in accordance with United States (US) and international ethical principles that have their origins in the Declaration of Helsinki Protection of Human Volunteers [21 Code of Federal Regulation (CFR) 50], Institutional Review Boards (21 CFR 84), and Obligations of Clinical Investigators (21 CFR 312), in compliance with the approved protocol, Good Clinical Practice (GCP) Food and Drug Administration (FDA) Title 21 part 312, European Union clinical-trial legislation (Directive 2001/20/EC), ICH guidelines, applicable government regulations, and institutional research policies and procedures. The investigator will ensure, through reporting to Corbus Pharmaceuticals, Inc. (hereafter called Corbus, which includes Corbus Pharmaceutics Inc. and its designees) that the relevant regulatory agencies are advised, according to their timelines for reporting, of all changes post study initiation that may in any way affect the safety of subjects.

4.2 Ethics Committee

This protocol will be submitted to the reviewing central or local Institutional Review Board or Independent Ethics Committee, hereafter referred to as the Ethics Committee (EC), for review and approval before the study is begun at any site. The EC must be constituted according to the local laws/customs of each participating country. Any protocol amendments will be submitted to the reviewing central or local EC for review and approval. The EC will review the Informed Consent and Assent Forms, their updates (if any), and any written materials given to the subjects. Any other documents that the EC may need to fulfill its responsibilities, including subject recruitment procedures and any compensation available to subjects will be submitted to the EC by the local monitor/investigator. The EC's written unconditional approval of the study protocol and the Informed Consent and Assent Forms

will be in the possession of the investigator and Corbus before the study is initiated. The EC's unconditional approval statement will be transmitted by the investigator or designee to Corbus before shipment of study drug supplies to the site. This approval must refer to the study by exact protocol title and number and should identify the documents by date and version reviewed, the date of review and any updates after initial approval.

Corbus will write any amendment to the protocol that is needed. Protocol and/or informed consent modifications or changes may not be initiated without prior written EC 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 EC, and written verification that the modification was submitted should be obtained. Where subject safety is at issue, with notification to Corbus, Corbus will assure that the FDA is notified according to the timelines established in 21 CFR 312 and all other relevant regulatory agencies are advised, according to their timelines for reporting.

The investigator or designee is required to notify the EC of:

- Revisions of documents originally submitted for review.
- Serious adverse events (SAEs) including Suspected Unexpected Serious Adverse Reactions (SUSARs) occurring during the study. Corbus will also be notified.
- New information that may adversely affect the safety of the subjects or the conduct of the study. Corbus will also be notified.
- Pregnancies occurring in female subjects or female partners of male subjects. Corbus will also be notified.
- Annual update and/or request for re-approval.
- Suspension or premature termination of the study. Review and approval by the EC is required for resumption of the study at a site, in the event the study is interrupted.
- Study completion.

The investigator must keep copies of all adverse event (AE) information, including correspondence with Corbus and the approving EC on file. The investigator will retain all EC records related to this investigation for at least 3 years, or as long as required by local regulations, after completion of the research. Where subject safety is at issue, with notification to Corbus, Corbus will assure that the FDA is notified according to the timelines established in 21 CFR 312 and all other relevant regulatory agencies are advised, according to their timelines for reporting. Corbus or its designee will maintain copies of all correspondence with FDA and all other relevant regulatory authorities.

Investigator will permit study-related monitoring, audits and inspections of all study related documents by the approving EC. Should direct access to medical records require a waiver or authorization separate from the subject's statement of informed consent/assent, the investigator or designee is obligated to obtain such permission in writing from the appropriate individuals.

4.3 Subject Information and Informed Consent

The investigator will prepare the Informed Consent Form, Assent and Health Insurance Portability and Accountability Act authorization (US only) and provide the documents to Corbus for approval before submission to the EC. The consent form and assent generated by the investigator must be acceptable to Corbus and approved by the EC. The written consent document will embody ICH elements of informed consent and comply with local regulations. The investigator will send EC-approved copies of the Informed Consent Form and Assent to Corbus for the study file.

The principles of informed consent in the current edition of the Declaration of Helsinki must be implemented before any protocol-specified procedures or interventions are carried out. The written consent document will also comply with local regulations. Informed consent will be obtained by the investigator or designee in accordance with 21 CFR 50.25 or Directive 2001/20EC, depending upon site location in the US or EU, respectively. Information will 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.

Consent/assent forms must be written at a level that can be understood by the prospective subject. The explanation of the investigation will be in language that is understandable to the individual. If non-English speakers will be enrolled, a translated consent/assent document will be available, and an appropriate person will conduct the consent process. Subjects who so choose will be given the opportunity to take the consent home for review with other family members or their medical doctor.

Before informed consent is obtained from potential adult subjects, the investigator or designee will explain the purpose, study design and potential benefits/risks of participation in the study including that some risks may be unforeseen. The explanation will include a statement that treatment in the study may involve risks to the subject or the fetus, if the subject should become pregnant.

Subjects must be informed about alternative treatments. Subjects must receive an explanation as to whether any compensation and any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained. They must be informed whom to contact for answers to any questions relating to the research project. The subjects must be informed that participation is voluntary and that they are free to withdraw from the study for any reason at any time, without penalty or loss of benefits to which they are otherwise entitled.

The Informed Consent Form will explain the option of allowing leftover blood and sputum samples to be kept for further analysis of biomarkers of inflammation related to cystic fibrosis (CF) and for metabolite analyses in patients treated with lenabasum or placebo in this study. If the subject declines to participate in this option, that choice will have no effect on his/her eligibility and will not interfere with the benefits to which he/she is otherwise entitled.

The extent of the confidentiality of subject records will be defined. Subjects will be informed that the study will comply with applicable data protection legislation. Health Insurance Portability and Accountability Act authorization (US only) will be obtained before conducting any protocol-related procedures, including screening evaluations. Subjects must be informed that, by signing the written Informed Consent Form, they are granting direct

access to their original medical records for verification of clinical trial procedures and/or data to the site monitor(s), Medical Monitor, auditor(s), EC representatives, and other regulatory authorities. Subjects' medical information obtained in this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form or separate authorization for use and disclosure of personal information signed by the subject, unless permitted or required by law.

In accordance with the ICH Harmonised Tripartite Guidelines for Good Clinical Practice, subjects who are below the age of consent (i.e., minors) and enrolled in the study with the consent of the subject's legally authorized representative will be informed about the study to the extent compatible with the subject's understanding and the subject will sign and personally date a written informed assent form. It is required that the assent be signed by each minor subject (in addition to the informed consent that is to be signed by his/her legal representative), if allowed by their country/local regulations and requirements.

5 INTRODUCTION

This document is a protocol for a human research study of lenabasum for treatment of CF.

Lenabasum is an investigational drug that is being tested for safety, tolerability, efficacy, mechanism of action, and pharmacokinetics in chronic and severe diseases with significant inflammatory and fibrotic components, including CF, systemic sclerosis, dermatomyositis, and systemic lupus erythematosus. Lenabasum is not approved by the European Medicines Agency (EMA), the United States FDA, or any regulatory body for any indication. Lenabasum triggers resolution of inflammation without immunosuppression.

5.1 Background Information on Cystic Fibrosis

Cystic fibrosis is an autosomal recessive genetic disorder that affects multiple organs, including the lungs, pancreas, liver, and intestine. Cystic fibrosis is caused by one of many different disease-causing mutations in the gene for the cystic fibrosis transmembrane conductance regulator (CFTR), a cyclic AMP-dependent chloride channel (Kunzelmann et al, 2013). Mutations in CFTR on airway epithelial cells in CF lead to defective Cl^- secretion and Na^+ hyperabsorption by airway epithelia (Knowles et al, 1983). CFTR also are found on cells of the immune system, such as neutrophils (Painter et al, 2006), monocytes (Ettorre et al, 2014), and T cells (Shanshiashvili et al, 2012), where loss of CFTR function leads to abnormal immune cellular function. In CF patients, disease-causing mutations in CFTR lead to abnormally thick mucus (Burgel et al, 2007) and aberrant immune responses (Cantin et al, 2015, Ratner and Mueller, 2012).

The net result is a propensity in CF patients for recurrent infections and over-exuberant, yet ineffective leukocyte recruitment, phagocytosis, killing, and clearance of pathogens. The bioburden of bacteria in the lungs is high with the microbiome skewed toward pathogens such as *Pseudomonas aeruginosa* (*P. aeruginosa*). Chronic lung infiltration with neutrophils and release of neutrophil elastase and other enzymes contribute to bronchiectasis and pulmonary fibrosis, which are a major cause of morbidity and mortality in CF.

Abnormalities in innate immune responses that lead to chronic inflammation contribute to the pathogenesis of CF (Hartl et al, 2012). These abnormalities include a decreased ratio of pro-resolving to pro-inflammatory lipid mediators (Karp et al, 2004, Ringholz et al, 2014a

Ringholz et al, 2014b), increased production of proinflammatory chemokines, such as interleukin (IL)-8 (Kim et al, 2013, Wojewodka et al, 2014), abnormal cell surface expression of toll-like receptors (TLRs), such as TLR5 (Simonin-Le Jeune et al, 2013), and enhanced or impaired signaling through TLRs. The abnormalities of innate immunity extend to functional disturbances in neutrophils (Ng et al, 2014), ineffective bacterial uptake and subsequent killing by immune cells, reduced autophagy and cellular apoptosis in phagocytes (Mayer et al, 2013), and decreased clearance of apoptotic cells.

Among the abnormalities of innate immunity reported in CF is the inadequate production of "Specialized Pro-resolving lipid Mediators" (SPMs) which are molecules that initiate the physiologic process of resolution of inflammation. The relative overproduction of pro-inflammatory lipid mediators to SPMs in CF (Karp et al, 2004, Urbach et al, 2013, Ringholz et al, 2014a, Ringholz et al, 2014b) provides a mechanistic link to the failure of CF patients to resolve inflammation.

In CF, the ratio of SPMs to pro-inflammatory mediators is disproportionately low, tissue inflammation is excessive and persistent, pathogens are not effectively cleared, and tissue fibrosis leads to irreversible and structural damage to lungs. Of note, the ratio of a key SPM, lipoxin A4, to a key proinflammatory lipid mediator leukotriene B4 is low in bronchoalveolar lavage fluid of CF patients (Karp et al, 2004), even in the absence of infection (Ringholz et al, 2014a). Lipoxin A4 is produced by lipoxygenase interactions resulting from trans-cellular cooperation of neutrophils, eosinophils, alveolar macrophages, platelets or airway epithelial cells, each expressing different lipoxygenase enzymes, which act in sequence in lipoxin A4 biosynthesis (reviewed in Urbach et al, 2013). Normally, CFTR are expressed on both neutrophils and platelets, and neutrophil-platelet interactions during acute inflammation initiate lipoxin A4 production (Serhan and Sheppard, 1990). Platelets from patients with CF produce about 40% less lipoxin A4 than healthy subjects (Mattoscio et al, 2010). In addition, 15-lipoxygenase expression, which is required for lipoxin A4 production, is reduced in CF (Ringholz et al, 2014a). In animal models of CF, mice deficient in CFTR have reduced production of lipoxin A4 by neutrophils and platelets (Wu et al, 2014). Importantly, in turn, lipoxin A4 increases CFTR protein expression (Yang et al, 2012).

Lenabasum is a synthetic molecule that activates resolution of inflammation. It is a preferential cannabinoid receptor type 2 (CB2) full agonist that has 12-fold greater affinity for CB2 than cannabinoid receptor type 1 (CB1) (Tepper et al, 2014). Lenabasum shows little evidence of psychotropic activity at likely therapeutic doses, because of limited ability to cross the blood-brain barrier and reduced affinity for CB1.

There are two major CB receptor subtypes: CB1, mainly expressed in the central and peripheral nervous system; and CB2, mainly distributed throughout immune and hematopoietic cells, epithelial cells, fibroblasts, osteoblasts, skin keratinocytes, and the peripheral nervous system (Rom and Persidsky, 2013). CB2 is preferentially expressed on activated immune cells.

Lenabasum induces "class switch" of arachidonic acid metabolism from proinflammatory lipid mediators to SPMs through effects on 15-lipoxygenase (Zurier et al, 2009) and possibly other lipid metabolizing enzymes. Agonists of CB2 are known to increase production of anti-inflammatory eicosanoids, such as prostaglandin (PG) J2 and cytokines, such as IL-10 (Shanshiashvili et al, 2012). Further, CB2 agonists including lenabasum can induce

apoptosis of T cells (Bidinger et al, 2003, Singh et al, 2012), and fibroblasts (Garcia-Gonzalez et al, 2009). Of direct relevance to treatment of CF, endocannabinoids and synthetic CB2 agonists blunt inflammation, innate immune responses and deposition of extracellular matrix, by:

- Inhibiting expression of TLR and nucleotide-binding oligomerization domain (NOD)-like receptors and TLR signal transduction (Downer et al, 2011, Duncan et al, 2013)
- Reducing production of early mediators of inflammation, including chemotactic factors, such as IL-8 (Selvi et al, 2008) and proinflammatory lipids
- Inhibiting tissue infiltration with leukocytes, by inhibiting leukocyte rolling and tissue infiltration (Mukhopadhyay et al, 2010), chemotaxis and differentiation of dendritic cells (Adhikary et al, 2012)
- Reducing production of proinflammatory cytokines by these infiltrating cells, including type 1 interferons, IL-1β, IL-6, tumor necrosis factor α (TNFα) and IL-17 (Zurier et al, 2003, Parker et al, 2008, Selvi et al, 2008, Kong et al, 2014)
- Inhibiting accumulation of myofibroblasts, production of transforming growth factor-β (TGFβ), connective tissue growth factor, and extracellular matrix components (Akhmetshina et al, 2009, Gonzalez et al, 2012, Börgeson et al, 2011, data on file)

"Class switching" of lipid mediators (Levy et al, 2001) to favor production of lipoxin A4 and other SPMs would be expected to have therapeutic benefit in CF, through effects on multiple pathologic pathways in CF. As examples, lipoxin A4:

- Enhances CFTR protein expression, at least in rat lungs (Yang et al, 2012)
- Decreases mucus thickness through effects on ion transport (Al-Alwani et al, 2014, Verrière et al, 2012)
- Increases airway epithelium integrity (Buchanan et al, 2013)
- Attenuates pulmonary fibrosis (Martins et al, 2009, Krönke et al, 2012). Lipoxin A4 inhibits fibroblast proliferation (Wu et al, 2006) and TGFβ receptor type 1 expression and responses to TGFβ (Brennan et al, 2013, Börgeson et al, 2011). Of note, high producer TGFβ1 genotypes are associated with severe lung disease in CF (Arkwright et al, 2000), TGF-β signaling and fibrosis are markedly increased in CF (Harris et al, 2013) and TGFβ may interfere with therapies directed at correcting the processing defect in CFTR in CF patients (Snodgrass et al, 2013).

Therapeutic approaches to reduce inflammation in patients with CF have shown clinical benefit, such as alternate-day corticosteroids and high dose ibuprofen (Konstan et al, 2007), but adverse effects and other considerations have limited their use. Alternative agents to reduce lung inflammation and resulting fibrosis are needed. The development of new therapies that will do this is a strategic priority for the Cystic Fibrosis Foundation.

Lenabasum is being investigated as a new therapy for CF because of its potential to resolve inflammation and stop pro-fibrotic processes in CF. Lenabasum triggers the physiologic process of resolution of inflammation. It reduces levels of pro-inflammatory mediators and increases levels of SPMs including lipoxins and resolvins in involved tissues. Lenabasum reduces polymorphonuclear leukocyte infiltrates and improves bacterial clearance in the

lungs in a mouse model of infection-induced inflammation in CF. Similarly, lenabasum reduces polymorphonuclear infiltration and pro-inflammatory mediators while hastening bacterial clearance in a human model of infection-induced innate immune response in the skin.

5.2 Findings from Nonclinical Studies with Potential Clinical Significance

Please see the IB for details of nonclinical studies.

5.2.1 Animal Safety Data

Nonclinical safety program for lenabasum includes safety pharmacology, general toxicology, reproductive and developmental toxicology, and genotoxicity studies. Major findings identified from the completed animal studies following repeated administration in duration up to 26 weeks in rats and 39 weeks in dogs are:

- Estimated single lethal doses are 400 mg/kg in rats and 600 mg/kg in mice
- A 13-week toxicology study (MAM0003) was conducted in the rat. The age of rats receiving lenabasum treatment were as young as 38 days at the start of twice-daily dosing. Based on animal and human comparative developmental schedules (Buelke-Sam 2003), the human-equivalent age of these rats appropriately covered the target adolescent ages of 12 to 17 years. There were no adverse effects noted at any dose evaluated.
- The NOAELs in 26-week rat toxicology study was 5 mg/kg BID, resulting in a gender-combined mean C_{max} value of 2363 ng/ml and AUC_{0-24} of 27050 ng·hr/ml. At NOAEL, the system exposure multiples were 3.7× and 3.7× higher than the clinical C_{max} and AUC_{0-24} value at 20 mg BID (40 mg/day total dose), respectively.
- The NOAELs in 39-week dog toxicology study was 2 mg/kg BID, resulting in a C_{max} value of 1171 ng/ml and AUC_{0-24hr} of 14,581 ng·hr/ml. At NOAEL, the system exposure multiples were 1.8× and 2.0× higher than the clinical C_{max} and AUC_{0-24} value at 20 mg BID (40 mg/day total dose), respectively.
- Clinical signs consistent with an effect on the central nervous system were seen at doses of 8 mg/kg and higher in dogs and 50 mg/kg and higher in rats.
- No clinical or anatomic pathology changes indicative of organ toxicity and no treatment related microscopic findings were observed in the repeat dose studies.
- There were no treatment-related organ weight changes in dogs in multiple dose studies. Organ weight changes in the 13-week study in rats were considered secondary to lower body weight.
- Minor potentially treatment-related alterations in clinical chemistry parameters were observed at high doses. Mild increases in blood urea, mild increases in urine volume and decreased osmolarities, with normal creatinine, mild decreases in serum glucose, mild increases in alkaline phosphatase, and mild decreases in protein and albumin were noted
- No teratogenicity in embryofetal development studies in rats and rabbits at any evaluated dose, 9.0× in rats and 1.2× in rabbits, respectively, higher than the clinical AUC exposure value at oral dose of lenabasum 20 mg BID.

- In a fertility and early embryofetal rat study (i.e., Segment 1), lenabasum had no effect on male and female fertility, and male reproductive performance at any evaluated dose, with a systemic AUC exposure value 3.9× higher than the clinical exposure at an oral dose of lenabasum 20 mg BID. The NOAEL for female reproductive function was determined to be 4 mg/kg/day with an AUC value 1.3× higher than clinical exposure at an oral dose of lenabasum 20 mg BID.
- Lenabasum was not mutagenic or clastogenic in *in vitro* or *in vivo* genotoxicity studies.
- Compared to morphine, lenabasum demonstrated a low potential for the development of physical dependence in an evaluation of potential for abuse in rats.
- No characteristic physiologic effects of peroxisome proliferator-activated receptor gamma activation such as edema/fluid retention, cardiac hypertrophy, or hematologic changes were observed in the chronic toxicology studies of lenabasum treatment duration of up to 26 weeks in rats and 39 weeks in dogs. These findings are consistent with in vitro assays of lenabasum that demonstrated relatively weak receptor occupation of peroxisome proliferator activated receptor gamma.
- Animals exposed to lenabasum in standard toxicology studies have not shown signs of immunotoxicity at doses above the NOAEL and up to 40 mg/kg three times daily for 13 weeks and 5 mg/kg BID for 26 weeks. The following signs of immunotoxicity were not observed at evaluated doses:
  - Leukocytopenia, granulocytopenia, or lymphopenia
  - Alterations in immune system organ weights and/or histology (e.g., changes in thymus, spleen, lymph nodes, and/or bone marrow. The sole exception is that in a non-pivotal 7-day gavage study in rats, a reduction in thymus weight was seen in female rats given 100 mg/kg daily
  - Reduction in serum globulins
  - Increased incidence of infections
  - Increased occurrence of tumors.

5.2.2 Animal Pharmacokinetics and Metabolism

Toxicokinetic analyses in the repeat-dose toxicity studies indicate that after oral administration of lenabasum to rats and dogs, increases in plasma exposures of lenabasum were generally dose-proportional, and no consistent gender differences were apparent. In both the rat and dog, time to peak plasma concentrations (T_{max}) was usually 1.5 to 3.0 hours post-dose indicating rapid absorption. The estimated $t_{1/2}$ ranged from approximately 3 to 5 hours. Because of its relatively short plasma half-life, lenabasum was administered BID or 3 times daily in toxicology studies; no accumulation occurred after repeated dosing.

In vitro metabolism studies of lenabasum in cryopreserved rat, dog, monkey, and human hepatocytes indicate minimal hepatocyte metabolism of lenabasum. The amounts of metabolites formed relative to unchanged lenabasum were < 2% for any single metabolite and < 5% for all 5 metabolites in total.

An *in vivo* metabolism study of lenabasum was conducted in rats and dogs. Samples were analyzed using a qualitative LC-MS/MS method. Lenabasum and up to 11 metabolites were

detected across the plasma samples analyzed. Consistent with the previously-conducted *in vitro* metabolism study results, unchanged lenabasum was the major circulating plasma component in rats and dogs. Several glucuronide conjugates were detected in both animal plasma samples, but the specific structures of the glucuronides have not been determined. They are not considered to be any safety concerns mainly because of low quantity and involvement of a major Phase II detoxification pathway.

Lenabasum did not inhibit human cytochrome P450 isozymes (CYP 1A2, CYP 2C9, CYP 2C19, CYP 2D6, and CYP 3A4/5) at concentrations up to 50 μM and the potential for drug interactions involving the CYPs tested was minimal.

Plasma protein binding generally was very high and exceeded 97% (i.e., > 97% protein-bound concentration) in any species or concentrations tested. In dogs and rats, lenabasum binding to plasma proteins slightly increased at higher lenabasum concentrations.

5.2.3 Animal Efficacy

The effects of lenabasum were tested in a murine model of CF with CFTR F508del mutations, gut corrected (Bonfield and Tepper, 2015). In this CF model, lung infection with *P. aeruginosa* is associated with excessive and prolonged lung inflammation and infection, increased weight loss and reduced survival. In these experiments, wild-type and CFTR-mutant mice were infected with *P. aeruginosa* with or without treatment with lenabasum 1 mg/kg BID or 5 mg/kg BID, then sacrificed at Day 10. There was no evidence of immunosuppression with lenabasum at Day 10 in wild-type or CFTR-mutant mice. At Day 10, the lenabasum-treated CFTR mice had reduced neutrophils in bronchoalveolar lavage fluid and reduced bacterial colony forming units in their lungs with levels similar to those in wild type mice. They also had an increase in weight and survival. These results are consistent with increased resolution of infection-activated innate immune responses in this animal model of CF.

Other studies of lenabasum demonstrated evidence of clinical efficacy in multiple animal models of inflammation and fibrosis. The exposure at which this activity was seen varied, and the human equivalent of the median effective dose (ED_{50}) or active doses in all these animal models were ≤ 20 mg per day, with a mean human equivalent ED_{50} of about 5 mg per day. The difficulties in translating ED_{50} doses in animal models to human equivalent ED_{50} doses are acknowledged. In these studies, lenabasum:

- Caused a 75% reduction in neutrophils invading the peritoneum in a mouse model of peritonitis and a 7-fold increase in lipoxin A4 (Zurier et al, 2009).
- Inhibited bleomycin-induced lung inflammation and fibrosis when administered in a prophylactic and therapeutic manner (data on file). This was associated with reduced myofibroblast accumulation, collagen production, TGFβ production and connective tissue growth factor production.
- Inhibited bleomycin-induced skin inflammation and fibrosis when administered in a prophylactic and therapeutic manner (data on file). This was associated with reduced myofibroblast accumulation and collagen production.
- Reduced joint inflammation and ankylosis (Zurier et al, 1998).

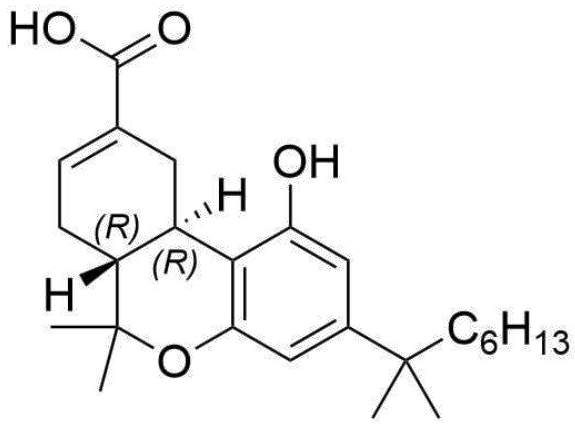
- Demonstrated potent anti-inflammatory and anti-allodynic effects in rodent paw edema and hot plate assay (Burstein et al, 1992, Dajani et al, 1999; Burstein et al, 1998).

5.3 Mechanism of Action of Lenabasum

5.3.1 Lenabasum as a Selective Cannabinoid Receptor Type 2 Agonist

Lenabasum is (6aR, 10aR)-3-(1,1-dimethylheptyl)-Δ8-tetrahydro-cannabinol-9-carboxylic acid (Figure 1), also known as JBT-101, anabasum, Resunab, ultrapure ajulemic acid, CT-3, IP751 and CPL7075. Lenabasum is a synthetic analog of the terminal metabolite of tetrahydrocannabinol. It is a selective CB2 agonist with 12.3-fold greater affinity for CB2 than cannabinoid receptor type 1 (CB1) (Tepper et al, 2014). The receptor binding constant or K_i of lenabasum for CB2 is 51 nM, and the receptor binding constant for CB1 is 628 nM (Tepper et al, 2014). This CB2 selectivity is based on a 7-residue side chain that includes 2 methyl groups. The structure of CB2 also includes a-COOH group that reduces lenabasum's ability to penetrate the blood-brain barrier, so that levels in the central nervous system are about 30% of those in the plasma, at least in rats (Dyson et al, 2005). The preparation of lenabasum that will be used in this study is a ≥ 97% pure synthetic preparation of a dimethylheptyl derivative of tetrahydrocannabinol-11-oic acid. Detailed study drug information can be found in the Investigator's Brochure.

Figure 1 Structural Formula of Lenabasum



Molecular Formula: $C_{25}H_{36}O_4$

Molecular Weight: 400.56

CAS Number: 137945-48-3

Appearance: White to off white to tan to orange powder

The maximal plasma concentrations (C_{max}) of lenabasum at 20 mg BID is ~ 550 to 650 ng/mL, or ~ 1400 to 1600 nM (see IB, data on file). Because lenabasum is ≥ 97% protein bound (see IB), the concentration of free lenabasum in the plasma at this dose would be ~42 to 48 nM. At this concentration, ~50-60% of the CB2 and ~6-7% of CB1 would be occupied by lenabasum. At these relative levels of receptor occupancy, lenabasum's pharmacological activity would be preferentially mediated by CB2.

In receptor binding studies, lenabasum selectively binds and activates CB2 compared to CB1. In functional assays, lenabasum has higher potency for CB2 than CB1 (Tepper et al, 2014). As expected from the results of the binding assays, *in vitro* experiments with CB2 and CB1 antagonists demonstrate that pharmacological activities of lenabasum are selectively mediated through CB2 (Tepper et al, 2014).

5.3.2 Regulation of the Resolution Phase of Innate Immune Responses by CB2

The resolution phase is normally initiated soon after the onset of an innate immune response, when interactions between neutrophils and platelets lead to a "class switch" in the bioactive lipid mediators that are produced (Levy et al, 2001). During the initiation of resolution, the balance of lipid mediators shifts from pro-inflammatory mediators to novel Specialized Pro-resolving Lipid Mediators or SPMs (Buckley et al, 2014; Serhan et al, 2014; Serhan and Chiang 2013; Serhan et al, 2008; Levy et al, 2001). Pro-resolving lipid mediators include 4 families with overlapping effects, called lipoxins, resolvins, protectins, and marescins.

The endocannabinoid system is an evolutionarily ancient neuro-immunomodulating system that has a significant role in regulating innate immune responses and associated wound healing, pain, and energy metabolism (Serhan et al, 2014; Buckley et al, 2014; Serhan and Chiang 2013; Serhan et al, 2008). Cannabinoid receptors are class A, rhodopsin-like, G-protein coupled receptors. There are 2 main CB receptor subtypes: CB1, mainly expressed in the central and peripheral nervous system, and CB2, mainly distributed throughout immune and hematopoietic cells (Castaneda et al, 2013; Munro et al, 1993). Following activation of an innate immune response, CB2 becomes expressed at 10- to 100-fold higher levels than CB1 on activated immune cells (Carayon et al, 1998; Galiègue et al, 1995; Munro et al, 1993). Once the immune response is resolved, cell surface expression of CB2 returns to baseline levels (Carayon et al, 1998).

The endocannabinoid and innate immune systems intersect. CB2 agonists trigger class switch of lipid mediators to favor pro-resolving lipid mediators (Shinohara et al, 2012; Zurier et al, 2009, data on file). Inability to express CB2 or inhibition of CB2 leads to prolonged and excessive inflammation and fibrosis. In response to challenges that activate innate immune responses, CB2 knock-out mice have more severe inflammation and fibrosis through increases in nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kβ activation), production of pro-inflammatory adhesion molecules, chemokines, cytokines, production of superoxide generating enzymes, immune cell recruitment, and reduced apoptosis of lymphocytes (Trebicka et al, 2011; Engel et al, 2010; Mukhopadhyay et al, 2010; Servettaz et al, 2010; Deveaux et al, 2009; Tschöp et al, 2009; Julien et al, 2005). For example, one mouse model uses hypochlorite injections to induce fibrosis in the lungs. When experiments are done in CB2 knockout mice, fibroblast proliferation and lung fibrosis, are all increased (Servettaz et al, 2010). In the same model, treatment with a CB2 agonist prevents the development of lung fibrosis and reduces fibroblast proliferation.

Thus, CB2 is a receptor shared by the endocannabinoid and innate immune systems that regulates the degree of inflammation and fibrosis that occurs following the onset of an innate immune response, by turning "on" resolution to turn "off" the innate immune response, restoring homeostasis. Activation of CB2 has the potential to limit inflammation and fibrosis that occurs in CF and provide clinical benefit.

5.3.3 Activity of Lenabasum in Cells Isolated from Humans with CF

To further test the potential of lenabasum to resolve lung inflammation in CF, studies tested direct effects of lenabasum on lung macrophages isolated from CF patients. Macrophages were isolated from lungs excised from two CF patients undergoing lung transplantation. To simulate their response to infection, the macrophages were stimulated with pseudomonas lipopolysaccharide at 100 ng/ml for 6 hrs. These macrophages were exposed to lenabasum

(1, 3, 10 μM) prior to, concomitantly, or after lipopolysaccharide stimulation. After 6 hours, TNFα, IL-1β, IL-6, and IL-8 were measured in culture supernatants using ELISA assays, and the mRNA level of transcription factor XBP-1 was measured by quantitative reverse transcriptase polymerase chain reaction.

Lenabasum reduced lipopolysaccharide-stimulated production of TNFα and IL-6 by CF lung macrophages in a dose-dependent fashion with up to >75% inhibition at 10 μM lenabasum. This inhibition occurred when lenabasum was added prior to, concomitantly, or after lipopolysaccharide stimulation. Furthermore, lenabasum inhibited the expression levels of XBP-1, the CF pulmonary macrophage transcription factor with a role in lipopolysaccharide-induced endoplasmic reticulum stress and inflammatory response by up to ~85% in a time-dependent manner with 24 hours treatment being maximal. The inhibition by lenabasum of TNFα and IL-6 production by CF lung macrophages provides evidence for direct effects of lenabasum on an important cell type and mediators in the pathogenesis of CF lung damage.

5.3.4 Proof of Mechanism of Action of Lenabasum in Humans

A human model of an acute inflammatory response to bacteria was used to determine pro-resolution properties of lenabasum (Motwani et al, 2017). In this model, ultraviolet light-killed *E. coli* is injected intradermally in healthy human volunteers and a suction blister over the site of injection is used to obtain blister fluid for analysis of cells and mediators in the underlying tissue (Motwani et al, 2016). Subjects received lenabasum 5 mg BID, 20 mg BID, placebo BID or 15 mg prednisolone QD for 4 days and were challenged with intradermal *E. coli* on the morning of the fourth day. Inflammatory cells and mediators were measured at the time of peak acute inflammation (4 hours) and the initiation of the resolution phase of acute inflammation (10 hours). Lenabasum 5 mg BID exerted a potent anti-inflammatory effect equivalent to that of 15 mg prednisolone in terms of inhibiting neutrophil infiltration during the activation phase of the innate immune response. At 20 mg BID lenabasum had similar effects on neutrophil infiltration and also triggered the synthesis of the SPMs lipoxin A_4, lipoxin B_4, resolvin D1 and resolvin D3. Lenabasum also dose-dependently and significantly inhibited the neutrophil chemoattractant leukotriene B_4 as well as prostaglandin E_2, thromboxane B_2 and prostaglandin $F_{2\alpha}$ biosynthesis, but did not affect the vasodilator prostacyclin. Lenabasum significantly cleared ultraviolet light-killed *E. coli* derived endotoxin from the injected site, which arose from the inhibition of anti-phagocytic prostanoids. Collectively, lenabasum had striking pro-resolving effects in this model.

5.4 Summary of Potential Clinical Benefit of Lenabasum in Cystic Fibrosis

Lenabasum is a novel synthetic selective oral agonist of cannabinoid receptor type 2 (CB2) that activates resolution of innate immune responses. Lenabasum is being developed as a chronic oral therapy for treatment of CF, to be used alone or in conjunction with other treatments for CF.

The physiologic process of resolution of inflammation is initiated during an innate immune response when lipid mediator production undergoes a class-switch from pro-inflammatory mediators that activate innate immune responses (such as leukotriene B4 and prostaglandin E1) to SPMs (members of the lipoxin, protectin, marescins, and resolvin families). During resolution of inflammation, production of mediators that activate inflammation decrease to

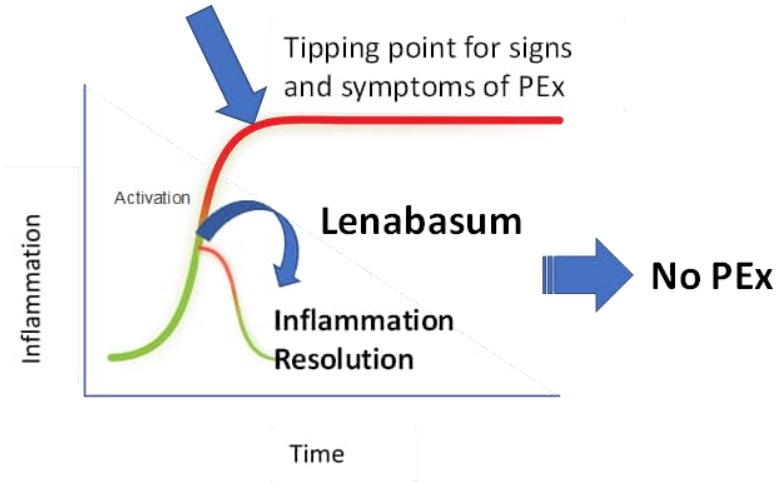
normal levels, new inflammatory cells do not infiltrate tissues, inflammatory cells that are in tissues die by apoptosis and their cellular debris is removed by efferocytosis by macrophages, clearance of any residual pathogens occurs, and wound healing processes are completed including restoration of fibrotic processes to basal levels (reviewed in Serhan et al, 2014).

Because resolution of inflammation is an active process that includes a network of physiologic activities that restore homeostasis of the innate immune system without immunosuppression, it is different from anti-inflammation (Serhan et al, 2014, Serhan et al, 2008). Activation of resolution of inflammation has the potential to provide benefit in CF.

Activation of resolution of inflammation provides promise for the potential benefit of lenabasum in reducing PEx in CF. Innate immune responses in CF are inherently aberrant, with an excessive, persistent and ineffective response to triggers such as infection. The lungs of CF patients are chronically inflamed and an acute increase in inflammation often precedes a PEx and a reduction in the acute inflammation generally occurs with resolution of a PEx.

Treatment with lenabasum is expected to reduce chronic levels of inflammation in the lungs in CF which should provide long-term benefit by reducing the rate of tissue destruction by inflammatory processes. Relevant to the proposed Phase 2 study, when acute inflammation is superimposed in the lungs by infection or other events, lenabasum is expected to reduce the maximum level of acute inflammation achieved and hasten resolution of that inflammation without impeding pathogen clearance. Through these effects in individuals with CF, lenabasum is expected to prevent lung inflammation from reaching a level high enough to cause signs and symptoms that warrant intervention with antibiotics, that is, a PEx (Figure 2).

Figure 2 Reduction in Inflammation by Lenabasum is Expected to Reduce PEx



5.5 Clinical Benefit of Lenabasum in Completed Trial JBT101-CF-001

5.5.1 Design of JBT101-CF-001

Data are available from a completed Phase 2 study (JBT101-CF-001) that evaluated multiple doses of lenabasum compared to placebo for safety and efficacy in stable individuals with CF. This double-blinded, randomized, placebo-controlled Phase 2 trial of lenabasum was done in 85 stable CF subjects ≥ 18 and < 65 years of age at 21 sites in the US and Europe.

Key inclusion criteria were FEV1 ≥ 40% predicted, stable baseline CF medications and no antibiotic treatment for a PEx within 14 days before Visit 1. Subjects continued baseline CF medications throughout the study including prophylactic antibiotics and CFTR-targeting drugs.

Safety and tolerability of lenabasum was the primary endpoint in this trial. Pulmonary exacerbations treated with IV antibiotics were called out as an event of special interest in the primary endpoint, knowing PEx were also a measure of efficacy.

Subjects were treated with lenabasum 1 mg QD (n = 26), 5 mg QD (n = 24) or placebo QD (n = 35) for 4 weeks, then all 51 lenabasum-treated and 10 placebo-treated subjects were randomly assigned to receive lenabasum 20 mg QD or 20 mg BID for the next 8 weeks while 24 placebo-treated subjects continued to receive placebo BID throughout the rest of the study.

Ten subjects discontinued early from the study; three withdrew consent; five withdrew due to adverse events (AEs), 2 subjects on placebo, 3 subjects on lenabasum; one subject was lost to follow-up; two withdrew for treatment-unrelated reasons. Three AEs that lead to early discontinuation were judged related to study drug: 1 placebo subject and 1 lenabasum subject each had lack of cognitive clarity and 1 lenabasum subject felt unmotivated.

5.5.2 Baseline Characteristics of Study Population in JBT101-CF-001

Baseline subject characteristics were similar in lenabasum and placebo cohorts at Visit 1 (Table 2) and Visit 3 when doses of study drug were changed (not shown).

Table 2 Baseline Characteristics of JBT101-CF-001 Phase 2 Study Population

Characteristic	Lenabasum 1 mg QD N = 26	Lenabasum 5 mg QD N = 24	Placebo N = 35
F508D: 2 alleles / 1 allele / 0 alleles†, n (%)	13 / 9 / 4 50% / 35% / 15%	14 / 7 / 3 58% / 29% / 13%	21 / 10 / 4 60% / 29% / 11%
FEV1 % predicted, mean (range)	65.6 (31.5 – 101.8)	63.1 (29.6 – 89.3)	65.3 (39.2 – 113.3)
PEx in last year, n, mean (range)	0.73 (0 – 2)	0.75 (0 – 3)	0.63 (0 – 3)
CFQ-R Respiratory Symptom Score, mean (range)	65.8 (33.3 – 94.8)	69.9 (16.7 – 100)	71.6 (27.8 – 88.9)
Baseline medications, n (%)			
• Azithromycin	8 (30.1)	16 (66.7)	21 (60.0)
• Inhaled tobramycin	12 (46.2)	10 (41.7)	16 (47.5)
• Any prophylactic antibiotic excluding azithromycin	13 (50.0)	12 (50.0)	16 (47.5)
• Lumacaftor/ivacaftor	6 (23.1)	7 (29.2)	8 (22.9)
• Ivacaftor	2 (7.7)	0	1 (2.9)
• Dornase alfa	23 (88.5)	19 (79.1)	29 (82.9)

QD = once per day dosing; CFQ-R = Cystic Fibrosis Questionnaire-Revised

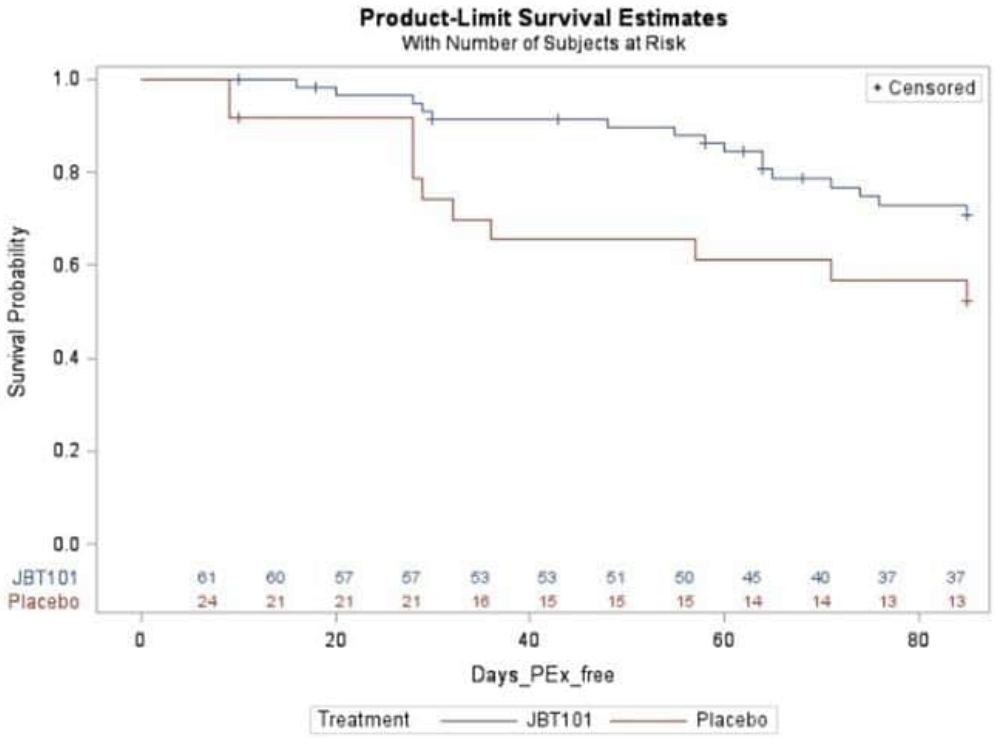
[a] Individuals may have two (homozygous), one (heterozygous), or no F508del mutations

5.5.3 Lenabasum Reduced Pulmonary Exacerbations in JBT101-CF-001

Over the 12 weeks of active dosing, PEx were reduced in subjects who received lenabasum.

An increase in time to first PEx was seen, as shown as proportion of subjects without a PEx in a Kaplan-Meier curve in Figure 3, p = 0.0467, Cox proportional hazards test, hazard rate = 0.426 adjusted for number of PEx in the previous year, FEV1 % predicted at baseline, treatment vs. no treatment with ivacaftor or ivacaftor/lumacaftor treatment and US versus European site. The effect size on difference in mean time to PEx was 0.55, a moderate to strong effect. The mean (SD) time to antibiotic use for PEx in lenabasum vs. placebo cohorts was 52.7 ± 20.9 vs. 37.5 ± 22.9 days, p = 0.097, 2-tailed t test.

Figure 3 Survival Curves for Time without PEx Treated with Any Inhaled, Oral, or Intravenous Antibiotic in Completed Phase 2 Study JBT101-CF-001



A reduction in event rate of PEx per 12 weeks was seen and is shown in

Figure 4 for PEx treated with IV antibiotics and in Figure 5 for PEx treated with any new antibiotic. The placebo group in the JBT101-CF-001 trial behaved as expected with regards to PEx rate. The proportion of placebo subjects with a PEx treated with any new antibiotic was ~0.55 in the 12-week JBT101-CF-001 study compared to ~0.65 for placebo subjects with a PEx treated with IV antibiotic in an ivacaftor-lumacaftor study.

Figure 4 Event Rate per 12 Weeks of PEx in JBT101-CF-001 Treated with Intravenous Antibiotics

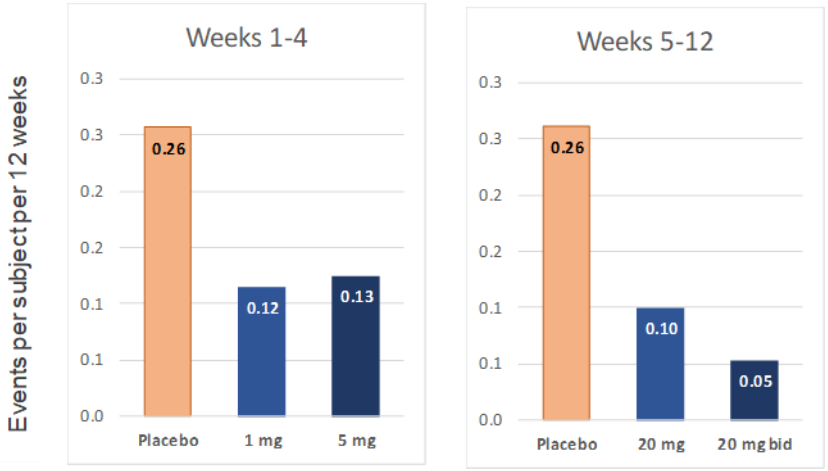
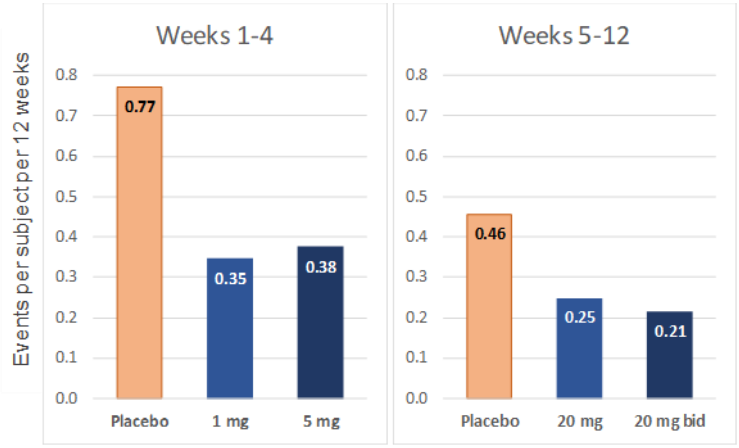


Figure 5 Event Rate Per 12 Weeks of PEx in JBT101-CF-001 Treated with Any New Systemic Antibiotic

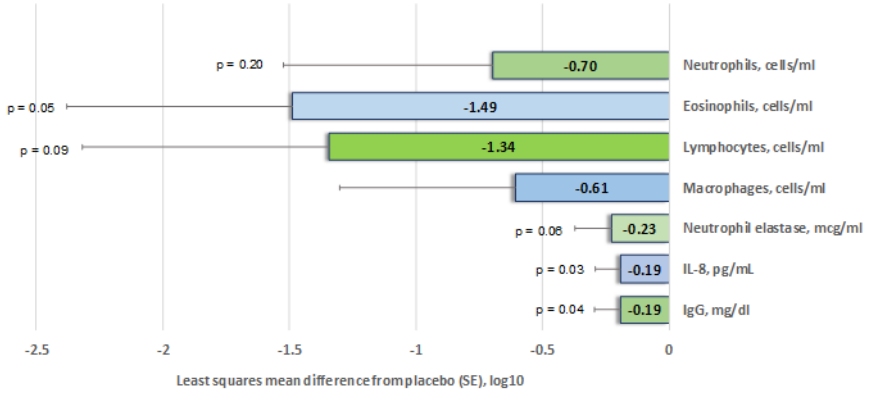


Characteristics of subjects who had a PEx during study JBT101-CF-001 were compared to those who did not. Subjects with a PEx had a history of more PEx treated with IV antibiotics in the previous year (mean 0.89 versus 0.47). Hypertonic saline (45% versus 23%), azithromycin (55% versus 43%) and inhaled tobramycin (40% versus 19%) were more likely to be used in subjects with PEx than those without PEx in JBT101-CF-001. Subjects with and without PEx had similar treatment with ivacaftor or ivacaftor/lumacaftor (34% versus 30%). These findings suggest physicians preferentially prescribe hypertonic saline and azithromycin for subjects who are known to their physicians to have more PEx and inhaled tobramycin for those who are also infected with pseudomonas, whereas the prescribe CFTR-modulating drugs primarily based on subject CFTR genotype rather than risk for PEx.

5.5.4 Lenabasum Improved Biomarkers of Inflammation in Sputum and Blood in JBT101-CF-001

Evidence of on-target biologic effects of lenabasum were seen in JBT101-CF-001. After 12 weeks of active treatment lenabasum-treated subjects had reduced total polymorphonuclear leukocytes, eosinophils, macrophages, lymphocytes, interleukin-8, neutrophil elastase, and IgG in sputum compared to placebo-treated subjects, especially with lenabasum 20 mg BID dosing (Figure 6). Lenabasum 20 mg BID also reduced CRP levels in the blood (not shown).

Figure 6 Lenabasum 20 mg BID Reduces Inflammatory Cells and Mediators in CF Sputum Compared to Placebo in Trial JBT101-CF-001

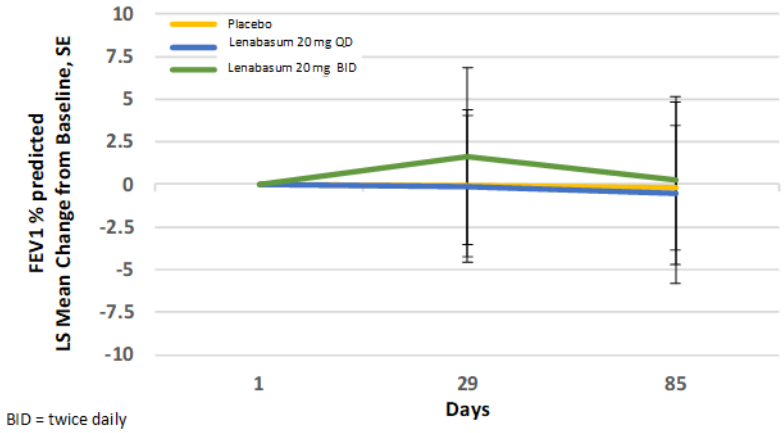


Data are shown as change from baseline, least squares mean difference ± standard error from placebo (log^{10}) for lenabasum 20 mg BID compared to placebo.

5.5.5 Other Efficacy Outcomes in JBT101-CF-001

Mean FEV1 % predicted values were stable throughout the study for lenabasum- and placebo-treated subjects (Figure 7). Mean CFQ-R respiratory symptom scores and other domain scores were also stable throughout the study (data not shown).

Figure 7 LS Mean Change (Standard Error) from Baseline in FEV1 % Predicted



BID = twice daily
LS = Least squares
QD = once daily

5.6 Clinical Benefit of Lenabasum in Completed Trial JBT101-SSc-001 in Systemic Sclerosis

5.6.1 Lenabasum Improved Multiple Efficacy Outcomes in JBT101-SSc-001

A double-blind, randomized placebo-controlled 16-week Phase 2 trial (JBT101-SSc-001) enrolled subjects with diffuse cutaneous SSc ≤ 6 years duration on stable medications including immunosuppressive drugs. Subjects received lenabasum 5 mg QD, 20 mg QD, or 20 mg BID x 4 weeks, then 20 mg BID x 8 weeks, or placebo x 12 weeks. Subjects were followed off study drug x 4 weeks. The primary efficacy outcome was American College of Rheumatology Combined Response Index in diffuse cutaneous Systemic Sclerosis.

Forty-two subjects received study drug: lenabasum N = 27 and placebo N = 15. Baseline patient characteristics were similar in both groups. There were no serious, severe or unexpected AEs) related to lenabasum. Severity and relationship of AEs to study drug were similar in both groups. AEs in ≥ 10% of lenabasum-treated subjects were dizziness and fatigue. Lenabasum subjects had greater improvement in American College of Rheumatology Combined Response Index in diffuse cutaneous Systemic Sclerosis scores than placebo-treated subjects over 16 weeks ($p = 0.044$). Lenabasum subjects had greater improvement and less worsening in modified Rodnan Skin Score, Patient Global Assessment, Physician Global Assessment and Health Assessment Questionnaire-Disability Index a patient-reported measure of functional disability.

5.6.2 Lenabasum Improved Biomarkers of Inflammation and Fibrosis in Skin from in Subjects in JBT101-SSc-001

Evidence of on-target biologic effects of lenabasum also have been demonstrated in systemic sclerosis. Lenabasum-treated subjects showed statistically significant reductions in inflammatory cell infiltrates and fibrosis in skin biopsies compared to placebo-treated subjects. They also had statistically significant reduction in gene transcripts in gene ontology pathways of inflammatory response, response to cytokine, extracellular matrix organization and collagen metabolism compared to placebo-treated subjects.

5.7 Safety Profile of Lenabasum

5.7.1 Overall Safety Profile of Lenabasum

A comprehensive assessment of the pharmacological, pharmacokinetic, and toxicological effects of lenabasum has been conducted that supports the continued clinical investigation of lenabasum in severe, life-threatening indications. Refer to IB for details.

When assessing safety risks of lenabasum, it is important to note that CB1 are preferentially expressed on neurons, and lenabasum has limited penetration of the blood-brain barrier (Dyson et al, 2005). When lenabasum is at steady state concentrations in animals, the brain concentration is about 30% to 40% of that in the plasma. Lenabasum's greater potency for CB2 than CB1, limited penetration of the blood-brain barrier, and a ~100-fold higher expression of CB2 compared to CB1 on activated immune cells increase the difference between exposures that activate CB2 on peripheral immune cells and those that activate CB1 in the brain. This difference reduces the risk of untoward effects from activation of CB1 in the central nervous system. To date, lenabasum has shown low potential for the development of physical dependence in pre-clinical animal models. In testing in humans, lenabasum has

shown no psychoactivity using the Addiction Research Center Inventory-Marijuana (ARCI-M) questionnaire and Freiburg List of Complaints, no effect on mood in the Mood Scale, and no evidence of attention or cognitive impairment on the Trail Making Test, and at therapeutic doses no difference from placebo in the proportion of subjects with psychiatric side effects.

Based on data from animal models of disease and Phase 2 clinical data, the likely therapeutic total daily dose range for resolving immune responses and pro-fibrotic processes is 0.5 to 60 mg. The therapeutic dose range for lenabasum is below the maximum tolerated total daily dose of lenabasum in humans of 180 mg. The dose limiting toxicity of lenabasum is the occurrence of several, usually mild, AEs in an individual subject, including combinations of dizziness or lightheadedness, fatigue, dry mouth, pallor, headache, loss of appetite, nausea, orthostatic hypotension, blurred vision, insomnia, somnolence, euphoric mood, inappropriate affect, and feeling abnormal or jittery. Of 29 AEs in 6 subjects who received 240 mg total daily dose, which is above the maximum tolerated dose and the top dose administered to humans to date, 27 (93%) AEs were mild and 2 (7%) were moderate in severity. Four subjects (67%) had dizziness.

In the lenabasum clinical development program, 277 subjects have received lenabasum in completed and unblinded studies. Additionally, an estimated 480 subjects are receiving blinded treatment in ongoing studies across the entire development program. Lenabasum has been studied in healthy subjects, in subjects with refractory neuropathic pain and in subjects with systemic sclerosis, cystic fibrosis, or dermatomyositis. Some subjects enrolled in open-label extension studies have been receiving study drug for over 2 years.

Refer to the IB for a detailed description of the lenabasum preclinical safety testing as well as the Reference Safety Information.

5.7.2 Safety of Lenabasum in Cystic Fibrosis in Trial JBT101-CF-001

In trial JBT101-CF-001, 85 subjects were dosed with study medication; 61 subjects received lenabasum and 24 subjects received placebo throughout the trial. Four out of 61 (6.6%) lenabasum-treated subjects withdrew following a TEAE, 2 of which were considered related to study drug. The 2 discontinuations considered related to lenabasum included lack of cognitive clarity (graded mild in severity) and feeling unmotivated (graded moderate in severity). One out of 24 (4.2%) placebo subjects withdrew following TEAE of difficulty focusing after taking study product (mild in severity).

The majority of reported treatment-emergent adverse events (TEAEs) in lenabasum-treated subjects were mild to moderate in severity. During Week 1 through Week 4, TEAEs occurred in 14 subjects (54%) in the lenabasum 1 mg cohort, 13 subjects (54%) in the lenabasum 5 mg cohort, and 15 subjects (43%) in the placebo cohort. During Week 5 through Week 12, TEAEs occurred in 21 subjects (68%) in the lenabasum 20 mg once per day cohort, 19 subjects (63%) in the lenabasum 20 mg BID cohort, and 14 subjects (58%) in the placebo cohort.

The most common TEAE was mild dry mouth reported by 8 lenabasum subjects (13%) and in no placebo subjects. As expected, the respiratory system was the most common source of TEAEs overall.

Nine SAEs occurred in lenabasum-treated subjects and six SAEs occurred in placebo-treatment subjects. None of the SAEs or severe TEAEs were assessed by investigator to be related to study drug. The SAEs comprised 13 pulmonary exacerbations (7 in the lenabasum cohort and 6 in the placebo cohort), 1 hand fracture (lenabasum recipient) and 1 thrombosis in a device (lenabasum recipient).

There were no observed clinically significant treatment effects on vital signs. Mean BMI was comparable in the lenabasum and placebo cohorts at baseline and at the end of the 16-week study. Triplet ECGs with QT/QTc interval measurements were done throughout the study and showed no significant changes from baseline. The ECG findings were similar in subjects who received lenabasum and placebo. Changes from baseline in the ARCI-M test were similar in lenabasum- and placebo-treated subjects.

Laboratory safety testing results showed no clinically significant changes from baseline. There was no observed clinically significant difference between lenabasum and placebo in hematology, chemistry, or urinalysis laboratory investigations. There was no clinically relevant reduction in leukocytes or leukocyte subsets.

Lenabasum achieved the primary objective of the study by demonstrating an acceptable safety and tolerability profile at all doses with no serious or severe AEs related to the study drug.

5.7.3 Safety of Lenabasum in Systemic Sclerosis in Trial JBT101-SSc-001

In the double-blinded, randomized, placebo-controlled portion of the Phase 2 trial in SSc, there were 2 treatment-emergent serious adverse events (SAEs), both a consequence of the underlying disease and unrelated to study product: one was moderate dehydration following an episode of vomiting in an lenabasum-treated subject and one was severe abdominal pain following gastric cryotherapy for vascular ectasias in a placebo-treated subject. There were no severe TEAEs in the lenabasum-treated subjects. Seventeen (63%) of lenabasum-treated subjects had a total of 66 TEAEs, and 9 (60%) of placebo-treated subjects had a total of 34 TEAEs. The severity and relationship of TEAEs to study product in lenabasum-treated subjects were like those in placebo-treated subjects. There was 1 discontinuation to a TEAE of moderate dizziness in a subject who was receiving lenabasum 20 mg once a day. Relationship of that TEAE to study product was probable.

The most common TEAE in the Phase 2 SSc trial was mild or moderate transient dizziness, often described as light-headedness, which occurred in 6 (22%) lenabasum-treated subjects and 2 (13%) placebo-treated subjects. Mild or moderate fatigue occurred in 5 (19%) of lenabasum-treated subjects and 1 (7%) of placebo-treated subject. There were no observed clinically significant treatment effects on vital signs. Mean body mass index was comparable in the lenabasum and placebo cohorts at baseline and at the end of the 16-week study. Assessment of ECGs and corrected QT intervals revealed no clinically significant prolongation of corrected QT intervals or other significant ECG findings. Changes from baseline in the ARCI-M test were similar in lenabasum- and placebo-treated subjects.

Laboratory safety testing results showed no clinically significant changes from baseline. There was no observed clinically significant difference between lenabasum and placebo in hematology, chemistry, or urinalysis laboratory investigations. There was no clinically relevant reduction in leukocytes or leukocyte subsets.

Trial JBT101-SSc-001 includes open-label dosing for subjects who completed the double-blinded placebo-controlled part of the trial. To date, subjects have received lenabasum treatment for a median of 234 days, range 29-295 days, in both parts of this trial. With open-label dosing, subjects received lenabasum 20 mg BID for a median of 194 days, range 25-207 days. At enrollment into open-label dosing, 92% of subjects were on concomitant immunosuppressive medications.

There have been no SAEs, severe TEAEs, or TEAEs leading to study discontinuation that have been related to lenabasum during open-label dosing in trial KBT101-SSc-001. Of the 36 enrolled subjects, 28 (78%) have had a least one TEAE during open-label dosing. Among these 28 subjects, the most severe TEAE experienced by an individual subject was unrelated to lenabasum in 25 (69%) subjects and related to lenabasum in only 3 (8%) of subjects. The most common TEAEs to date have been mild fatigue in 5/26 (14%) subjects and mild or moderate upper respiratory illnesses in 4/36 (11%) subjects. Mild dizziness has occurred in only 2/36 (6%) subjects.

5.7.4 Safety of Lenabasum in Dermatomyositis in Trial JBT101-DM-001

Study JBT101-DM-001 is a double-blind, placebo-controlled, randomised Phase 2 study being conducted at one centre in the US. Lenabasum or placebo is administered at 20 mg once per day for 28 days, escalating to 20 mg twice per day for an additional 56 days in subjects with skin-predominant dermatomyositis. To date, 22 subjects have completed dosing with study product, and it is estimated that 11 subjects received lenabasum and 11 subjects have received placebo. The unblinded results of the study have not been released.

- Following reviews of blinded safety data, a Safety Monitoring Committee recommended no change to the protocol or safety monitoring plan.
- There were no serious, severe, or unexpected AEs in the study. Most AEs have been mild in severity.
- An open-label extension of the study has started; to date, 21 of 22 eligible subjects have enrolled.

5.7.5 Pooled Analysis of Adverse Effects

A pooled analysis of numbers and percentages of subjects with treatment emergent AEs in all completed studies of lenabasum dosing was done, with AEs summarised by organ system and by dose (see IB for full table). In these pooled data, AEs that occurred in ≥ 5% of lenabasum-treated subjects were dizziness (15.4%), nausea (10.1%), dry mouth (10.1%), infective pulmonary exacerbation of cystic fibrosis (8.2%), upper respiratory tract infection (6.7%), fatigue (6.3%), haemoptysis (5.8%), and cough (5.8%). There were no AEs or laboratory abnormalities that indicated immunosuppression or an increase in rate of infection.

The only AEs reported in ≥ 5% of placebo-treated subjects were infective pulmonary exacerbation of cystic fibrosis (7.7%) and cough (6.6%). (Note that in study JBT101-CF-001, adverse events were collected during the follow-up period, 4 weeks after the end of treatment.)

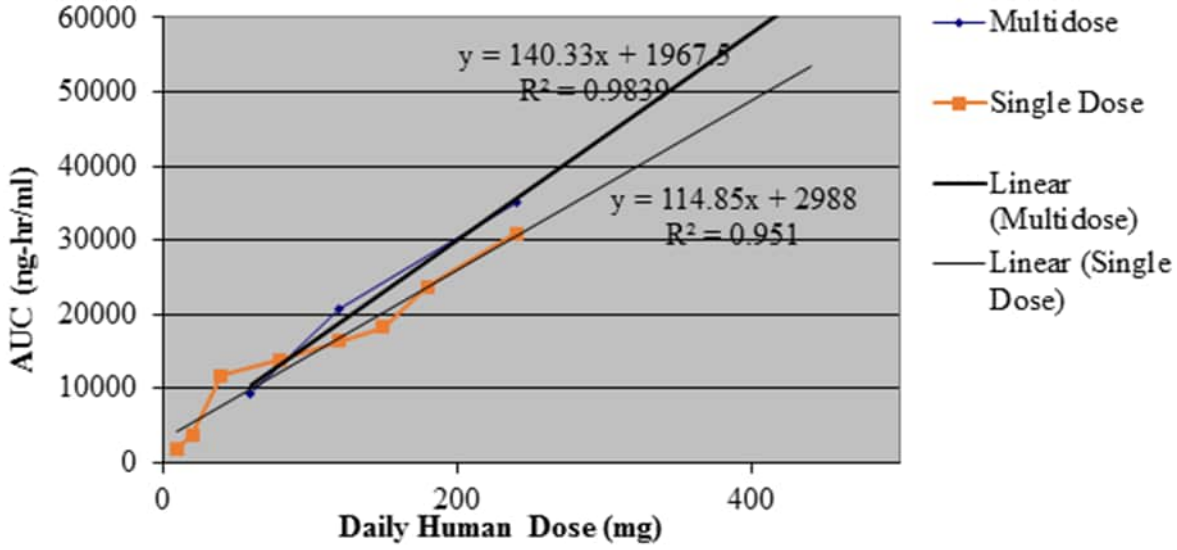
5.8 Population Pharmacokinetic Modeling to Support Inclusion of Subjects 12-17 Years of Age in JBT101-CF-002

To support inclusion of subjects 12-17 years of age in this Phase 2 trial, a population pharmacokinetic model was developed and all available human exposure data were analyzed. Data from two human Phase 1 (CT-3-01/P000029 and CPL7075-100-01) and two human Phase 2 studies (JBT101-SSc-001 and JBT101-CF-001) have been used to build and test the model. The pharmacokinetic profile of lenabasum appears well-described by a two-compartment model with lagged, first-order absorption. The covariates tested for association in this population pharmacokinetic model were population [healthy volunteers general, elderly healthy volunteers (≥68 years old), CF and SSc], demographic variables (weight, gender, BMI, age, ethnicity and creatinine clearance), co-morbidities (gastroesophageal reflux disease and pancreatic insufficiency), food effects, concomitant dedications (proton pump inhibitors and pancreatic enzymes). There was no association of body weight with lenabasum systemic exposure (i.e., C_{max} or AUC).

Together with the *in vivo* metabolism study results show that lenabasum is minimally metabolized in rats, dogs and humans, the pharmacokinetic profile in subjects 12-17 years of age is expected to be similar to that in adults at doses of 5 mg BID and 20 mg BID to be used in this trial. The rationale for this expectation follows.

Human pharmacokinetic data from prior clinical studies show that the relationship between dose and systemic exposure is approximately dose-proportional for lenabasum with respect to AUC and C_{max}. As shown in Figure 8 using the pharmacokinetics dataset from the Phase I study (CPL7075-100-01), exposures were approximately dose proportional for both the single and three times per day dosing of lenabasum. Exposures with BID dose regimen vs. $AUC_{0\text{-}24hr}$ of lenabasum were estimated using a linear regression analysis.

Figure 8 Linear Regression of $AUC_{0\text{-}24h}$ vs Lenabasum Dose in Humans



Using this relationship, the dose of lenabasum from 5-50 mg/dose was extrapolated to determine the human exposure of different dosing regimens (Table 3). Using these figures

and actual C_{max} values of single doses, Table 4 shows the expected C_{max} and AUC_{0-24} levels for 5 mg BID and 20 mg BID dosing in subjects 12 years of age and weight ≥ 40 kg.

Table 3 Extrapolated Lenabasum Human Exposure Levels by Dosing Frequency

Dose, mg	AUC (ng-hr/ml)		
	QD	BID	Three times per day
5	**3562**	**3371**	**4072**
10	4137	4774	6177
20	**5285**	**7581**	**10387**
30	6434	10387	14597
40	7582	13194	18807
50	8731	16001	23017

Table 4 Predicted Mean Lenabasum Exposure in Subjects 12 Years of Age with Weight ≥ 40 kg and 5 mg BID or 20 mg BID Dosing

Parameter	5 mg BID	20 mg BID
C_{max} (ng/ml)	165*	638**
Daily AUC (hr*ng/ml)^	3371	7581

*Actual 6 mg dose C_{max}. ** Actual 20 mg single dose C_{max}. ^Extrapolated AUC_{0-24hr}

Table 5 shows the expected safety factors with lenabasum 5 mg BID and 20 mg BID dosing for subjects 12 years of age with weight ≥ 40 kg. These estimates indicate the predicted lenabasum exposures for the 5 mg BID and 20 mg BID doses in subjects 12 years of age and weight 40 kg will be ≥ 4.3-fold and ≥ 1.9-fold, respectively, below the systemic AUC exposure at NOAELs determined in 26-week rat and 39-week dog toxicology studies. Based on the lack of significant accumulation observed after dosing in animals and humans, no accumulation of lenabasum with BID dosing is expected in subjects 12 years of age with body weight ≥ 40 kg. The safety factors shown in Table 5 should be representative of BID dosing in subjects 12 years of age and weight ≥ 40 kg.

Table 5 Predicted Safety Factors for Lenabasum 5 mg BID and 20 mg BID Dosing in Subjects 12 Years of Age with Weight ≥ 40 kg and Based on 26-week Rat and 39-week Dog Toxicology Studies

Dosing in 40 kg Subject	Species	NOAEL (mg/kg BID)	NOAEL AUC_{0-24hr}[a]	AUC-based Exposure Multiple
5 mg BID	Rat	5 mg/kg BID	27,050	8.0-fold
	Dog	2 mg/kg BID	14,581	4.3-fold
20 mg BID	Rat	5 mg/kg/BID	27,050	3.6-fold
	Dog	2 mg/kg BID	14,581	1.9-fold

Thus, the expected exposure to lenabasum for subjects 12-17 years of age with weight ≥ 40 kg at lenabasum 5 mg BID and lenabasum 20 mg BID doses are within ranges that have an acceptable safety profile and have been well tolerated to date.

5.9 Potential Risks and Benefits

Lenabasum is a novel synthetic oral agonist of cannabinoid receptors that activates the endocannabinoid system. It selectively binds and activates CB2 compared to CB1. Lenabasum activates naturally occurring pathways to resolve active innate immune responses and pro-fibrotic processes. Lenabasum's selective potency for CB2 than CB1, limited penetration of the blood-brain barrier, and preferential expression of CB2 versus CB1 on activated immune cells increases the therapeutic window.

In nonclinical testing, lenabasum inhibits production of TNFα and IL-6 and reduces mRNA levels of transcription factor XBP-1 by CF lung macrophages. Lenabasum significantly inhibits inflammation in a mouse model of CF lung inflammation induced by infection with *P. aeruginosa*. Lenabasum inhibits inflammation and fibrosis of the lungs and skin in bleomycin-induced murine models. In completed Phase 2 testing in CF in JBT101-CF-001, lenabasum demonstrated evidence of clinical benefit with a reduction in PEx. This clinical finding was supported by biomarker data that showed reduction inflammatory cells and mediators in sputum. Similarly, in completed Phase 2 testing in systemic sclerosis in JBT101-SSc-001, lenabasum showed consistent evidence of clinical benefit across multiple efficacy outcomes, often reaching and occasionally exceeding minimum important difference. Mechanism of action testing in JBT101-SSc-001 showed that lenabasum has significant and inhibitory effects on inflammation and fibrosis in the skin and gene transcript pathways associated with disease processes.

Lenabasum is being developed as a chronic oral therapy, self-administered either once or twice a day, for treatment of the serious and rare or uncommon diseases such as CF, SSc, dermatomyositis and systemic lupus erythematosus, diseases characterized by pathologic immune responses and often excessive pro-fibrotic processes.

5.9.1 Potential Risks

Nonclinical toxicology and toxicokinetic studies support further clinical testing at the doses of lenabasum that are administered in clinical studies. As anticipated, clinical signs consistent with a CB1 effect on the central nervous system were seen at high doses in single and repeat dose studies in animals. There were no clinical or anatomical pathology changes or treatment-related microscopic findings indicating organ toxicity in any of the repeat dose studies. The ages of rats receiving lenabasum treatment were as young as 38 days at the start of the twice-daily dosing in a 13-week repeat dose study in rats. The human-equivalent age of these rats appropriately covered the target adolescent ages (≥12 years). In reproductive and development studies in rats and/or rabbits, no effects of treatment were seen on fertility and fetal external, visceral, and skeletal evaluations, indicating a lack of developmental toxicity. Lenabasum was not mutagenic or clastogenic in genotoxicity studies. In several animal studies (rats and dogs), handling-induced convulsions (seizures) have been observed while lenabasum was administered for 3-6 months (i.e. chronic treatment) at or slightly above clinically relevant exposure levels. However, in all human studies to date, no convulsions have been reported by subjects taking lenabasum. In an animal experiment specifically designed to look for potential of lenabasum to cause seizures, lenabasum did not increase the the seizure-threshold for chemically-induced seizures. Lenabasum has shown low potential for abuse in preclinical testing in rats. Testing with human biomaterials shows that

lenabasum is tightly bound to plasma proteins (≥ 97%) and shows no cytochrome P450 inhibition at pharmacological drug levels.

Anticipated AEs in clinical trials with lenabasum include those related to the disease being studied, concomitant medications that subjects may be taking, AEs caused by lenabasum, and common AEs in the general population. The potential benefits are a reduction in PEx and improvement from baseline in lung function and patient-reported outcomes in CF. Evidence of this clinical benefit was seen in the completed Phase 2 study JBT101-CF-001 (Section 5.5.3).

Adverse events that occur in a general population are expected in any clinical study with lenabasum. These AEs would include events such as mild changes in vital signs, sore throats, mild skin, upper or lower respiratory tract or genitourinary infections, some of which may require topical or oral antibiotics, asymptomatic bacteriuria, headaches, nausea, vomiting, mild rashes, accidents, and mild to moderate abnormalities in laboratory testing of complete blood count testing, platelets, differential cell counts, metabolic panels including liver function tests and electrolytes, and urinalyses.

CB1/CB2 agonists can produce AEs in humans, and many of these are probably caused by the activation of central CB1 rather than of CB2 or peripheral CB1. Adverse effects most often observed in previous clinical trials with CB1/CB2 agonists have been dizziness/light-headedness, dry mouth, tiredness/fatigue, muscle weakness, myalgia (muscle pain) and palpitations (Pertwee, 2009). Other less frequently reported side effects of CB1/CB2 agonists include disorientation, feeling of drunkenness, 'high sensation', mental clouding, altered time perception, impairment of memory or ability to concentrate, tremor, balance impairment or lack of coordination, nausea/feeling sick, vomiting, hypotension, blurred vision, constipation or diarrhea, confusion, dysphoria/depression, disorientation, paranoia and hallucinations (Pertwee, 2009). Any of these AEs could be expected with lenabasum exposure. There have been no significant differences between lenabasum and placebo in tests of psychoactivity or in rate of psychiatric AEs in the clinical trials.

Some AEs associated with CB1/CB2 agonists have been observed in subjects exposed to lenabasum and future subjects are at risk for the AEs listed in the IB. The frequency and severity of AEs have been dose-related. The most common adverse reaction observed in reported lenabasum studies is dizziness, often described as light-headedness, that is usually mild and transient. Dizziness occurred in only 1/85 subjects in the completed Phase 2 CF study.

Laboratory safety testing results have shown no clinically significant changes from baseline. Assessment of ECG and corrected QT intervals in triplet ECGs at the time of C_{max} in CF and SSc subjects revealed no clinically significant prolongation of corrected QT intervals or other significant ECG findings.

Studies of human reproduction have not been performed with lenabasum. It is not known if lenabasum can cause fetal harm when administered to pregnant women or if it can negatively affect reproductive capacity. Women of childbearing potential (WOCBP) should not be pregnant or breastfeeding at the start of the study and should avoid becoming pregnant during the study and for at least 28 days after the last dose of the study product.

Refer to the IB for additional safety information about lenabasum.

5.9.2 Potential Benefits

Lenabasum has not been approved for any indication anywhere.

In the two Phase 2 studies (JBT101-CF-001 and JBT101-SSc-001) where efficacy has been assessed, positive efficacy results were noted. An analgesic signal was seen in the refractory neuropathic pain trial at total daily doses up to 80 mg. In the 16-week study in CF, lenabasum provided clinical benefit as assessed by time to PEx and event rate of PEx.

Based on findings of clinical benefit in Phase 2 testing in CF, efficacy of lenabasum will be measured in this study JBT101-CF-002; however, no benefits are claimed for the individuals who choose to participate. The information that will come from this study will address the efficacy, safety, tolerability, and plasma concentrations and metabolites of lenabasum in subjects ≥ 12 years of age with CF.

5.9.3 Risk-Benefit Conclusions

Overall, lenabasum has been found to be well-tolerated in studies conducted to date with only mild or moderate adverse reactions observed. The most common adverse reaction consistent with the pharmacological action of lenabasum during placebo-controlled dosing has been mild dry mouth in CF and mild/moderate dizziness in SSc. In the dose range applicable to currently conducted and planned clinical trials, there was a lower frequency of AEs overall and of AEs of central nervous system effects than at doses higher than the anticipated therapeutic range.

Positive efficacy results have been noted in the completed Phase 2 CF, SSc and neuropathic pain trials. Results from preclinical safety, toxicology and pharmacokinetic studies, efficacy studies in animal models of disease, studies with human biomaterials, and safety, pharmacokinetic, and mechanism of action studies to date in humans support a favorable benefit-risk profile of lenabasum in CF.

These data justify its continuing investigation in clinical trials in rare and serious diseases with significant unmet medical need, such as cystic fibrosis.

6 STUDY OBJECTIVES AND ENDPOINTS

Primary efficacy objective	**Primary endpoint**
To evaluate the efficacy of lenabasum 20 mg twice per day (BID) compared to placebo in the treatment of cystic fibrosis (CF) by assessing the rate of pulmonary exacerbations (PEx) using primary definition of PEx	Rate of PEx using primary definition of PEx with lenabasum 20 mg BID, compared to placebo, during the treatment period
Secondary efficacy objective	**Secondary endpoints**
1. To evaluate the efficacy of lenabasum 20 mg BID compared to placebo in the	a. Event rate of PEx using secondary definition of PEx with lenabasum 20 mg BID compared to placebo

treatment of CF by assessing other efficacy endpoints	b. Time to first new PEx using primary definition of PEx with lenabasum 20 mg BID compared to placebo c. Time to first PEx using secondary definition of PEx with lenabasum 20 mg BID compared to placebo d. Change from baseline in CFQ-R respiratory symptom domain with lenabasum 20 mg BID compared to placebo e. Change from baseline in FEV1 % predicted with lenabasum 20 mg BID compared to placebo
2. To evaluate the efficacy of lenabasum 5 mg BID compared to placebo in the treatment of CF	a. Rate of pulmonary exacerbations (PEx) using primary definition of PEx with lenabasum 5 mg BID compared to placebo, during the treatment period b. Event rate of PEx using secondary definition of PEx with lenabasum 5 mg BID compared to placebo c. Time to first new PEx using primary definition of PEx with lenabasum 5 mg BID compared to placebo d. Time to first PEx using secondary definition of PEx with lenabasum 5 mg BID compared to placebo e. Change from baseline in CFQ-R respiratory symptom domain with lenabasum 5 mg BID compared to placebo f. Change from baseline in FEV1 % predicted with lenabasum 5 mg BID compared to placebo
Tertiary efficacy objectives	**Tertiary endpoints**
1. To evaluate the efficacy of lenabasum 20 mg BID and lenabasum 5 mg BID compared to placebo in the treatment of CF by assessing change from Visit 1 in the prespecified endpoints	a. Change in inflammatory biomarkers in sputum and blood b. Primary and secondary efficacy endpoints excluding change in biomarkers in subgroups of subjects, including subgroup of adolescents (12-17 years old) and adults c. Forced vital capacity (FVC) % predicted and ml

	d. Chronic Respiratory Infection Symptom Scale (CRISS) score e. Cystic Fibrosis Questionnaire – Revised (CFQ-R) domain scores f. Body mass index (BMI) g. Numbers of common CF pathogens in sputum cultures
2. To evaluate recovery from PEx for lenabasum 20 mg BID, lenabasum 5 mg BID and placebo	a. Proportion of early rapid responders b. Proportion of subjects with FEV1 improvement to pre-PEx FEV1 values defined by study baseline and FEV1 prior to PEx by study completion c. Event rate of subsequent PEx d. Time to subsequent PEx e. Sputum granulocytes and neutrophils, actual values and change in number of granulocytes and neutrophils from pre- to post-PEx
[redacted]	
Safety objectives	**Safety endpoints**
To evaluate safety of lenabasum 20 mg BID and lenabasum 5 mg BID treatment and placebo treatment	• TEAEs • Changes in vital signs, physical examination, blood and urine laboratory safety tests and electrocardiograms

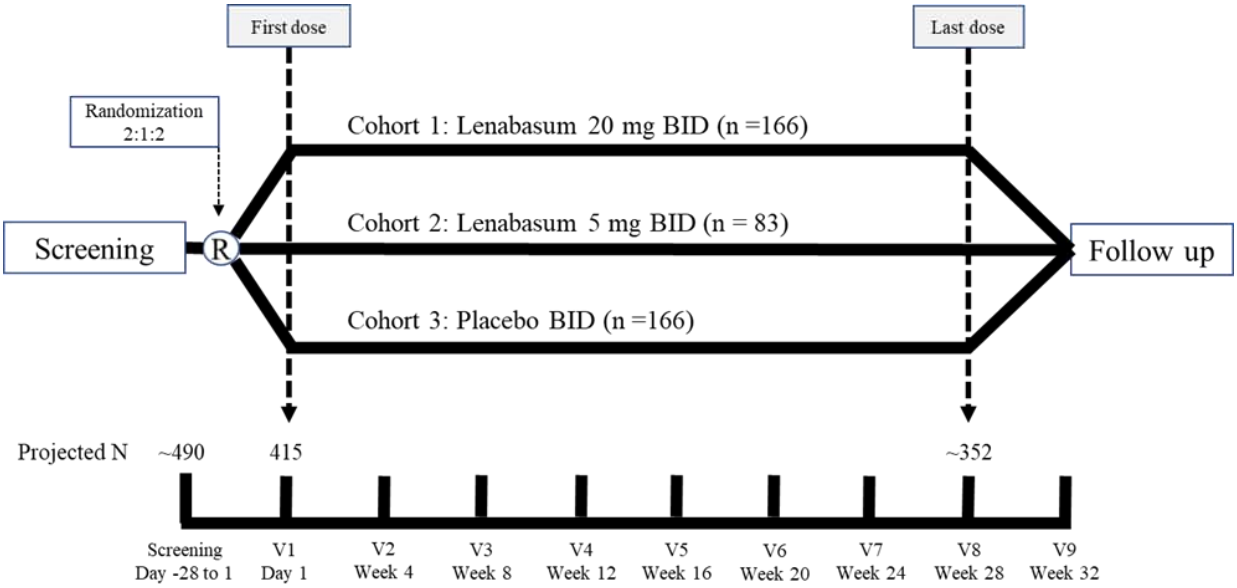
To evaluate tolerability of lenabasum 20 mg BID and lenabasum 5 mg BID treatment	Treatment discontinuations with lenabasum treatments compared to placebo

7 INVESTIGATIONAL PLAN AND METHODS

7.1 Study Design and Plan Description

This is a multicenter, double-blind, randomized, placebo-controlled, parallel group assessment of efficacy and safety of 28 weeks of treatment of CF patients with lenabasum 20 mg BID and lenabasum 5 mg BID.

7.1.1 Study Schematic



R = randomization; V = Visit; N = number of subjects; BID = twice daily

7.1.2 Study Population

The target population is males and females with CF ≥ 12 years of age with FEV1 ≥ 40% predicted and < 100% predicted within 12 months before screening and who have had 2 to 3 PEx treated with IV antibiotic therapy within 12 months before screening or as an alternative, 1 PEx treated with IV antibiotics and at least 1 PEx treated with oral antibiotics in the last 12 months before screening.

Target enrollment is 415 eligible subjects. Assuming a screen failure rate of ~15%, ~490 subjects will be screened to identify a target of 415 eligible subjects who will be enrolled at up to ~100 multi-national sites. Assuming a ~15% drop-out rate, ~352 subjects will complete the study.

7.1.3 Screening

Screening can occur up to 28 days before Visit 1. Refer to Section 7.2.3 for the detailed list of screening assessments and Sections 7.2.4 and 7.2.5, respectively, for inclusion and exclusion criteria. A subject that has screen failed may re-screen at a later date at the discretion of the site investigator. A new subject code will be allocated at re-screening.

7.1.4 Duration of the Study

The screening period is up to 4 weeks before Visit 1.

Active dosing with study drug is 28 weeks. There will be 8 scheduled study visits during active dosing with study drug, labeled Visits 1-8, which occur at Visit 1 and at the completion of Weeks 4, 8, 12, 16, 20, 24, and 28.

Subjects who complete Visit 8 on study drug will have a Safety Follow-up Visit labeled Visit 9 at 28 (± 7) days after Visit 8.

Subjects who discontinue early from the study drug and do not withdraw consent will be asked to return for off-treatment safety and efficacy assessments at Visit 5 and Visit 8, as applicable. Otherwise, they will return 28 (± 7) days after the last dose of study drug for a Safety Follow-up Visit that is identical to Visit 9 assessments.

All subjects who develop acute signs and symptoms of worsening lung disease will be asked to return to the site for evaluation at a Possible PEx Visit (assessments detailed in Section 10.2.6).

Unscheduled Visits may be necessary to assess the subject for safety purposes unrelated to new respiratory symptoms or a PEx.

During Visit 8 (or ET) subjects may be asked to participate in a two-year observational safety follow-up study. Subjects who agree to participate in the follow-up study will be consented under a separate protocol.

All scheduled visits after Visit 1 are ± 1 week.

See Section 10.2 for the timing and description of protocol procedures scheduled for each visit.

The start of the study is defined as the first subject's first visit. The end of the study is defined as the last subject's last visit.

7.1.5 Blinding

Dosing will be done in a double-blinded, randomized, placebo-controlled manner. Refer to Section 8.6 for blinding methods and rationale.

7.1.6 Treatment Groups, Allocation and Dose Adjustment

7.1.6.1 Treatment Groups

Subjects will be randomized centrally to treatment assignment before dosing. Randomization will be stratified by factors that influence risk of PEx in the next 6 months or may be associated with differences in standard-of-care including treatment with CFTR-targeting treatments: number of previous PEx requiring IV antibiotics in the previous year (1 versus 2 or 3), FEV1 % predicted at baseline (< 70% versus ≥ 70% predicted) and location of site (United States versus Canada and Europe).

Treatment groups are:

- Cohort 1: lenabasum 20 mg BID (n = 166)
- Cohort 2: lenabasum 5 mg BID (n = 83)
- Cohort 3: placebo BID (n = 166).

Twice per day dosing consists of a dose in the morning and a dose in the evening. Ideally doses should be about 12 hours apart and at a minimum there should be at least 8 hours between any 2 doses. Subjects will self-administer study drug, which will be taken orally and with no requirement as to fed or fasting state. Refer to Section 8 for the description of the formulation and presentation of the study drugs.

7.1.6.2 Dose Adjustment

To potentially reduce drop-out rates from AEs or tolerability issues during the study, the treating physician may choose to reduce the dose of study drug by 1 capsule per day for safety or tolerability reasons, but only after discussion with the Medical Monitor about the safety or tolerability reasons. The reasons for this physician decision will be documented in the electronic Case Report Form (eCRF). Criteria leading to a permanent reduction from BID to QD dosing of study medications include:

- The occurrence of AEs that are persistent or recurrent over at least 2 weeks AND
- Are at least moderate in severity AND
- Are probably- or definitely-related to study medication AND
- In the absence of dose reduction, would lead to permanent discontinuation of study product or discontinuation from the study AND
- All permanent dose reductions require prior Medical Monitor approval

For clarity, it is the intended that the subject remains on BID dosing throughout the study. The above criteria are to be used only if the subject will otherwise discontinue the study product or the study.

The impact of any reduction in dose will be assessed in sensitivity analyses of efficacy outcomes. See Section 7.2.8 for guidelines for interruption or discontinuation of dosing.

7.1.7 Efficacy Assessments

Refer to Section 9.1 for the definition of efficacy variables and description of efficacy assessments and Section 10 for the tabulation and detailed listing of efficacy assessments scheduled at each visit. The following efficacy assessments will be done:

- Antibiotic use for respiratory signs and symptoms questionnaire (AUR-Q) at screening, Visits 1- 9 and Possible PEx Visits
- Spirometry at screening, Visits 1- 9 and Possible PEx Visits
- CRISS questionnaires at screening, Visits 1-9 and Possible PEx Visits
- BMI at screening, Visits 1- 9 and Possible PEx Visits
- CFQ-R questionnaire at screening, Visit 1, Visit 5, Visit 8 and Possible PEx Visits
- Biomarkers in blood and sputum at Visit 1, Visit 2, Visit 5, Visit 8 and Possible PEx Visits
- Common CF pathogens in sputum at Visit 1, Visit 5, Visit 8 and Possible PEx Visits.

7.1.8 Safety Assessments

See Section 9.2 for the definition of safety variables and description of safety assessments and Section 10 for the tabulation and detailed listing of safety assessments scheduled at each visit. The following safety assessments will be done:

- Concomitant medications/vaccinations from screening until the subject completes or discontinues from the study
- AEs including SAEs at screening and Visits 1-9, Possible PEx Visits, and Unscheduled Visits
- Vital signs consisting of systolic and diastolic blood pressure (BP), pulse rate (P), respiratory rate (R), body temperature (T), weight, height, and O_2 saturation at screening and Visits 1-9, Possible PEx Visits, and Unscheduled Visits. Body mass index (BMI) will be calculated centrally
- Laboratory safety tests at screening and Visits 1-9 and as indicated during Possible PEx Visits and Unscheduled Visits
- ECGs questionnaire will be completed by subjects at Visit 1 before and 3 ± 0.5 hours after administration of the first study drug dose, at Visit 5 and at Visit 8.

7.1.9 Data Collection

Remote data entry will be done using eCRF. Certain data will be recorded directly into eCRFs to facilitate web-based adjudication. Refer to Section 13.1 for description of source data and record keeping.

7.1.10 Discussion of Study Design and Control Group

The study is being conducted in the target population of subjects with confirmed CF which is the indication under investigation. Subjects at higher risk of PEx during the study period will be enrolled which reduces sample size and facilitates testing over 6 months rather than a year.

Based on resolution of inflammation and improved bacterial clearance, lenabasum is expected to reduce the number and severity of PEx. This efficacy will be assessed in primary and secondary efficacy outcomes that measure and define PEx in several different ways. On-target activity of lenabasum in the lungs showing modification of the underlying disease process of lung inflammation in CF will be assessed during the study as a secondary efficacy outcome.

The double-blind design and random assignment to treatment in this study provide stringent methods of elimination of bias in the planned assessments of efficacy and safety variables. This study is multicenter and placebo-controlled.

Cystic fibrosis is a variable disease in its manifestations and outcomes. A matching placebo will be used to provide the benchmark for comparison to lenabasum during this interventional study design. To minimize safety risk, lenabasum and placebo treatments will be given in addition to standard-of-care treatments the subject is receiving.

Subjects 12-17 years of age who weigh at least 40 kg will be enrolled. These subjects will be at significantly higher risk of recurrent PEx and decline in lung function near-term than other adolescents with CF. Based on modeling of pharmacokinetic data, exposure in these subjects 12-17 years of age at the higher dose of lenabasum is 20 mg BID will be lower than the NOAEL in animal toxicology studies, including toxicology studies in adolescent rats. The safety profile to lenabasum in 248 subjects as of May 2017 including subjects with CF has been acceptable with no severe or serious AEs related to lenabasum. The efficacy results

from the completed Phase 2 study in adults with CF offers potential for clinical benefit in these subjects 12-17 years of age with high unmet medical need.

7.1.10.1 Justification of dose

The maximum dose of Lenabasum to be used in this study is 40 mg per day (administered as 20 mg BID). This dose level has been administered in CF patients in a prior study as reported in Section 5 of this document, where it was well tolerated and demonstrated an acceptable risk benefit profile. Overall lenabasum has been administered to 299 subjects in doses ranging from 1 mg to 240 mg with duration of dosing ranging from a single dose to over one year of dosing (DSUR data lock point 05 March 2018). The data generated to date supports progression of 20 mg BID dose as likely efficacious dose.

The lower dose level of 5 mg BID is being investigated to profile the dose response and is projected to be less efficacious than the 20 mg BID dose level.

Justification for these doses in subjects aged 12 – 17 is provided in Section 5.8.

7.2 Selection of Study Population

7.2.1 Target Population

The target population is subjects with documented CF who are at least 12 years of age and are at high risk for PEx in the next 6 months.

7.2.2 Definition of Pulmonary Exacerbation and Related Terms

For this study, the following definitions will be used:

PEx definition for primary endpoint:

- Physician diagnosis of pulmonary exacerbation
- Prescription of new oral, intravenous or inhaled antibiotics (regularly given prophylactic antibiotics do not count as new antibiotic unless the dose is increased, or given off schedule).
- At least 4 out of 12 Fuch's criteria are met.

  Note: For a new exacerbation event, there needs to be at least 28-day gap from last use of antibiotics to the new antibiotics (regularly given prophylactic antibiotics do not count to determine the gap). The 28-day gap will be counted centrally for efficacy analysis.

Secondary definition of PEx:

- Physician diagnosis of pulmonary exacerbation.
- New antibiotics- oral, intravenous or inhaled, with same 28-day gap as above from the last antibiotic use.

Start day of a new PEx

The day the physician initiates antibiotic treatment for the new PEx.

Stop day of a new PEx

The last day of antibiotic treatment for a new PEx.

Time to first pulmonary exacerbation

Days from the first dose of study drug to the day a physician initiates systemic antibiotic(s) for the first new PEx after enrollment.

Early Rapid Responder

Early rapid responders will be defined in several ways including but not limited to achieving a certain degree of improvement in FEV1, improvement in CRISS score, and improvement of other related measurements within a certain period of time.

7.2.3 Screening Assessments

Subjects will be recruited from clinics run by the investigators or at which the investigators participate. See Section 7.2.7 for a description of recruitment strategies. Written informed consent/assent will be obtained before any study-related procedure is performed for a subject. After obtaining written informed consent/assent, eligibility for study enrollment will be assessed using the protocol-defined inclusion and exclusion criteria.

7.2.4 Inclusion Criteria

Individuals who meet **ALL** the following criteria at screening are eligible for enrollment:

1. Documentation of a CF diagnosis as evidenced by 1 or more clinical features consistent with the CF phenotype and 1 or more of the following criteria:
   a. Sweat chloride ≥ 60 mEq/L by quantitative pilocarpine iontophoresis test
   b. Two known disease-causing mutations in the CFTR gene.
2. Twelve years of age or older at the time Informed Consent/Assent is signed.
3. Weight ≥ 40 kg.
4. FEV1 ≥ 40% predicted and < 100 % predicted within the last 12 months.
5. Physician-initiated treatment with an IV antibiotic 2 or 3 times in the last 12 months for a new PEx. See Table 6.
6. As an alternative to inclusion criterion 5, physician-initiated treatment with an IV antibiotic 1 time in the last 12 months plus physician-initiated treatment with oral antibiotic(s) 1 or more times in the past 12 months for a new PEx. See Table 6.
7. Completion of the last course of antibiotics prescribed for any PEx ≥ 28 days before Visit 1.

Table 6 Eligibility Criteria for Prior Pulmonary Exacerbation Within 12 Months Before Screening

New PEx Treated with IV Antibiotics[1], N	New PEx Treated with Oral Antibiotics[1], N	Timing	PEx Eligibility Criteria Met
0			No
1	0		No
1	≥ 1	Antibiotic-free interval between at least 2 PEx must be ≥ 28 days. Antibiotic treatment for any PEx must be completed ≥ 28 days before Visit 1.	Yes, #6 and #7
2 to 3	No requirement	Same as above	Yes, #5 and #7
> 3			No

[1] Excludes prophylactic antibiotics.

8. Able to perform pulmonary function tests. Optional use of a bronchodilator before testing is allowed to facilitate testing if the bronchodilator is used consistently starting with Visit 1.
9. Willing to provide repeat sputum specimens. If a subject is unable to reliably spontaneously expectorate sputum, induced sputum collection is acceptable. Optional collection of induced sputum specimens is allowed if induced sputum specimens are consistently collected starting with Visit 1. Adolescents should try to produce sputum spontaneously and can opt out of sputum induction.
10. Willing not to use any cannabinoids or any illegal substance of abuse from screening through Visit 9.
11. Women of childbearing potential must not be pregnant or breastfeeding at Visit 1 and must be using at least one highly effective or an acceptable method of contraception for at least 28 days before Visit 1 and be willing to continue to use at least one highly effective or an acceptable method of contraception throughout the study and for at least 28 days after discontinuation of study drug (See Appendix A).
12. Male participants must be willing to follow contraceptive requirements and should not get anyone pregnant while they are taking the study product or within 28 days after taking the last dose of the study product, during which time period they or their partner must be willing to use at least one highly effective or an acceptable method of contraception (See Appendix A).
13. Able to adhere to the study visit schedule and other protocol requirements.

7.2.5 Exclusion Criteria

Individuals who meet **ANY** of the following criteria are not eligible for enrollment:

1. Severe or unstable CF at screening or Visit 1, such as:
    a. Change in dose, or initiation of any new chronic therapy for CF lung disease within 28 days before Visit 1
    b. Treatment with any systemic corticosteroids > 10 mg per day prednisone or equivalent within 14 days before Visit 1

c. Actively listed on an organ transplant list or have had an organ transplant other than corneal transplant.

2. Significant diseases or conditions other than CF that may influence response to the study drug or safety, such as:
   a. Active hepatitis B or C infection
   b. Human immunodeficiency virus infection
   c. A history of cancer except basal cell carcinoma or *in situ* carcinoma of the cervix treated with apparent success with curative therapy ≥ one year before Visit 1.
3. Subject's with a history of any seizure within the last 2 years.
4. Pregnant, trying to become pregnant or lactating female.
5. Current evidence of alcohol abuse (defined as 4 or more drinks per day on at least 4 days of the week) or history of abuse of illegal and/or legally prescribed drugs such as barbiturates, benzodiazepines, amphetamines, cocaine, or opioids during the 1 year before screening.
6. Any investigational agent within 30 days or five therapeutic half-lives of that agent whichever is longer, before Visit 1.
7. Any of the following values for laboratory tests at screening:
   a. A positive pregnancy test
   b. Hemoglobin < 10 g/dL in males and < 9 g/dL in females.
   c. Neutrophils < 1.0 x 10^9/L
   d. Platelets < 75 x 10^9/L
   e. Creatinine clearance < 50 ml/min according to Modification of Diet in Renal Disease (MDRD) Study equation in adults and Schwartz eGFR formula in adolescent population.
   f. Serum transaminase(s) > 2.5 x upper normal limit
8. Any other condition or concurrent medical therapy at screening or Visit 1 that causes the investigator to determine it is not safe for the subject to participate or that may influence response to study drug or interfere with study assessments.

When in doubt about whether a subject meets an eligibility criterion, the investigator or designee should discuss the situation with the Medical Monitor.

7.2.6 Women, Minorities, and Children (Special Populations)

Women and minorities will be recruited. Because the incidences of CF in people of African, African American, Hispanic, and Asian ancestry are lower than in people of Central or Northern European ancestry, it is expected that their percentages in this study will be lower than their representation in the general population of Central Europe, Northern Europe and North America. However, the percentages of women and minorities in the study are expected to reflect their percentages in the CF eligible populations in Central Europe,

Northern Europe, and the US. Urban sites will be included, to increase opportunities to enroll minority subjects.

Subjects 12-17 years of age will be recruited. Because of the requirements for a certain number of PEx in the previous 12 months and the relative infrequency of PEx in children compared to adults, it is expected that about 15-20% of subjects will be subjects 12-17 years of age.

7.2.7 Strategies for Recruitment and Retention

The target enrollment is 415 eligible subjects. Most subjects will be recruited from the clinics run by the investigators or at which the investigators participate. A need to advertise for subjects outside the sites is not anticipated, although it is acceptable.

To encourage retention in the study, every effort will be made to be respectful of the subject's time. The total time required from the subject for study visits will vary with the efficiency of each site and is expected to be 15 to 22 hours plus travel time over 32 weeks.

Subjects will be encouraged to stay in the study at each visit by study personnel and reminded of the date and time of their next visit. If the subject agrees, e-mail or text message reminders of visits also will be sent.

To reduce missing data, subjects who discontinue study drug for reasons of safety or tolerability will be asked to return for Visit 5, if they have not already had it, and Visit 8 to collect off-treatment safety and efficacy data. These off-treatment safety and efficacy data will be included in data analyses.

7.2.8 Removal of Subjects from Therapy or Assessment

7.2.8.1 Interruption of Dosing in an Individual Subject

The intent is to continue study drug during any PEx.

Interruption of continued dosing in individual subjects may occur for safety reasons and at the discretion of the investigator or Medical Monitor, if it is felt that interruption of dosing is in the best interest of the subject. Other than in urgent situations, it is recommended that the investigator discuss the reasons for interruption of dosing with the Medical Monitor, before interruption.

Multiple on-off periods of treatment with study drug are permitted if in the best medical interest of the subject according to the investigator. The Medical Monitor may contact the investigator to discuss appropriateness of continuing an individual subject in the trial because of multiple on-off periods, for example, if the subject exceeds more than 14 days off study drug.

If there is interruption of the drug, the original visit schedule should be followed, therefore it is expected that with interruption(s), total treatment duration in an individual patient will be less than 28 weeks.

7.2.8.2 Individual subject's withdrawal from the study

Lost to follow-up: If a subject does not return for scheduled study visits, at least 3 attempts will be made to contact the subject by phone by site staff. A certified letter to update him/her

on the study status will also be sent following the third attempted phone contact. If the subject does not respond to these attempts, he/she will be considered lost to follow-up.

Withdrawal of consent for the study participation: An individual subject who withdraws consent will not receive any further study drug or evaluation after consent is withdrawn. For the subjects who discontinue the treatment, but do not withdraw consent, refer to Section 7.2.8.3.

7.2.8.3 Discontinuation of Dosing in an Individual Subject

An individual subject will have study drug permanently discontinued before completion of Visit 8 if any of the following occur in the subject in question:

- Lost to follow-up
- Withdrawal of consent for the study participation
- Pregnancy
- Any serious or life-threatening TEAE probably or definitely-related to lenabasum
- Any AE, which in the opinion of investigator, can jeopardize the safety of an individual subject
- Subject's decision to discontinue treatment

Subjects lost to follow up or who withdraw consent for the study participation will be handled as per Section 7.2.8.2.

Subjects who are withdrawn due to pregnancy will be followed per the procedures outlined in Pregnancies, Section 9.2.6.8.

Participants who are discontinued permanently from study drug due to a serious or life-threatening TEAE will be followed until resolution or stabilization of the event. Subjects withdrawn for any of the above reasons except lost to follow-up will be evaluated at the time of their withdrawal (Visits 2-7 or an unscheduled visit). Unless consent is withdrawn or the subject is lost to follow-up, subjects who have study drug permanently discontinued prematurely will be asked to return for Visit 5 (if they have not already had Visit 5) and Visit 8, for assessment of PEx and other efficacy and safety endpoints. If they decline, they will be asked to return for a Safety Follow-up Visit 28 ± 7 days after the last dose of study drug.

If it is a subject's decision to discontinue treatment, the subject will be asked for the reason, and if it is due to an adverse event, it should be marked as discontinuation due to adverse event. Subjects who discontinue study product (but do not withdraw consent) may be asked to participate in a two-year observational safety follow-up. Subjects who agree to participate in the follow-up study will be consented under a separate protocol.

The investigator or designee must enter the information about discontinuation of treatment in the electronic data capture (EDC) system. Study drug will be stopped without tapering or adding additional treatments. All remaining study drug must be returned to site staff.

Abrupt discontinuation of treatment with lenabasum has not been shown to cause any harmful effects although any clinical benefit from treatment such as protection from PEx may be lost when treatment is stopped.

Narratives will be generated for all patients who discontinue the study drug early for any reason.

7.2.8.4 Premature Termination or Suspension of the Study

This study may be suspended or prematurely terminated by Corbus independently or at the request of a regulatory authority, with sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by Corbus to the regulatory authority and the investigators. If the study is suspended or prematurely terminated, the investigator will promptly inform his/her EC and will provide the reason(s) for the suspension or termination. Review and approval by an investigator's EC and possibly the country regulatory agency is required for resumption of the study at that site in the event the study is interrupted because of any of the events listed below.

If any of the following events occur during the enrollment period, study entry and randomization of new subjects into the study will be suspended until expedited review of the event in question occurs by the independent, unblinded DMC:

- Death in any subject judged to be probably or definitely-related to lenabasum
- A life-threatening clinical event judged to be probably or definitely related to lenabasum. NOTE: The term 'life-threatening' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it was more severe.
- Determination of unexpected, significant, or unacceptable risk to subjects that contraindicates dosing of additional subjects, in the opinion of the Chief Medical Officer of Corbus.
- Any information about the execution of the trial that in the opinion of the Chief Medical Officer of Corbus contraindicates further study entry and randomization of new subjects. Possible reasons for termination of the study could be, but are not limited to, the following: unsatisfactory enrollment with respect to quantity or quality; insufficient adherence to protocol requirements; data that are not sufficiently complete and/or evaluable to interpret study results; falsification of records; or determination of futility of demonstrating efficacy.

Administration of study drug may continue during the time of review in subjects who are already receiving study drug at the discretion of the Chief Medical Officer of Corbus.

An expedited and cumulative review of safety data and the circumstances of the event(s) in question will be conducted by the DMC with additional external expertise as needed to make recommendations to Corbus whether screening, randomization, and/or dosing can resume or should be discontinued, whether the protocol should be modified or whether the study should be discontinued permanently. The study can be discontinued permanently by Corbus upon consideration of a cumulative review of safety and other data.

7.2.9 Replacement Policy

Subjects will not be replaced.

8 STUDY PRODUCT

8.1 Dosage, Preparation, and Administration

No onsite preparation or masking of clinical supplies is required by site personnel. Study drugs are powder-in-capsules of lenabasum 20 mg, lenabasum 5 mg and placebo.

Study drug will be dispensed at Visit 1 according to randomization schedule and the subject will take the first dose of study drug at the site. Subjects will be observed at the site for at least 30 minutes following the first dose of study drug. Thereafter, subjects will self-administer study drug, which will be taken by the oral route BID with at least 8 hours between the two doses.

The study drug must be taken per the following regimen:

- Capsules should be swallowed whole
- Ideally, morning and evening doses will be about 12 hours apart. Morning and evening doses should be at least 8 hours apart
- If a dose is missed, it should be taken as soon as possible on the same day. If it is missed for the entire day, it should not be made up
- Doses can be taken without regard to fed state
- Subjects who take more than the prescribed dose of study drug should be instructed to contact site staff immediately and to seek emergency medical care, if needed.

8.2 Study Medication Supply

After ensuring the subject meets eligibility criteria, the investigator or designee will request subject randomization by an interactive web-based randomization system (IWRS) generally 4-7 days before first dose of study drug. After randomization, IWRS will generate an e-mail to Corbus' distributor of the study drug and request shipment of the correct study drug and dose if needed. Study drug will be shipped to the site pharmacy or investigator before Visit 1. Certain sites at the beginning of the study may have a supply of study drug on site to facilitate dosing of the first subjects entered.

Study drug will be supplied in bottles of 35 capsules, corresponding to treatment assignment. Each bottle will be numbered, and the sites will receive instructions which bottles and kits to dispense to which subject and when, based on treatment assignment. Two study bottles will contain a 28-day supply of study drug (BID dosing) plus packaged overage to allow treatment to continue for up to seven extra days, in case of unexpected and unavoidable delays in follow-up visit. For clarity, study visits are expected to occur on the stipulated day with minimal variation.

The overage will be collected before dispensing the next 28-day supply of study drug. No study drug will be distributed unless the subject returns unused study drug, when applicable for a given visit. In exceptional circumstances, based on his/her judgment, the investigator can authorize dispensing the next 28-day supply of study drug in the absence of returning the unused overage from the previous 28 days. If a subject should fail to return overage at the designed visit, that overage can be collected at the next visit. If not previously collected, all unreturned overage must be collected on Visit 9.

Detailed instructions will be in a manual supplied to each site by Corbus.

8.3 Description of Study Drug

Lenabasum is (6aR,10aR)-1-Hydroxy-6,6-dimethyl-3-(2-methyl-2-octanyl)-6a,7,10,10a-tetrahydro-6H-benzo[c]chromene-9-carboxylic acid (Figure 1, previously known as anabasum, ajulemic acid, CT-3, IP751 and CPL7075 and also known as JBT-101. Detailed study product information can be found in the Investigator's Brochure.

8.4 Description of Comparator Product

Placebo is microcrystalline cellulose (no active ingredient).

8.5 Packaging and Labeling

Lenabasum and placebo capsules will be packaged in the same type bottle with the same number of capsules in each bottle.

All study drug will have an expiry date that exceeds the last date when the study drug will be administered to that subject.

The bottles will be indistinguishable from each other in appearance.

Lenabasum will be dispensed to study subjects in the original packaging with a label clearly indicating that the contents are for investigational purposes only. The label will bear Corbus Pharmaceuticals, Inc.'s name and the quantity of drug contained. Additional labels must not cover the caution label or the name of the manufacturer.

8.6 Masking and Unblinding

8.6.1 Masking Procedures

Lenabasum and placebo capsules will have similar physical appearance and will be packaged, labeled and handled so that subjects and site staff are not able to distinguish between the two. Identical assessments and procedures will be followed during the study for subjects assigned to lenabasum and placebo cohorts.

This study is double-blinded. The blinding of the trial must be maintained throughout the trial until all data entry and processing are complete and the database has been locked. Except for emergency unblinding (see Section 8.6.2), all Corbus medical and clinical operations staff associated with this study, both internal Corbus staff and CRO staff, and including the Medical Monitor, project management, and site monitors, will remain blinded to treatment randomization until the study is completed and the database is closed.

Study subjects and the site staff, including the investigators who will do safety and clinical assessments, designees, study nurses, and study coordinators will be blinded to intervention groups during the study. The final unblinding of all study participants will occur only after the data analysis set has been locked. If the treatment allocation for a subject otherwise becomes known to the investigator or other clinical site staff, the investigator or designee must notify Corbus immediately.

Corbus clinical supply and logistics services personnel will be unblinded to the study drug randomization. They are required not to reveal randomization information to others, unless a formal unblinding of information for a given subject is undertaken for safety reasons.

A limited number of contract laboratory personnel who will perform and interpret assays such as lenabasum concentrations may be unmasked during the study. These results will be provided to the Medical Monitor and other clinical personnel associated with the study using dummy subject identifications until the database is locked. Certain data management, programming, biostatistician, and pharmacokinetics personnel at Corbus may be unmasked. These unmasked Corbus personnel will not be associated with the clinical conduct of the study and will not reveal to any clinical personnel involved in the study the treatment to which a subject is assigned.

8.6.2 Unblinding Procedures

8.6.2.1 Emergency Unblinding Procedures

To maintain the overall quality of data collected during of the study, breaks in blinding during the conduct of the study should occur only in exceptional circumstances when knowledge of the actual treatment is essential for further management of the subject. Unblinding of the study drug for an individual can be done during the study period in the case of:

- A medical emergency or SUSAR where knowledge of the treatment assignment is necessary to treat the subject
- A child accidentally takes the study drug.

Unblinding will occur only in situations that also call for study drug discontinuation in an individual subject.

In the event of a safety concern that requires unblinding of treatment assignment for an individual subject, the investigators will have 24-hour access to an IWRS through which the code can be broken for that subject. Systematic procedures for unblinding through the IWRS will be described in a manual supplied to the site. In all circumstances other than a medical emergency, unblinding will be done only by the Medical Monitor, and only after discussion with the requesting investigator. In an emergency, investigator will be able to unblind the subject, but should discuss with the medical monitor as soon as feasible.

Emergency unblinding must be reported to the Medical Monitor immediately. When it is necessary to break the blind, the investigator must notify the EC. Corbus will be notified through the IWRS regarding the unblinding, and Corbus will notify the other investigators with the reasons for unblinding, if applicable.

The subject will have either a routine scheduled visit if due or an unscheduled visit as soon as possible related to emergency unblinding with appropriate testing and follow-up thereafter to evaluate the safety concern that caused the emergency unblinding. Unless consent is withdrawn, the subject will be asked to return for Visit 5 and Visit 8, as applicable.

After emergency unblinding, the investigator should not disclose the treatment assignment to the subject or other study personnel until after database lock and disclosure of treatment assignment to all patients.

8.6.2.2 Unblinding Procedures at the End of the Study

After study completion when all the data are collected, all queries have been resolved, the DMC has had its final review of the safety data and the database has been locked, then the

lead statistician will generate a request to the IWRS to break the treatment code for all subjects for purposes of data analyses. This will be done to determine the effect of lenabasum when all the data are present.

After the treatment code has been broken for the study, the investigators will be notified by e-mail that they or their designees can obtain the treatment code for individual subjects at their own sites. The investigators will be asked to inform subjects of their blinded treatment allocation, if the subjects choses to know and EC requirements for disclosure, if any, have been met.

8.7 Conditions for Storage and Use

Bottles of study drug are to be stored at the site at room temperature away from temperature and humidity extremes. In the US, storage conditions must be appropriate for small quantities of Controlled Drugs Act Schedule 1 substances. In the US, study drug that is returned by the subjects to the site will be stored under conditions appropriate for small quantities of Controlled Drugs Act Schedule 1, until returned to Corbus for destruction. In other countries, storage conditions must meet country and local requirements.

The site pharmacist, investigator or designee will maintain accurate logs of drug shipments received, returned to Corbus or destroyed to ensure the appropriate amount of study drug is kept on site and that it is used for research purposes only. He/she will perform drug accountability procedures such as checking drug shipments against the shipping contents form, maintaining a log of the amount of study drug provided to individual subjects, and reconciling used and unused drug supply by subjects and the study unit.

If any lenabasum is lost or damaged, its disposition should be documented in the source documents. Lost or damaged lenabasum should be reported to the Drug Enforcement Agency (DEA) in the US and as required by authorities in other countries.

Subjects will be instructed to store study drug at home at room temperature, away from temperature and humidity extremes, in areas that are not accessible to children. All study drug that is not ingested by study subjects will be disposed of according to instructions provided to the sites or returned to Corbus, as requested by Corbus.

Detailed instructions will be in a manual supplied to the site by Corbus.

8.8 Method of Assigning Subjects to Treatment Groups

The IWRS will be used for assignment of a unique Subject Identification number (SID), randomization to a treatment, and assignment of study drug vial numbers to each subject. A subject is considered randomized into the study upon receipt from the IWRS of the SID.

Subjects will be randomized before Visit 1 to one of Cohorts 1 to 3. A central randomization scheme will be used. Randomization does not require the subject's presence at the site. The randomization steps are the following:

- Before accessing the IWRS the investigator or designee should confirm the subject meets all eligibility criteria
- The investigator or designee contacts the IWRS confirms the site and subject ID and that subject meets eligibility criteria.

- The IWRS randomizes the subject to a treatment cohort (cohorts 1, 2 or 3) and generates a shipment request
- The investigator or designee will receive a randomization confirmation notification via fax or email
- Based on the randomization, the appropriate study drug will be sent by the distributor to the site
- At or just before Visit 1 the IWRS will be accessed to assign the appropriate bottles to the subject.

At the time of study start up, a supply of study drug may be shipped to some sites ahead of subject randomization. In that case, the same randomization process will be followed except the investigator or designee will be instructed which bottles of drug to dispense and will not need to wait for drug to be shipped to the site.

8.9 Dispensing, Compliance, and Accountability

8.9.1 Dispensing

The study drug will be dispensed from the site pharmacy or the investigator's storage cabinet in a blinded fashion upon request from the investigator or designee. The study drug dispensed to the subject will be based on treatment assignment for that individual. No more than a 28-day supply of study drug plus packaged overage in the bottle(s) may be provided to the subject at time of dispensing. Detailed instructions will be in a manual provided to the site by Corbus.

8.9.2 Compliance with Treatment

The number of capsules of study drug returned to the site will be counted and recorded as a measure of subject compliance with treatment. For subjects receiving lenabasum, lack of compliance with treatment will be suspected for subjects whose trough plasma concentrations of lenabasum are more than two standard deviations from the mean for other subjects receiving the same dose. This assessment will occur only after the study blind has been broken.

8.9.3 Accountability

A repository of study drug will be held at distribution depots. Study drug will be distributed to the site pharmacy or investigator by express mail with tracking.

Depending upon the arrangements at the individual site, either the investigator or designee or the designated site pharmacist is responsible for maintaining accountability for the receipt, dispensing and return of all study medication. Procedures for tracking shipment, receipt, distribution and collection of unused study drug will be in a manual provided by Corbus to each site.

8.10 Prior and Concomitant Therapy

The intent is that each subject is maintained on all his/her baseline medications for CF from screening through Visit 9, unless the investigator or treating physician judges a change in therapy is needed to provide best medical care for the subject. Information about the

concomitant medications and treatments will be collected at each Visit. All concomitant medications given to the subject during the study will be recorded on the eCRF.

Concomitant therapies taken for the long-term treatment of pre-existing conditions may be continued during the study provided they are in accordance with the exclusion criteria. It is preferred that these medications be stabilized before entry and continued wherever practical without variation of dose or regimen during the study.

During the study, new medications should be administered at the discretion of the investigator to provide the subject with the best medical care. Because of the unavailability of toxicology data and limited clinical experience with lenabasum in combination with other therapeutic agents, it is recommended that changes in ongoing treatments or introduction of new therapies are kept to a minimum. The risk/benefit to the subject should be carefully assessed and consideration given to the timing of any introductions of new medications.

The intent is that all medications used to treat CF are allowed as concomitant medications except corticosteroids in doses > 10 mg/day oral prednisone or equivalent. Among the permitted concomitant medications for CF during the study are the following:

- Mucolytics including dornase alfa
- Hypertonic saline
- Inhaled and oral prophylactic antibiotics
- Bronchodilators
- Anticholinergics
- Membrane stabilizers
- Anti-inflammatory agents such as azithromycin and ibuprofen
- CFTR-targeting drugs
- Corticosteroids ≤ 10 mg QD oral prednisone or equivalent
- Multivitamins
- Nutritional supplements
- Digestive enzymes
- Stool softeners and other medications for constipation
- Proton pump inhibitors and other medications for gastrointestinal reflux
- Antihistamines
- Corticosteroid nasal sprays.

A list of disallowed medications is provided in Table 7.

Table 7 Disallowed Medications

Drug Class	Requirements
Corticosteroids > 10 mg per day oral prednisone or equivalent	Prohibited for **14 days** before Visit 1
Investigational agents	Prohibited for **30 days** or 5 therapeutic half-lives before Visit 1, whichever is longer, and during the study
Any cannabinoid or cannabinoid derivative, including recreational marijuana, medicinal marijuana, or other prescription cannabinoids	Prohibited from screening to the end of the study

Corticosteroids > 10 mg per day oral prednisone or equivalent may be needed to treat PEx in some subjects during the study and are allowed for that purpose. It is anticipated that such use would be temporary and related to a PEx, except in a rare case where higher dose of corticosteroid use is for longer duration (e.g. for allergic bronchopulmonary aspergillosis). In all such cases corticosteroid use, and continued use of investigational drug should be assessed by investigator, and preferably be discussed with medical monitor.

9 EFFICACY, SAFETY, PHARMACOKINETICS ASSESSMENTS

9.1 Efficacy Variables

9.1.1 Primary Efficacy Variable: PEx

The primary efficacy variable will be based on the occurrence of new PEx. The occurrence of a new PEx will be assessed throughout the active dosing and safety follow-up periods.

At screening and again at Visit 1, subjects and/or their legally acceptable representative will be instructed when and how to call the site staff to report new or worsening respiratory or systemic symptoms. Subjects who experience new or worsening respiratory symptoms or have received a prescription for a new antibiotic from a physician other than a study physician will contact the site staff and return for an unscheduled Possible PEx Visit if directed to do so.

At each visit, the investigator will assess the subject for the presence of any new or worsening respiratory symptoms. The physician will assess medical history for changes from last visit, perform physical examination of the lungs and physical examination of other organs as indicated by change in medical history, and complete the antibiotic use for respiratory signs and symptoms questionnaire (AUR-Q; Appendix B). This questionnaire includes Fuchs criteria (Fuchs et al, 1994) and also a list of additional signs and symptoms, that may have led a physician to make a diagnosis of pulmonary exacerbation. The physician does not need to determine if there is a 28-day gap from last use of antibiotics to the new antibiotics for efficacy analysis purposes. The 28-day gap will be determined centrally.

9.1.2 PEx as secondary variable

Time to first new PEx using the primary definition of PEx will be a secondary endpoint. In addition, an alternative definition of PEx as defined in the protocol will be a secondary variable that will be collected.

9.1.3 Cystic Fibrosis Questionnaire – Revised Respiratory Symptom Score

The CFQ-R is a well-established disease-specific health-related quality of life measure for children, adolescents and adults with CF (Quittner et al, 2005, Dill et al, 2013). It is a profile measure of health-related qualify of life which consists of self-reported items and has proven reliability and validity. 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 Adolescent/Adult version of the CFQ-R will be used for subjects ≥ 14 years of age at the time of consent. For subjects ages 12-13 at the time of consent, two versions of the questionnaire will be administered; the Child version for ages 12-13 will be given to the subject, and the Parent/Caregiver version for ages 6-13 will be administered to one of the subject's parents or legal representatives (all efforts should be made to have the same parent fill out this questionnaire at each required study visit, if possible). The subject will be provided the CFQ-R in their native language, if not fluent in English, and will be asked to fill out the questionnaire before other interactions with site staff.

9.1.4 Forced Expiratory Volume in One Second and Forced Vital Capacity

Spirometry including measurements of FEV1 and FVC will be done at screening, at Visits 1-9 and all Possible PEx Visits. FEV1 is the volume of air that can be blown forcibly out of the lungs in 1 second, after full inspiration. FVC is the amount of air which can be forcibly exhaled from the lungs after taking the deepest breath possible. Both FEV1 and FVC results will be calculated as % predicted and mL (absolute).

The same equipment and operator should be used for each measurement, for a given subject.

For a given subject, the investigator must determine at Visit 1 whether measurements at all Visits for that subject will be done without bronchodilator pre-treatment or with bronchodilator pre-treatment. The measurements must be done at all Visits for a given subject using a consistent procedure. It is preferred that measurements be done without pre-bronchodilator treatment. In this case, any treatment with short-acting bronchodilators will be held for four hours before the pre-bronchodilator spirometry, unless medically necessary. Some subjects with low FEV1 measurements may not tolerate spirometry without pre-bronchodilator treatment. For these subjects, it is acceptable to pre-treat with a short-acting bronchodilator 10-20 minutes before spirometry. For these subjects, pre-treatment with bronchodilator should be done before every spirometry procedure.

Ideally, FEV1 values will be measured on 3 spirograms of acceptable quality and reproducibility. The largest FEV1 will be reported. Other spirometry values will be taken from the spirogram with the largest FEV1 (e.g., FEF25-75). The calculation of absolute and percent predicted FEV1 and FVC will be done centrally. It is acknowledged that for subjects with low FEV1 or a PEx it may not be possible to get 3 spirograms of acceptable quality, in which case the largest FEV1 will be reported.

Detailed methods for spirometry will be in a manual provided to each site by Corbus.

9.1.5 Cystic Fibrosis Respiratory Symptom Diary (CFRSD) - Chronic Respiratory Infection Symptom Score (CRISS)

The 16 – item CFRSD questionnaire (Goss et al, 2009) will be completed at screening for training purposes, at Visits 1-9 and all Possible PEx Visits. This is a validated disease-specific tool. The CFRSD-CRISS is a symptom measure that is part of the CFRSD and takes about 5 minutes to complete. The CFRSD-CRISS is referred to as the CRISS throughout this protocol.

9.1.6 Sputum Evaluation

Sputum specimens should be obtained from each subject at Visit 1, Visit 2, Visit 5 and Visit 8 and any Possible PEx Visit. Assessments of sputum include cell counts, soluble biomarkers of inflammation, and quantitative of bacteria. Analyses of cell counts and soluble biomarkers include at least numbers and percentages of total cells, neutrophils, eosinophils, lymphocytes, monocytes/macrophages, basophils, neutrophil elastase, myeloperoxidase, interleukin-8, and immunoglobulin G levels. Other biomarkers of inflammation may be analyzed and reported separately.

To reduce variability in results, it is important that the same method – spontaneous or induced – is used to obtain sputum from a given subject throughout the study.

At screening and Visit 1, subjects will be instructed how to provide a spontaneous sputum sample. If the subject thinks they will not be able to produce a sputum sample spontaneously at each visit when required, the subject will be asked to produce sputum sample via induction instead. Adolescents should try to produce sputum spontaneously and can opt out of sputum induction. The choice of method – spontaneous or induced - will be made at Visit 1 after instructions on how to produce a spontaneous sample and discussion between site staff and the subject and before collection of sputum.

Sputum will be collected in a sterile specimen cup. Spontaneously produced sputum can be collected anytime during the visit. Sputum collection by induction should occur after spirometry. Sputum induction should be performed in accordance with standard operating procedure at the site.

9.1.7 Blood Biomarkers of Inflammation

High sensitivity c-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) measure systemic inflammation and will be assessed at visits specified in the schedule of assessments. Other biomarkers of inflammation may be analyzed and reported separately.

9.1.8 Body Mass Index

Lower BMI is associated with worse pulmonary function in CF. Body mass index will be calculated centrally at each visit for all subjects from weight and height. Weight will be measured with coats, jacket, and footwear removed. Height will be measured with footwear removed. The BMI Z scores also will be calculated centrally for subjects ≤ 20 years of age.

9.2 Safety Variables

9.2.1 Adverse Events

The primary safety outcome of lenabasum is the occurrence of TEAEs. A TEAE is defined as an AE that is not present before the initiation of the treatments or any event already present that worsens in either intensity or frequency following exposure to the treatments.

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Another definition of AE is any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of the study drug, whether or not considered related to the study drug. Intercurrent illnesses or injuries will be regarded as AEs. Any event of abuse, misuse or addiction should be reported as an adverse event. Drug abuse is defined as the intentional, non-therapeutic use of a drug product or substance, even once, to achieve a desired psychological or physiological effect. Drug misuse is defined as the use of a substance for a purpose not consistent with legal or medical guidelines. According to American Psychiatric Association, addiction is a complex condition, a brain disease that is manifested by compulsive substance use despite harmful consequence.

When collecting AEs, record the diagnosis when possible, as opposed to recording a list of signs and symptoms only. If a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

This definition also includes accidental injuries, reasons for any change in medication (drug administration and/or dose) other than planned titration, reasons for admission to a hospital or reasons for surgical procedures (unless for minor elective surgery for a pre-existing condition). It also includes AEs commonly observed and AEs anticipated based on the pharmacological effect of the study medication.

Abnormal results of any laboratory test or diagnostic procedure will be considered AEs if the event has any of the following characteristics:

- Results in study withdrawal.
- Is associated with a SAE.
- Is associated with clinical signs or symptoms.
- Leads to additional treatment or to further diagnostic tests (beyond single repeat).
- Is considered by the investigator to be of clinical significance.

Wherever possible the Investigator should report the clinical, rather than the laboratory term (e.g., anaemia versus low haemoglobin value).

The Investigator will assess all abnormal laboratory results for their clinical significance. If any abnormal laboratory result is considered clinically significant, the investigator must

provide details about the action taken with respect to the study drug and about the subject's outcome.

Adverse events will be captured from the time the subject signs the informed consent to the end of the subject's participation in the study. Adverse events should be recorded as diagnoses, if available. If not, separate sign(s) and symptom(s) are recorded. One diagnosis/symptom should be entered per record.

Death is not considered an AE, but the cause of death is. An exception is the event of sudden death of unknown cause. Similarly, hospitalizations and procedures are not AEs; however, the reasons for hospitalization and procedures are. A report of death or hospitalization without a cause provided will be recorded initially as an SAE until the underlying cause is identified. However, if deemed necessary by the investigator, a procedure can be captured as an AE, along with the reason for conducting the procedure. An overdose or medication error is not an AE unless it is temporally associated with an unfavorable or unintended sign or symptom.

The investigator or designee will report all directly observed AEs and all AEs spontaneously reported by the trial subject using concise medical terminology. In addition, each trial subject will be questioned about AEs.

All adverse clinical experiences, whether observed by the investigator or reported by the subject, must be recorded, with details about the duration and intensity of each episode, the action taken with respect to the study drug, and the subject's outcome.

9.2.2 Serious Adverse Events

Serious adverse events are a subset of AEs. A serious adverse events (SAE) is defined as any adverse event that meets any of the following criteria:

- Results in death.
- Is life-threatening.

The term "life-threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly or birth defect in the offspring of a subject.
- Is an important medical event.

Medical judgment should be exercised in deciding whether expedited reporting is appropriate in situations where none of the outcomes listed above occurred. Important medical events that may not be immediately life-threatening or 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 should also usually be considered serious. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the

development of drug dependency or drug abuse. A new diagnosis of cancer during treatment should be considered as medically important.

An AE caused by an overdose or medication error is considered serious if the event results in one of the outcomes listed above. Serious AEs also include any other event that the investigator or the Medical Monitor judges to be serious or which is defined as serious by regulatory authorities.

9.2.3 Disease worsening

Any medically significant worsening in cystic fibrosis, as judged by the investigator, will be recorded as an AE. Examples of such events include but are not limited to pulmonary exacerbation.

9.2.4 Adverse events of special interest

Adverse events of special interest (AESI) will also be recorded in detail and narratives will be generated for those. Adverse events of special interest are noted in Table 8.

Table 8 Adverse events of special interest and information to be collected

Adverse event of special interest	Additional information to be collected
Dizziness/light-headedness	• If intermittent or a single event, average duration of episode in minutes • Temporal relationship to dose (when was the last dose of study drug prior to start of AE) • Was it associated with vertigo • Was it positional (orthostatic) • Any other associated symptoms (if yes please report them separately in AE)

9.2.5 Procedures for Assessing, Recording, and Reporting Adverse Events and Serious Adverse Events

Throughout the duration of the study, the investigator or designees will closely monitor each subject. All AEs which occur during the study, whether observed by the investigator or by the subject, and whether or not thought to be related to study drug will be recorded. The description of the AEs as recorded on the eCRF will include a description of event, start date, stopping date, intensity, if it was serious, relationship to study drug, what actions were taken with respect to the study drug, if treatment was required and the subject's outcome.

The investigator must evaluate each AE for its relationship to the study drug and for its seriousness. All AEs related to study drug must be followed until resolution or until they become stable.

9.2.5.1 Time and Frequency for Event Assessment and Follow-up

Safety events will be assessed from the time of signing of informed consent through the last visit which can include a withdrawal visit.

At each study visit, the investigator will inquire about the occurrence of AEs since the last visit. Adverse events related to study drug will be followed for outcome information until resolution or stabilization.

Reporting guidelines will be followed.

9.2.5.2 Characteristics of Adverse Events

Criteria for Defining the Severity of an Adverse Event

Severity is used to describe the intensity of a specific AE. The following standard with 3 grades will be used to measure the severity of AEs, including abnormal clinical laboratory values and SAEs:

- Mild: No disruption of normal daily activities
- Moderate: Affect normal daily activities
- Severe: Inability to perform daily activities.

Relationship to Study Intervention

After naming and grading the AE, the investigator must assign an attribution to the AE using the following categories:

Table 9 Adverse Event Causality Grading

Relationship	Attribution	Description
Unrelated to study product	Unrelated	The AE is clearly **not related** to the study product
	Unlikely	The AE is **doubtfully related** to the study product. Disease or other concomitant medications provide more plausible explanations for the AE. Time to drug intake makes a relationship with AE improbable
Related to study product	Possible	The AE **may be related** to the study product. AE could also be explained by disease or other drugs. Reasonable time relationship to drug intake
	Probable	The AE is **likely related** to the study product. AE is unlikely to be attributed to disease or other drugs. AE has a plausible time relationship to drug intake
	Definite	The AE is **clearly related** to the study product. AE cannot be explained by disease or other drugs. AE has a plausible time relationship to drug intake

Adverse events listed as 'possibly, probably, or definitely' related to the study product are considered to have a suspected 'reasonable causal relationship' to the study product.

Suspected adverse reaction means any AE for which there is a reasonable possibility that the study product caused the AE. "Reasonable possibility" means there is evidence to suggest a causal relationship between the study product and the AEs. Suspected adverse reaction implies less certainty about causality than adverse reaction, which means any AE caused by the study product.

9.2.5.3 Reporting Procedures

The reporting of the study will comply with all relevant regulatory authorities and site-specific EC requirements.

Controlled Substance Reporting

As required, the site pharmacist or investigator or designee will complete and keep a copy of controlled substance forms.

Unanticipated Problem Reporting to Institutional Review Board/Independent Ethics Committee

An unanticipated problem is one that is unexpected, related to participation in research and suggests that the research places subjects or others at greater risk of harm. Incidents or events that meet the criteria for unanticipated problems that need to be reported to the EC as per the relevant reviewing regulatory authority require the completion of an unanticipated problem eCRF by the investigator or designee within 24 hours of learning of the event, which

will prompt an immediate notification to the Medical Monitor. Through this mechanism, the Medical Monitor will receive an alert that the report has been or is being filed with the reviewing EC. The investigator will follow his/her reviewing EC procedures when reporting an AE or any other incident, experience, or outcome as an unanticipated problem to the EC.

To satisfy the requirement for prompt reporting, unanticipated problems will be reported using the following timeline or per the reviewing EC requirements, whichever is shorter:

- SAEs will be reported to the EC within 7 days of the investigator becoming aware of the event and to regulatory authorities per their published timeframes.
- Any other unanticipated problem will be reported to the EC within 14 days of the investigator becoming aware of the problem.
- All unanticipated problems should be reported to other appropriate institutional officials as required by that institution's written reporting procedures.

SAE Reporting
All SAEs must be reported immediately to the Sponsor (or their designated representative) no more than 24 hours after becoming aware of the event.

Any AE that meets the specified SAE criteria will be recorded on an SAE CRF, by the investigator or qualified designee. The investigator must complete and save the SAE eCRF immediately, which will prompt an electronic notification to the Sponsor (or their designated representative). Follow-up information on the SAE will be provided in a timely manner to the Medical Monitor and recorded on eCRF form(s).

Reporting of SAEs and AEs to Country Regulatory Agencies

The mandatory reporting of safety events to regulatory authorities will be followed as required by applicable regulatory authority, and as per the applicable reporting timelines.

9.2.6 Other Safety Variables

9.2.6.1 Tolerability

Tolerability is defined as discontinuation of study drug as the result of TEAE(s) that are probably or definitely-related to study drug. Subjects who discontinue study drug due to SAE/AE must be clearly distinguished from subjects who discontinue for other reasons. Investigators will follow subjects who discontinue/withdraw from study as result of SAE/AE until resolution of the event.

9.2.6.2 Medical History and Use of Contraception

Medical history includes subject demographics, documentation of history of CF and current treatment for CF. The medical history will also include concurrent illnesses, other current medications, past relevant medical history, child-bearing potential, last menstrual period (LMP) for women, and review of systems. Date of LMP and method of contraception will be assessed at screening and all visits in women of childbearing potential (WOCBP).

9.2.6.3 Concomitant Medications

A list of current prescription and over-the-counter medications and supplements will be obtained. Concomitant medications will be recorded on the concomitant medication eCRF at

screening and all visits. The medication, dose, frequency, route, start date, stop date and indication will be captured.

9.2.6.4 Physical Examinations

Physical examinations will be performed at screening, Visits 1-9, and Possible PEx Visits by a physician, nurse practitioner, or physician's assistant in accordance with the local law who will determine findings and assess any abnormalities as to clinical significance.

A full physical examination will include the following assessment: alertness and orientation, general appearance, skin, head, eyes, ears, nose, and throat, lungs, heart, abdomen, musculoskeletal examination, and lymph nodes. Breast and genitourinary examinations are not required.

A brief physical examination will include general appearance, lungs, heart, abdomen, and any other organ system as indicated by change in medical history from last visit.

Visit 1 medical examination will be used as baseline. Medically significant changes that reflect worsening from baseline will be considered AEs and recorded as such.

9.2.6.5 Vital Signs

For purposes of this study vital signs include BP, P, R, T, weight, height, and O_2 saturation measurements. Vital signs will be measured at each visit.

Systolic and diastolic BP should be measured with the subject supine for at least 5 minutes and will be recorded twice at least 1 minute apart. The same arm should be used for the measurement throughout the study. The average value of both measurements should be used. O_2 saturation, P and R will also be measured with the subject supine for at least 5 minutes. Body temperature will be measured on the skin or in the mouth. Weight will be measured with coats, jacket, and footwear removed. Standing height will be measured with footwear removed.

9.2.6.6 Laboratory Safety Tests

Blood and urine laboratory safety tests will be performed at each visit. The results of all tests will be reviewed by the investigator or designee, who will make judgments on the medical significance of any new or worsening abnormal value. New medically significant abnormal laboratory results that are related to safety of study drug should be repeated as soon as possible to confirm the abnormality.

The results of clinical laboratory tests at the time of last measurement prior to study drug administration on Visit 1 will provide baseline references against which any fluctuations in these indices can be compared.

All blood laboratory tests will be performed in a licensed, central clinical laboratory, to provide appropriate longitudinal and cross-site comparisons. The following blood tests will be performed by a central laboratory:

- Serum βhCG in women of childbearing potential.
- Follicle stimulating hormone for women > 45 and ≤ 55 years of age with no menses for < 2 years.
- Hepatitis B and C tests.

- Human immunodeficiency virus tests.
- Complete blood count with differential cell count and platelets.
- Metabolic panel comprising glucose, urea nitrogen, creatinine, sodium, potassium, chloride, carbon dioxide, calcium, total protein, albumin, total bilirubin, alkaline phosphatase, aspartate aminotransferase, and alanine aminotransferase.
- High sensitivity CRP, ESR and other inflammatory biomarkers.

Urine laboratory tests will be performed on site:

- Urine pregnancy tests on women of childbearing potential.
- Urine dipstick for blood, albumin/protein, and glucose.

9.2.6.7 Electrocardiograms

A 12-lead ECG will be obtained at Visit 1 before administration of the first dose of study drug, 3.0 ± 0.5 hours after first dose of study drug and at Visit 5 and Visit 8.

Twelve-lead ECGs are to be recorded with the subject in a rested supine for at least 10 minutes before the test, using centrally supplied ECG machines. The ECGs will be read centrally. After central reading, the medical significance of any new ECG abnormality will be assessed by the investigator.

9.2.6.8 Pregnancies

The effect of lenabasum in pregnancy is unknown. Women subjects of childbearing potential will be instructed to inform the investigator if they become pregnant during the study and within 28 days after taking the final dose of study product. If the pregnancy occurs during the treatment period, the investigator should immediately discontinue the study product and instruct the subject to return any unused portion of study product to the study staff. Pregnancies occurring while the subject is on lenabasum or within 28 days after the subject's last dose of lenabasum should be reported by the site to the Sponsor within 24 hours of the site being made aware. The investigator will counsel the subject about the risks of the pregnancy and the possible effects on the fetus.

To report pregnancies in subjects, the investigator must complete a Pregnancy Reporting Form within 24 hours after learning of the pregnancy, which will prompt an electronic notification to the Sponsor (or their designated representative). The pregnancy must be reported to the EC within 24 hours of the investigator's knowledge of the pregnancy. The subject should be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counselling. The investigator or qualified designee will follow the subject until completion of the pregnancy and 30 days after the birth, and report follow-up findings to the EC.

Please note that pregnancy in the female partner of a male study subject is also a reportable event, and the same timelines and reporting procedures should be followed.

If the outcome of the pregnancy meets the criteria for immediate classification as a SAE (i.e., spontaneous abortion [any congenital anomaly detected in an aborted fetus is to be documented], stillbirth, neonatal death, or congenital anomaly), the investigator should

follow the procedures for expedited reporting of SAEs. All neonatal deaths that occur within 30 days of birth should be reported as SAEs without regard to causality.

9.3 Pharmacokinetic Variables

Plasma samples will be collected on Visit 1 before and at 3 ± 0.5 hours after administration of the first dose of study drug and at Visit 2, Visit 5 and Visit 8 pre-dose to assess trough concentration levels. Lenabasum plasma concentrations will be measured using a quantitative LC-MS/MS method and lenabasum metabolites will be detected using a qualitative LC-MS/MS method.

To obtain trough concentrations of lenabasum on Visit 2, Visit 5 and Visit 8, the blood sample for lenabasum plasma concentration should be obtained between 8 and 16 hours after the last dose of study drug. The site staff should instruct the subject to hold the dose of study drug on the morning of those visits or take the dose earlier on that morning if necessary to ensure that the blood sample will be drawn within this 8- to 16-hour window. For example, if the subject takes the evening dose of study drug at 10 PM and blood will be drawn between 6 AM and 2 PM or 8-16 hours later, then the subject would be instructed to hold the morning dose until the blood sample is obtained. If that same subject will have blood drawn after 2 PM, then that subject should be instructed to take the morning dose at least 8 hours prior to the anticipated time of blood drawing, for example 8 AM for blood to be drawn at 4 PM for an 8-hour interval. This instruction whether to take or hold the dose on the morning of Visit 2, Visit 5 and Visit 8 requires that the site staff knows when the subject takes their study drug and the likely time of blood drawing at the visit.

The time of last dose of study drug will be recorded. If the subject held the morning dose of study drug, the subject may take that dose of study drug as convenient after blood for plasma concentration and metabolites of lenabasum is drawn.

10 STUDY PROCEDURES AND FLOW CHART

10.1 Schedule of Assessments

STUDY ACTIVITY	Screening Day -28 to 1	Visit 1[1] Day 1 --	Visit 2[1] Day 29 Week 4	Visit 3[1] Day 57 Week 8	Visit 4[1] Day 85 Week 12	Visit 5[1] Day 113 Week 16	Visit 6[1] Day 141 Week 20	Visit 7[1] Day 169 Week 24	Visit 8[1] Day 197 Week 28	Visit 9[1] 28 (± 7) days from Visit 8 Week 32	Possible PEx Visit[16]
ELIGIBILITY AND DISEASE CHARACTERIZATION											
Informed Consent/Assent[2]	X										
Verify eligibility criteria	X	X									
Medical history and confirmation of CF diagnosis[3]	X[3]										
Record concomitant medications	X	X	X	X	X	X	X	X	X	X	X
Contraceptive assessment for WOCBP[4]	X	X	X	X	X	X	X	X	X	X	
Record date of LMP for WOCBP	X	X	X	X	X	X	X	X	X	X	
Serum beta human chorionic gonadotropin, WOCBP	X										
Follicle stimulating hormone[5]	X										
Urine beta human chorionic gonadotropin, WOCBP		X	X	X	X	X	X	X	X	X	
RANDOMIZATION											
Randomize before Visit 1		X									
STUDY PRODUCT ADMINISTRATION											
Administer first dose of study drug at the site		X									
Dispense study drug for home administration		X	X	X	X	X	X	X			
Count capsules of any returned study drug			X	X	X	X	X	X	X	X	
EFFICACY ASSESSMENTS											
Training of subjects[6]	X	X									
CRISS questionnaire	X	X	X	X	X	X	X	X	X	X	X
CFQ-R questionnaire[7]	X	X				X			X		X
Spirometry	X	X	X	X	X	X	X	X	X	X	X
Antibiotic use for respiratory signs and symptoms questionnaire(AUR-Q)[8]	X	X	X	X	X	X	X	X	X	X	X
Blood for high sensitivity CRP, ESR and other inflammatory biomarkers		X	X			X			X		X
Sputum specimen for culture, cells and biomarkers[9]		X	X			X			X		X
SAFETY ASSESSMENTS											
Adverse event monitoring (to begin at signing of informed consent)	X	X	X	X	X	X	X	X	X	X	X
Vital signs, weight, height[10]	X	X	X	X	X	X	X	X	X	X	X
Full physical examination[11]		X								X	
Brief physical examination[12]	X		X	X	X	X	X	X	X		X
Blood and urine for safety testing[13]	X	X	X	X	X	X	X	X	X	X	X

12-lead ECG[1]		X				X			X		
PHARMACOKINETIC ASSESSMENTS											
Lenabasum and metabolites plasma concentration[15]		X	X			X			X		

CF = cystic fibrosis; ECG= electrocardiogram; LMP = last menstrual period; PEx = pulmonary exacerbation; WOCBP = women of childbearing potential.

1 For Visits 1-9, the window for each visit is ± 7 days or 1 week. Week listed is at the completion of that week. If a patient is hospitalized and unable to adhere to the visit time window, the visit should be scheduled as soon as feasible, thereafter, the original visit schedule should be followed.

2 Informed consent/assent must be signed before the performance of any study procedure. An informed assent must be signed by each minor subject (in addition to the informed consent that is to be signed by his/her legal representative), if allowed by their country/local regulations and requirements.

3 Medical history at screening includes subject demographics, documentation of history of CF and current treatment for CF. The medical history will also include concurrent illnesses, other current medications, past relevant medical history, child-bearing potential, last menstrual period (LMP) for women and review of systems. Date of LMP and method of contraception will be assessed in women of childbearing potential (WOCBP) at screening, Visits 1-9, and Safety Follow-Up Visit for subjects who withdraw early from the study. Diagnosis criteria are one or more clinical features consistent with the CF phenotype and one or more of the following according to medical history: (1) Sweat chloride > 60 mEq/L by quantitative pilocarpine iontophoresis test; (2) Two disease-causing mutations in the cystic fibrosis transmembrane conductance regulator gene.

4 Refer to Appendix A for the criteria for determining reproductive potential and highly effective methods of contraception.

5 For women > 45 and ≤ 55 years of age with no menses for < 2 years to determine childbearing potential.

6 At screening, subjects will be instructed: 1) how to complete CRISS and CFQ-R questionnaires; 2) how to perform spirometry; and 3) how to provide a spontaneous or if necessary an induced sputum sample.

At Visit 1, subjects will be instructed 1) how to contact site staff; 2) to contact site staff as soon as possible for new or worsening respiratory or systemic symptoms; 3) to contact site staff as soon as possible if another physician prescribes new antibiotics for respiratory or systemic symptoms. Subjects will have repeat training: 1) how to perform spirometry; and 2) how to provide a spontaneous or, if necessary for that subject, an induced sputum sample.

7 The Adolescent/Adult version of the CFQ-R will be used for subjects ≥ 14 years of age at the time of consent. For subjects ages 12-13 at the time of consent, two versions of the questionnaire will be administered. The Child version for ages 12-13 will be given to the subject, and the Parent/Caregiver version for ages 6-13 will be administered to one of the subject's parents or legal representatives.

8 Physician to complete - AUR-Q (Appendix B).

9 The specimen will be collected in a sterile specimen cup.

10 Vital signs, weight and height measurements will be performed at each visit. Systolic and diastolic BP should be measured with the subject supine for at least 5 minutes and should be recorded twice at least 1 minute apart. The same arm should be used for the measurement throughout the study. The average value of both measurements will be used. Oxygen saturation, P and R will also be measured with the subject supine for at least 5 minutes. Body temperature will be measured on the skin or in the mouth. Weight will be measured with coats, jacket, and footwear removed. Standing height will be measured with footwear removed. BMI will be calculated from height and weight measurements and will be reported as an efficacy outcome.

11 A full physical examination will include the following assessments: alertness and orientation, general appearance, skin, head, eyes, ears, nose, and throat, lungs, heart, abdomen, musculoskeletal examination, and lymph nodes. Breast and genitourinary examinations are not required.

12 A brief physical examination will include general appearance, lungs, heart, abdomen, and any other organ system as indicated by change in medical history from last visit.

13 The following tests will be done at all visits: blood for complete blood count with cell differential and platelets and metabolic panel; urine dipstick for blood, albumin/protein, and glucose. Metabolic panel is glucose, urea nitrogen, creatinine, sodium, potassium, chloride, carbon dioxide, calcium, total

protein, albumin, total bilirubin, alkaline phosphatase, aspartate aminotransferase, and alanine aminotransferase. At screening, hepatitis B, hepatitis C and human immunodeficiency virus testing will be done.

14 ECGs are to be recorded with the subject in a rested supine for at least 10 minutes before the test, using centrally supplied ECG machines. ECG's will be recorded pre-dose and again 3.0 ± 0.5 hours post-dose. The ECGs will be read centrally. The medical significance of any ECG abnormality will be assessed by the investigator.

15 Lenabasum and metabolites plasma concentrations will be measured on Visit 1 before and 3 ± 0.5 hours after administration of the first dose of study drug and on Visit 2, Visit 5 and Visit 8, 8-16 hours after administration of study drug (study drug should be taken the night before and held the day of the visit until after lab assessment). On Visit 1, the time of the first dose of study drug and blood collection will be recorded. On Visit 2, Visit 5 and 8, the time of last dose of study drug before blood sample collection and time of blood collection will be recorded.

16 Please refer to Section 10.2.6 for the possible PEx assessments to be conducted for visits occurring at the clinic or over the phone.

10.2 Visits

10.2.1 Screening (Day -28 to Day 1)

The following will be assessed at screening:

- Informed consent/assent.
  - Adverse event monitoring to begin at signing of informed consent.
- Verify eligibility criteria.
- Concomitant medications and over-the-counter treatments from 28 days before screening.
- Contraceptive assessment for WOCBP.
- Vital signs: systolic and diastolic BP will be measured with the subject supine for a minimum of 5 minutes and will be recorded twice with at least 1 minute between measurements. Pulse, respiration, and O_2 saturation will also be measured with the subject supine for at least 5 minutes. Temperature will be measured on the skin or in the mouth, weight will be measured with coats, jackets, and footwear removed, and height will be measured with footwear removed. Hereafter, this set of assessments is simply called "vital signs". Body mass index will be calculated centrally. The BMI Z scores will be calculated centrally for subjects ≤ 20 years of age
- Physician assessment of:
  - Medical history including:
    - History of CF, including disease-causing mutations, clinical manifestations, concomitant medications for CF and maximum FEV1 % predicted and mL in the last 12 months.
    - Number of new PEx in the last 12 months treated with IV antibiotics, number of new PEx in the last 12 months treated with oral antibiotics, and date of completion of last antibiotic treatment for a PEx. Any PEx treated with both oral and IV antibiotics will be counted only once as a PEx treated with IV antibiotics.
    - History of other medical problems and concomitant medications, demographics, child-bearing potential, and last menstrual period (LMP) and review of systems (record date of LMP for WOCBP).
  - Brief physical examination (including general appearance, lungs, heart, abdomen).
  - AUR-Q.
  - Laboratory safety tests, which include the following set of assessments:
    - Complete blood count with cell differential and platelet count.
    - Metabolic panel that includes aspartate aminotransferase, alanine aminotransferase, albumin, alkaline phosphatase, carbon dioxide, total bilirubin, blood urea nitrogen, calcium, chloride, creatinine, gamma glutamyl transferase, glucose, potassium, sodium, total protein, and creatinine clearance calculated by modified Cockcroft-Gault equation.

- Urine dipstick for blood, albumin/protein, and glucose.
- Serology for hepatitis B, hepatitis C, and human immunodeficiency virus.
- Serum β human chorionic gonadotropin hormone for women of childbearing potential.
- Follicle stimulating hormone for women > 45 and ≤ 55 years of age with no menses for < 2 years to determine childbearing potential.

- Instructions by site staff to subjects:
  - How to complete CRISS and CFQ-R questionnaires.
  - How to perform spirometry.
  - How to provide a spontaneous or if necessary an induced sputum sample.
- Following instruction by site staff and to familiarize the subject with the assessments or procedures prior to collection of baseline data at Visit 1, complete CRISS and CFQ-R questionnaires and spirometry.

10.2.2 Visit 1 (Day 1)

The following will be assessed at Visit 1 before the subject receives the first dose of study drug:

- Verify eligibility criteria including verification that the subject is not having a new PEx at Visit 1.Subject-reported outcomes preferably obtained from the subject before other visit assessments:
  - CRISS questionnaire.
  - CFQ-R questionnaire.
- AE monitoring.
- Record concomitant medications.
- For WOCBP assess contraceptive status and record date of LMP.
- Vital signs and central BMI calculations
- Twelve-lead ECG with QT/QTc intervals recorded pre-dose (ECGs are to be performed with the subject rested in a supine position for at least 10 minutes).
- Blood and urine tests
  - CBC with differential cell count and platelets
  - Metabolic panel
  - Lenabasum metabolites and plasma concentration
  - High sensitivity CRP, ESR and other inflammatory biomarkers
  - Urine dipstick
  - Urine βHCG for WOCBP

- Repeat instruction to subjects on how to perform spirometry and obtain spirometry at Visit 1. It is preferred that spirometry is done without short-acting bronchodilators at all visits; however, if the subject needs a short-acting bronchodilator 10-20 minutes prior to performing spirometry to obtain readings that meet quality standards, then obtain spirometry at Visit 1 and all subsequent visits after short-acting bronchodilator.
- Instruct subject how to collect expectorated or if necessary induced sputum and collect sputum. Decide how all sputum samples will be collected (expectorated or induced) for that subject at Visit 1 and all subsequent visits.
  - Collect sputum sample in sterile specimen cup.
- Instruct subjects on the following:
  - How to contact site staff.
  - To contact site staff for new or worsening respiratory or systemic symptoms.
  - Not to start new antibiotic treatment or alter the timing of any prophylactic antibiotic treatment without notifying the study staff, if possible.
  - To contact site staff if another physician prescribes new antibiotics for respiratory or systemic symptoms.
  - Subjects will have repeat instruction for:
    - How to complete CRISS and CFQ-R questionnaires.
    - How to perform spirometry.
    - How to provide a spontaneous or if necessary an induced sputum sample.
- Physician assessment of:
  - Full physical examination (including alertness and orientation, general appearance, skin, head, eyes, ears, nose, and throat, lungs, heart, abdomen, musculoskeletal examination, and lymph nodes - breast and genitourinary examinations are not required).
  - Need for new antibiotic therapy for a new PEx. If yes, the subject is not eligible.
  - Completion of AUR-Q.

Following the procedures above, subject will receive first dose of study drug:

- Dispense study drug according to randomization schedule for home administration.
- Administer first dose of study drug and record time of dose.
- Observe subject at the site for at least 30 minutes until stable. Repeat systolic and diastolic BP, P, R at 30 minutes.
- Twelve-lead ECG with QT/QTc intervals recorded 3.0 ± 0.5 hours post-dose (ECGs are to be performed with the subject rested in a supine position for at least 10 minutes).
- Obtain blood sample for lenabasum plasma concentration pre-dose and 3 $\pm$ 0.5 hours post-dose.

- Instruct subjects to hold their morning dose of study drug on the day of Visit 2 if blood drawing will occur < 8 hours after their last dose of study drug.
- Blood and urine samples obtained for safety testing.

For subjects who have their screening CBC with differential cell count and platelets and metabolic panel tested within 7 days of Visit 1, these blood tests do not need to be repeated on Visit 1. The values at screening will serve as baseline in these instances.

10.2.3 Visit 2 (Day 29 ± 7)

Before visit: If the study visit is to occur less than 8 hours after the subject's last dose of study drug, subject should be instructed to hold the morning dose on the day of the visit.

The following assessments will be completed:

- Subject-reported outcome, preferably obtained from the subject before other visit assessments.
  - CRISS questionnaire.
- AE monitoring.
- Record concomitant medications.
- For WOCBP assess contraceptive status and record date of LMP.
- Vital signs and central BMI calculations.
- Blood and urine tests.
  - CBC with differential cell count and platelets.
  - Metabolic panel.
  - Plasma concentrations of lenabasum and metabolites. Record time of last dose of study drug.
  - Urine dipstick.
  - Urine βHCG for WOCBP.
  - High sensitivity CRP, ESR and other inflammatory biomarkers.
- Spirometry.
- Sputum collection.
- Physician assessment of:
  - Brief physical examination
  - AUR-Q
- Collect study drug from previous visit and count capsules - dispense new study drug for home administration.

10.2.4 Visit 3 (Day 57 ± 7), Visit 4 (Day 85 ± 7), Visit 6 (Day 141 ± 7) and Visit 7 (Day 169 ± 7)

The following procedures will be completed at Visits 3, 4, 6, and 7:

- Subject-reported outcome preferably obtained from the subject before other visit assessments.
  - CRISS questionnaire.
- AE monitoring.
- Vital signs and central BMI calculations.
- Record concomitant medications.
- For WOCBP assess contraceptive status and record date of LMP.
- Blood and urine tests:
  - CBC with differential cell count and platelets.
  - Metabolic panel.
  - Urine dipstick.
  - Urine βHCG for WOCBP.
- Spirometry.
- Physician assessment of:
  - Brief physical examination.
  - AUR-Q.
- Collect study drug from previous visit and count capsules - dispense new study drug for home administration.
- During Visits 4 and 7, instruct subjects to hold their morning dose of study drug on the day of Visit 5 and Visit 8, respectively, if blood drawing will occur < 8 hours after their last dose of study drug.

10.2.5 Visit 5 (Day 113 ± 7) and Visit 8 (Day 197 ± 7)

Before visit: If blood drawing is to occur less than 8 hours after the subject's last dose of study drug, subject should be instructed to hold the morning dose on the day of the visit.

The following assessments will be completed at Visit 5 and 8:

- Subject-reported outcome preferably obtained from the subject before other visit assessments:
  - CRISS questionnaire.
  - CFQ-R questionnaire.
- AE monitoring.
- Record concomitant medications.
- For WOCBP, assess contraceptive status and record date of LMP.
- Vital signs and central BMI calculation.
- Twelve-lead ECG with QT/QTc intervals.

- Subjects should be rested in a supine position for at least 10 minutes prior to ECG assessments.

- Blood and urine tests:
  - CBC with differential cell count and platelets.
  - Metabolic panel.
  - Plasma concentration of lenabasum and metabolites. Record time of last dose of study drug
  - Urine dipstick.
  - Urine βHCG for WOCBP.
  - High sensitivity CRP, ESR and other inflammatory biomarkers.
- Spirometry.
- Sputum collection.
- Physician assessment of:
  - Brief physical examination.
  - AUR-Q.
- Collect study drug from previous visit and count capsules - dispense new study drug for home administration.

Note: New study drug will not be dispensed at Visit 8. Subjects may be asked to participate in a separate two-year observational follow-up study during Visit 8.

10.2.6 Possible Pulmonary Exacerbation Visit

Subjects who experience new or worsening respiratory symptoms or have received a prescription for a new antibiotic from a physician other than a study physician should contact the site staff and return for a Possible PEx Visit if instructed to do so. If determined that a visit is needed a Possible PEx Visit should be scheduled as soon as possible. Though it is expected that this visit will be in person at the study sites, there may be occasions that this visit is completed over the telephone by the investigator.

If the visit is completed in person (preferred), the following assessments will be done:

- Subject-reported outcomes, preferably obtained from the subject before other visit assessments.
  - CRISS questionnaire.
  - CFQ-R questionnaire.
- AE monitoring.
- Record concomitant medications.
- Vital signs and central BMI calculations.
- Blood and urine tests.
  - CBC with differential cell count and platelets.

- Metabolic panel.
- Urine dipstick.
- High sensitivity CRP, ESR and other inflammatory biomarkers.

- Spirometry.
- Attempt sputum collection.
- Physician assessment of:
  - Brief physical examination.
  - AUR-Q.

If the visit is completed over the telephone, the following assessments will be done:

- AE monitoring.
- Record concomitant medications.
- Physician assessment of:
  - Antibiotic use for respiratory signs and symptoms questionnaire (AUR-Q)

10.2.7 Visits to Other Physicians for PEx

Some subjects may receive antibiotic therapy for new or worsening pulmonary symptoms or systemic symptoms from a physician other than the study investigator. In this case, site staff will ask the subject to return for a Possible PEx Visit as soon as feasible. Though it is expected that this visit will be in person at the study sites, there may be occasions that this visit is completed over the telephone by the investigator. The investigator will assess the subject and complete the AUR-Q.

10.2.8 Follow-up Visits for Subjects Who Prematurely Discontinue Study Drug

Subjects who discontinue the study drug and do not withdraw consent will be asked to return for Visit 5 and Visit 8, as applicable, for safety follow-up so clinical data can be obtained on these subjects at these scheduled times. Subjects also may be asked to participate in a separate observational two-year safety follow-up study. No new study drug will be dispensed at these visits.

10.2.9 Visit 9 or Safety Follow-Up Visit for Subjects Who Prematurely Discontinue Study Drug

Visit 9 is a safety visit held 28 ± 7 days after discontinuation of study drug for subjects who complete Visit 8 in the study. Subjects who prematurely discontinue study drug, do not withdraw consent, and do not agree to return for Visit 5 or Visit 8, as applicable, will have a Safety Follow-up Visit 28 ± 7 days after the last dose of study drug that includes the same assessments performed at Visit 9.

The following will be assessed at the Visit 9 and any Safety Follow-up Visit:

- Subject-reported outcome, preferably obtained from the subject before other visit assessments:
  - CRISS questionnaire.

- AE monitoring.
- Record concomitant medications.
- For WOCBP, assess contraceptive status and record date of LMP.
- Vital signs and central BMI calculations.
- Blood and urine tests:
  - CBC with differential cell count and platelets.
  - Metabolic panel.
  - Urine dipstick.
  - Urine βHCG for WOCBP.
- Spirometry.
- Physician assessment of:
  - Full physical examination.
  - AUR-Q.
- Collect study drug from previous visit, if any.

10.2.10 Other Unscheduled Visits

Unscheduled visits may be necessary to assess the subject for safety purposes unrelated to new respiratory symptoms or a PEx. In this case, the following evaluations should be obtained, at a minimum:

- AE monitoring.
- Record concomitant medications.
- Vital signs and central BMI calculations.
- Medical history as relevant to the reason for the unscheduled visit.
- Physical examination as relevant to the reason for the unscheduled visit.
- Laboratory tests as relevant to the reason for the unscheduled visit.
- Antibiotic use for respiratory signs and symptoms questionnaire.

11 STATISTICAL METHODS PLANNED AND SAMPLE SIZE

11.1 Sample Size

The study is expected to enroll approximately 415 subjects, with ~166 subjects each in the lenabasum 20 mg BID and placebo BID cohorts and ~83 subjects in the lenabasum 5 mg BID cohort (accounting for an approximate 15% dropout rate). The study provides 80% power to detect a significant difference between the lenabasum 20 mg BID dose and placebo in the primary endpoint (PEx event rate) at a two-sided alpha of 0.05. This is based on an event rate ratio of 0.65 (a 35% event rate reduction in the lenabasum group), when the the event rate in the control group is 0.80 (modified assumptions from Sponsor briefing document for Orkambi, 2015).

This also provides 90% power to detect a significant difference between lenabasum 20 mg BID and placebo BID in the secondary endpoint, time to first PEx. This is based on an estimate of the probability of an event (PEx) in the placebo group of 0.60, an estimated hazard ratio of 0.60 (risk reduction 0.40), and the probability of an event in the lenabasum group of 0.36

11.2 Analysis Populations

There will be four analysis populations. The modified intent to treat (mITT) population will consist of all randomized subjects who received study drug. These will be categorized by planned treatment. This population will be used for the primary analysis. The safety set (SS) will consist of all subjects who received study drug. This population will be categorized by actual treatment.

The per protocol set (PPS) will consist of the mITT population minus subjects with major protocol deviations. Major protocol violations are defined as those that may have a substantial effect on the efficacy assessment and will be determined before database lock. The PPS will be used in sensitivity analyses.

The pharmacokinetic analysis set (PKAS) will consist of all subjects from the SS whose pharmacokinetic data are adequate for the calculation of primary PK parameters. Inclusion in the PKAS of subjects with missing data or protocol violations or inadequate dosing will be considered on a case-by-case basis. The PKAS will be the analysis set used for all pharmacokinetic analyses.

11.3 Data Presentation

All data will be provided in data listings sorted by treatment groups, subject number and visit. Summary data will be presented in tabular format by treatment group. Categorical data will be summarized by the number and percentage of subjects in each category. Continuous data will be summarized by descriptive statistics including n, mean, standard deviation, median, and range. All percentages will be rounded to 1 decimal place. Differences between treatment groups will be calculated as active – placebo. The baseline measure will be defined as the last non-missing measure before initiation of study drug at Visit 1.

11.4 Efficacy Analyses

The overall type I error rate will be controlled for primary and secondary efficacy outcomes with a fixed sequence independent hierarchical assessment of efficacy. The order of the secondary endpoint tests for treatment effect will be pre-specified in the statistical analysis plan. Statistical significance within an endpoint (including the primary endpoint) must be achieved to continue in the assessment of the next endpoint.

Efficacy comparisons will be made between each dose of lenabasum and placebo. The event rate of new PEx will be compared between the lenabasum and placebo groups using a Poisson regression model. A sensitivity analysis will be performed using a negative binomial regression model.

For time to first PEx, a Cox-proportional hazards (regression) model will be used for comparing the covariate-adjusted difference in event time distributions between the active and placebo groups. Covariates in the model will include all stratification variables. A log rank test will also be performed as a sensitivity analysis.

Continuous variable endpoints such as change in CRISS, change in CFQ-R domain scores, change in FEV1 % predicted, change in FEV1 ml, change in FVC % predicted, change in FVC ml and change in BMI will be analyzed using an MMRM (mixed model repeated measures). The MMRM model will include stratification factors, visit, treatment, and treatment-by-visit interaction as fixed effects and baseline as a covariate.

The treatment comparisons for the proportion of subjects who improve by predefined criteria (for CRISS, CFQ-R, and FEV1 % predicted) will be performed using a Cochran-Mantel-Haenszel test.

Assessment of recovery from PEx will be analyzed for the proportion of subjects who are rapid responders and the proportion of subjects with FEV1 improvement using Fisher's exact tests.

Data from subjects who discontinue study drug but do not discontinue the study and return for off-treatment Visit 5 and Visit 8, as applicable, will be included as data for that cohort. Thus, both on-treatment assessment of PEx and assessments of PEx after treatment discontinuation (for subjects who discontinued dosing early) will be included in primary analyses.

11.5 Safety Analyses

No formal statistical testing will be performed to compare the safety in different cohorts.

The number and percentage of subjects with AEs will be summarized for each treatment by system organ class and preferred term. Similar summaries will be presented for AEs related to study drug, AEs leading to permanent discontinuation of study drug, SAEs, and AEs resulting in death. Any AE with a relationship category of possible or probable is considered related to study drug. The AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). All reported AEs will be provided in separate data listings.

Descriptive statistics will be used to summarize clinical laboratory parameters, vital signs and their corresponding change from baseline for each treatment by scheduled timepoint.

The number and percentages of subjects with normal, abnormal and clinically significant), and abnormal and not clinically significant ECG findings during treatment will be summarized for each treatment by scheduled timepoint.

[redacted]

12 STUDY OVERSIGHT

12.1 Data Monitoring Committee

Oversight of subject safety in this trial will be provided by a DMC subcommittee of the Cystic Fibrosis Foundation Therapeutics Data Safety Monitoring Board and will be an independent group of CF experts that will advise Corbus. The members of the DMC will serve in an individual capacity and provide their expertise and recommendations. The members of the DMC will be recommended to Corbus by the Cystic Fibrosis Foundation Therapeutics Data Safety Monitoring Board Operations Center at the University of Arizona and the European Cystic Fibrosis Society Clinical Trials Network and will include members from both the United States and Europe. Besides CF experts, a member who is experienced in the monitoring of central nervous system AEs will be included in the DMC.

The primary responsibilities of the DMC will be to: 1) periodically review and evaluate the accumulated study data for participant safety, study conduct and progress, and, when appropriate, efficacy; and 2) make recommendations to Corbus concerning the continuation, modification, or termination of the trial.

The DMC will be responsible for defining its deliberative processes, including event triggers that would call for an unscheduled review, stopping guidelines, unblinding and voting procedures before initiating any data review. The DMC is responsible for maintaining the confidentiality of its internal discussions and activities as well as the contents of reports provided to it.

During the trial, the DMC will review cumulative study data to evaluate safety, study conduct, and scientific validity and integrity of the trial and will review efficacy data for a futility analysis. The DMC is expected to review all reported AEs in an unblinded manner. The DMC is also expected to review confirmatory pharmacokinetic (PK) data from a subset of approximately 20 adolescents to estimate the exposure in comparison to about 20 adults. This should yield approximately 8 adolescents receiving lenabasum 20 mg BID and 4 adolescents receiving lenabasum 5 mg BID (8 adolescents receiving placebo). The DMC will have unblinded access to the available PK data and all safety data during this review which will include, at the minimum, Visit 1 post-dose PK data from the subjects under review. The Sponsor, investigative sites and regulatory agencies will remain blinded to the treatment assignments for these DMC reviews and analyses. If indicated by the data, the DMC may recommend changes to dosing in adolescents.

The individual DMC members must be satisfied that the timeliness, completeness, and accuracy of the data submitted to them for review are sufficient for evaluation of the safety and welfare of study participants and futility analysis. Items reviewed by the DMC will be outlined in the DMC Charter and may include:

- Interim/cumulative data for evidence of study-related AEs
- An interim unblinded review of PK data for the first 20 adult and 20 adolescent subjects including available safety data
- Data quality, completeness, and timeliness
- Performance of individual sites
- Adequacy of compliance with goals for recruitment and retention, including those related to the participation of women and minorities
- Adherence to the protocol
- Factors that might affect the study outcome or compromise the confidentiality of the trial data
- Factors external to the study such as scientific or therapeutic developments that may affect participant safety or the ethics of the study
- Interim data for futility analyses.

If there are any unanticipated safety problems during the course of the study, the sponsor's designee will submit available information related to the unanticipated problem to the DMC chair for review. The DMC chair will determine if the unanticipated problem warrants calling an unscheduled full DMC meeting or not. In the case that an unanticipated problem requires a full DMC meeting, the DMC will make a recommendation to the Sponsor regarding suggested corrective actions.

The DMC should conclude each review with their recommendations to Corbus as to whether the study should continue without change, be modified, or terminated.

12.2 Medical Monitoring

Medical Monitors have the responsibility to review and evaluate information relevant to the product safety throughout the development and implementation of the protocol. This data and safety review facilitates early detection of safety signals and maximizes the chances for continued appropriateness of the research and protection of human subjects. This oversight includes providing applicable recommendations about subject safety. The Medical Monitors will provide recommendations about subject safety to the Chief Medical Officer of Corbus, who, as appropriate, will report concerns about subject safety to Corbus management.

12.3 Medical Care and Day-to-Day Safety of Subjects at the Site

The investigator is responsible for all clinical trial-related medical decisions at his/her site and will oversee the day-to-day safety of subjects at his/her site. In conjunction with site staff, the investigator will review all AEs, laboratory results, safety data regarding the subjects' clinical course and side effect profiles for subjects at that site. The investigator will regularly assess the number and type of AEs at that site.

Any qualified healthcare provider may provide medical care when necessary. The investigator will advise subjects if medical care beyond the scope of the study is needed. Additionally, it is recommended that a subject's primary care physician be notified of a subject's participation in this research study.

13 DATA QUALITY

13.1 Source Data and Record Keeping

All investigators will keep accurate and well-organized records to ensure that the conduct of the study is fully documented. The investigators or their designee will ensure that the source documents and participant study files are legible and complete for each participant. The investigators will be responsible for the regular review of the conduct of the study, for verifying adherence to the protocol and for confirming completeness, consistency and accuracy of all documented data and accuracy of source documentation verification at his/her site.

13.1.1 Data Handling, De-identification and Source Records

The investigators and designees will maintain appropriate records for this study, in compliance with ICH E6, Section 4.9 and regulatory and institutional requirements for the protection of confidentiality of subjects. All study records will be maintained in accordance with Corbus' policies and applicable regulatory requirements. There may be circumstances for which Corbus is required to maintain study records and, therefore, Corbus should be contacted before removing study records for any reason.

Source data/records contain all the information, which is necessary for the reconstruction and evaluation of the study. The primary source document for this study will be the subject's medical record on site stored in paper form or in an electronic medical record. If separate research records are maintained by the investigator, both the medical records and the research records will be considered the source documents for the purposes of auditing the study. Data recorded on source documents will be transcribed by site staff onto eCRFs provided by Corbus or its designee.

In addition, in this study at the time of the office visit, study-specific original data elements such as responses to questionnaires will be entered directly into a web-based system without first being transcribed on other media such as paper. There will be no separate source document for data entered directly into the web-based system.

Source data/records are: 1) original records; 2) certified copies of original records; 3) observations; 4) laboratory reports; and 5) eCRFs and/or data sheets. Source data/records are to be kept by investigator until the end of the regulatory retention period. All clinical findings, observations, laboratory results, subject correspondence, SAE reports, and other information related to subject participation in the study must be maintained in subject binders that contain source documents and other data collection instruments designed specifically for this investigation. Completed eCRF pages will be reviewed by Corbus or Corbus authorized personnel.

The investigator will permit study-related monitoring, audit(s), EC review(s) and regulatory inspection(s), with direct access to all the required source documents. Site staff will permit authorized representatives of Corbus, EC and government regulatory agencies to examine (and when required by applicable law, to copy) study records for the purposes of quality assurance reviews, audits, and evaluation of the study safety, progress and data validity.

13.1.2 Privacy and Confidentiality of Subject Information

Privacy and confidentiality of a subject will be respected throughout the study. Consented subjects who meet eligibility for the study will receive a unique SID. These SIDs rather than names will be used during collection, storage and reporting of subject information. This number will be linked only through a secure SID log that connects each subject to his/her data.

Information about subjects will be kept confidential and managed per the requirements of the relevant regulatory authority. These regulations require a signed subject authorization informing the subject of the all the following:

- What protected health information will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their protected health information.

If a subject revokes authorization to collect or use protected health information, Corbus by regulation will retain the ability to use all information collected before the revocation of subject authorization. For subjects that have revoked authorization to collect or use protected health information, attempts will be made to obtain permission to collect at least vital status that the subject is alive at the end of their scheduled study period.

Should direct access to medical records require a waiver or authorization separate from the subject's statement of informed consent, the investigator is obligated to obtain such permission in writing from the appropriate individuals.

13.1.3 Data Management Responsibilities at the Study Site

Data collection and accurate documentation are the responsibility of the investigator and site staff under the supervision of the investigator. All source documents and laboratory reports must be reviewed by the study team and data entry staff, who will ensure that they are accurate and complete. A Clinical Research Associate for Corbus will ensure the data are collected and maintained correctly and in compliance with GCP.

13.1.4 Data Capture Method

Electronic data capture on eCRFs will be used, using internet access with password protection and data quality checks. It is expected that the eCRFs will be submitted coincident with the subject visit or within 1 business day.

13.1.5 Types of Data

Data will be collected on subject demographics, medical history including medication, physical examination, AEs, vital signs, laboratory safety tests, ECGs, efficacy outcomes, and lenabasum plasma concentrations and metabolites.

13.1.6 Protocol Deviations and Reporting

The investigator should not implement any deviation from or changes of the protocol without agreement by Corbus and prior review and documented approval from the reviewing EC, except where necessary to eliminate an immediate hazard to trial subjects or when the change

involves only logistical or administrative aspects of the trial (e.g., change in monitor[s], change of telephone number[s]). A change of the protocol that is deemed substantial will be submitted to the regulatory authority and an independent Ethic Committee by the sponsor for notification and approval.

The investigators and site staff are responsible to follow the written protocol as provided by Corbus and approved by their EC. The investigator or designee shall prepare and submit complete, accurate, and timely reports of all protocol deviations.

A protocol deviation is an excursion from the protocol that is not implemented or intended as a systematic change and that has not received prior approval by the reviewing EC. There are several types of protocol deviations with different requirements for reporting each type of deviation.

An emergency protocol deviation occurs in an emergency when an excursion from the protocol is required to protect the life or physical well-being of a participant. The Medical Monitor and the reviewing EC must be notified as soon as possible, but not later than 5 days after the emergency occurred. The Medical Monitor will be notified through the EDC system.

A major protocol deviation occurs in a non-emergency when the subject, investigator or Corbus fails to adhere to significant protocol requirements affecting the inclusion, exclusion, subject safety or primary endpoint criteria. Major protocol violations for this study include but are not limited to any of the following:

- Failure to comply with GCP guidelines.
- Failure to meet eligibility criteria at randomization or Visit 1.
- Use of a prohibited concomitant medication.
- Failure to query the subject about potential adverse events at each visit.
- Failure to obtain AUR-Q.

Major protocol deviations must be reported to Corbus within 5 days of first time the investigator or site staff becomes aware of the deviation and must be reported to the EC within that EC's guidelines. Corbus will determine if an emergency or major protocol deviation should result in early discontinuation of study treatment for a subject. An investigator's failure to report promptly any known major protocol deviation is itself an incident of non-compliance.

A copy of the Protocol Deviation Form will be filed in the site's regulatory binder and in Corbus' files. The site will report the violation to their EC in accordance with their EC reporting requirements.

A minor or administrative protocol deviation is an excursion from the protocol that does not affect the scientific soundness of the research plan or the rights, safety, or welfare of human subjects. Examples of minor or administrative deviations could include: follow-up visits that occurred outside the protocol required time frame because of the participant's schedule or blood samples obtained at times close to but not precisely at the time points specified in the protocol. If a protocol deviation occurs which meets this definition, the deviation should be reported to the reviewing EC (if reporting is required) at the time stipulated such as when the

continuing review application is submitted. These minor or administrative deviations will be reported in the Clinical Trial Management System within 28 days after their occurrence or identification.

13.1.7 Schedule and Content of Report

Reports will be generated for Corbus to monitor enrollment and study conduct. Blinded safety monitoring reports will be generated for the Medical Monitors and the Medical Officer of Corbus and un-blinded safety reports will be generated for the DMC.

The final study report will be generated separately and only after the database is locked. The final study report that will be generated will be stipulated in the final SAP and any amendments to that SAP.

13.2 Original Records

This study will use direct data entry of clinical trial data into an EDC system. Clinical trial data will be entered by the investigator or designee or in cases of certain questionnaires by the subject or parent/guardian of minor subjects into a validated 21 CFR Part 11 compliant internet-based EDC system. Changes to the clinical trial data can only be performed by the investigator or designee through the change management methodology that is subject to a full audit trail.

The investigators and designees will be trained on the EDC system before enrollment of the first subject at their site. A list of the status of each user, including an audit trail of status changes, will be maintained.

At the end of the study, the completed online eCRF must be reviewed and signed electronically by the investigator or a designated co-investigator authorized to sign. A certification must be obtained from all authorized persons to sign electronically indicating that their electronic signature is equivalent to their hand-written signature.

13.3 Quality Control and Quality Assurance

13.3.1 Study Monitoring Plan

The investigator will monitor data quality from his/her site on a regular basis throughout the study and monitor for compliance with the protocol, applicable government regulations, Good Clinical Practice, the site's standard operating procedures, and the local EC, when applicable. The investigator will allocate adequate time for these monitoring activities.

The investigator and institutions involved in the study will permit study-related monitoring by Corbus, government agencies and other regulatory groups, if requested and provide direct access to all study records at the site and to the facilities. Adequate time and space for monitoring visits should be made by the investigator and site staff.

Data quality will be monitored by Corbus on a regular basis throughout the study period. The electronic record will be monitored/audited for the purposes of the study. A site monitor representing Corbus will visit study facilities at periodic intervals, in addition to maintaining necessary contact through telephone, e-mail, and letter. The monitor will assess: subject enrollment and informed consent procedures; investigational product storage, dispensing, administration and accountability; compliance with protocol procedures; completeness and accuracy of data entered onto the EDC; and the occurrence of AEs. All aspects of the study

will be carefully monitored for compliance with the protocol, applicable government regulations, GCP, and the site's standard operating procedures.

The investigator or a member of the study team must be available to the monitor during monitoring visits to review data, resolve queries and review the subjects' records (e.g., medical records, doctor office and hospital charts and study-related information) for source data verification.

The monitor will discuss the conduct and progress of the study with the investigator and site staff. The investigator must cooperate with the monitor to ensure that any problems noted during monitoring are resolved.

13.3.2 Audit and Inspection of Sites

Participation by the investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable institutional compliance and quality assurance offices. During the conduct of the study, Corbus may conduct audits of any data and facility participating in the study. The investigators and institutions involved in the study will permit such study-related audits and provide direct access to all paper study records not contained within the electronic medical record or eCRFs and to the facilities. The investigator must maintain a comprehensive and centralized filing system of all study-related documentation that is not part of the electronic medical record or eCRFs and that is suitable for inspection by Corbus or its designated site monitors, Quality Assurance monitors, EC representatives, and representatives of government regulatory bodies. The investigators agree to participate in audits conducted at a convenient time in a reasonable manner.

Government regulatory authorities or representative from ECs may also perform inspections either during or after the study. In the event of an inspection by any regulatory authority, the investigators will promptly notify Corbus and will allow Corbus representatives to be present during the audit, if permitted by the regulatory authority. The investigators agree to cooperate fully with inspections conducted by regulatory authorities and to allow representatives of the regulatory authority access to all study records. The investigator will forward to Corbus a copy of any inspection records received.

13.4 Data Management

A Clinical Data Monitoring Plan will be created to specifically identify how data management will be performed for the study. The following summarizes this plan:

- The clinical database will be held and managed by an EDC vendor. The EDC will be used for online edit checks, batch edit checks and query management
- Data validation will be performed per the specifications in a Data Validation Plan. Within the Data Validation Plan, there will be validation checks:
    - Online checks performed by the EDC system during data entry
    - Batch edit checks
    - Manual checks performed by the site monitor and/or Data Management.

Queries are handled within the EDC application. The monitors and data managers can generate a query. Under direction of the investigator, the site team addresses the query. If the query is due to a data entry error, the site staff can immediately make the corrections in

the applicable eCRF pages. If the query needs clarification, the site staff contacts the investigator for resolution. The Coordinator then enters the correct value or submits an answer to the query without modifying the data. The monitor then reviews the corrected eCRF pages and/or answer. If the data are changed correctly or the answer is acceptable, the monitor closes the query. If the answer is not acceptable, the monitor submits an additional query for clarification. All changes to the database require a "Reason for Change" and are subject to an audit trail. The audit trails identify the changed data, reason(s) for change, who changed the data and the time and date of the change.

Centralized monitoring will be performed at an agreed-upon frequency as defined in the Clinical Monitoring Plan. The sites will receive feedback about data quality and data management issues at their own sites. Corrective actions will be implemented as necessary.

Routine EDC management reports will be available to view the data for consistency. Additional management reports will be obtained and reviewed, as indicated during the study.

13.5 Trial Master File

The Trial Master File for Corbus will be maintained within an electronic document storage system using 21 CFR Part 11 compliant software.

13.6 Record Retention

The investigator must ensure that the following records and documents pertaining to the conduct of the study and the distribution of study drug are retained for as long as needed to comply with national and international regulations (generally 2 years after discontinuing clinical development or after the last marketing approval): copies of the study specific documents and other sources of information such as original medical documents, data and records (such as hospital records, clinical and office charts, laboratory notes, memoranda, documents regarding subject treatment and study drug accountability, and original signed informed consents). All EC records related to this investigation will be retained by the site for as long as required by the local EC.

In the event the investigator retires, relocates or for any other reason withdraws from the responsibility for maintaining records for the time required, custody of the records may be transferred to any other qualified person who will accept responsibility for the records. Notice of such a transfer must be given in writing to Corbus. The investigator must contact Corbus before disposal of any records related to this study. No records will be destroyed without the written consent of Corbus, if applicable. It is the responsibility of Corbus to inform the investigator when any study documents stored at his/her site no longer need to be retained.

13.7 Confidentiality of Subject Data

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 Corbus. Additional subject confidentiality issues (if applicable) are covered in the Clinical Study Agreement.

14 REPORTING AND PUBLICATION

14.1 Confidentiality of Study Data

Any information relating to the study drug or the study including any data and results from the study will be the exclusive property of Corbus. The investigators and any other persons involved in the study will protect the confidentiality of this proprietary information belonging to Corbus.

14.2 Publication Policy

Corbus will conduct this clinical study in an ethical and rigorously scientific manner, in collaboration with clinical experts in CF. Corbus will facilitate publication of the clinical data from this study in a timely, objective, accurate, and balanced manner. The goal is to have submission of the primary manuscript for peer-review within 12 months of generation of the full set of Tables and Listings. Corbus will follow publication guidelines that are consistent with requirements of the International Committee of Medical Journal Editors, the Consolidated Standards of Reporting Trials group, and the individual journal. Corbus will work with investigators on this clinical study to produce any manuscripts for peer-reviewed publication. Publication by the site of any data from this study must be carried out in accordance with the clinical trial agreement.

This clinical study will be listed on websites as required by relevant regulatory authorities. Synopses of the clinical results will be provided on those same sites per timeframes established by those regulatory authorities.

The electronic study database for this clinical study will reside at an external vendor selected by Corbus. Corbus retains unlimited access to and use of the study database. Plans for data analyses by biostatisticians are part of this study protocol. All authors of a planned publication will be provided with the statistical analysis plan and the statistical report, redacted to be relevant to the planned publication. For the primary report of this clinical trial, this will include a full accounting of subject disposition. Corbus will allow investigators to review the complete study database, on request.

Corbus will provide a copy of clinical trial protocol and statistical analysis plan to a medical journal when a submitted manuscript is being considered for publication on request by the journal. Corbus will allow the journal to post on its website, at the time of publication, the key sections of the protocol that are relevant to evaluating this study, such as sections describing the study objectives and hypotheses, the subject inclusion and exclusion criteria, the study design, outcomes, and procedures and the statistical analysis plan. Corbus will allow a medical journal editor to review the study database on request.

Corbus will provide all investigators with the trial results and encourages investigators to share the results with the subjects in this study as appropriate.

Publication by the site of any data from this study must be carried out in accordance with the clinical study agreement. Corbus maintains the right to be informed of any plans for publication and to review any resulting abstracts, presentations or manuscripts before they are submitted.

The study database will be available to Corbus and relevant regulatory agencies as required.

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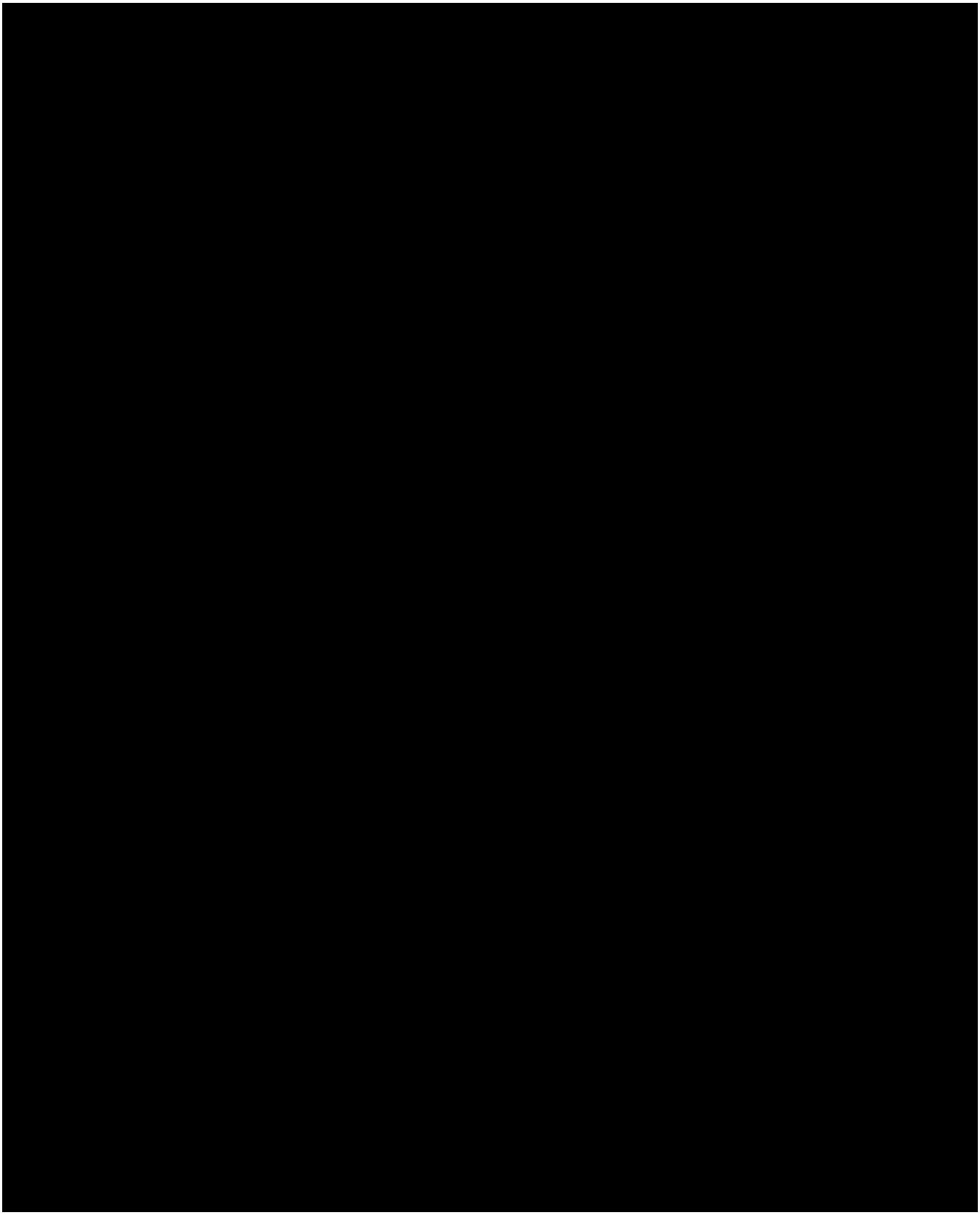

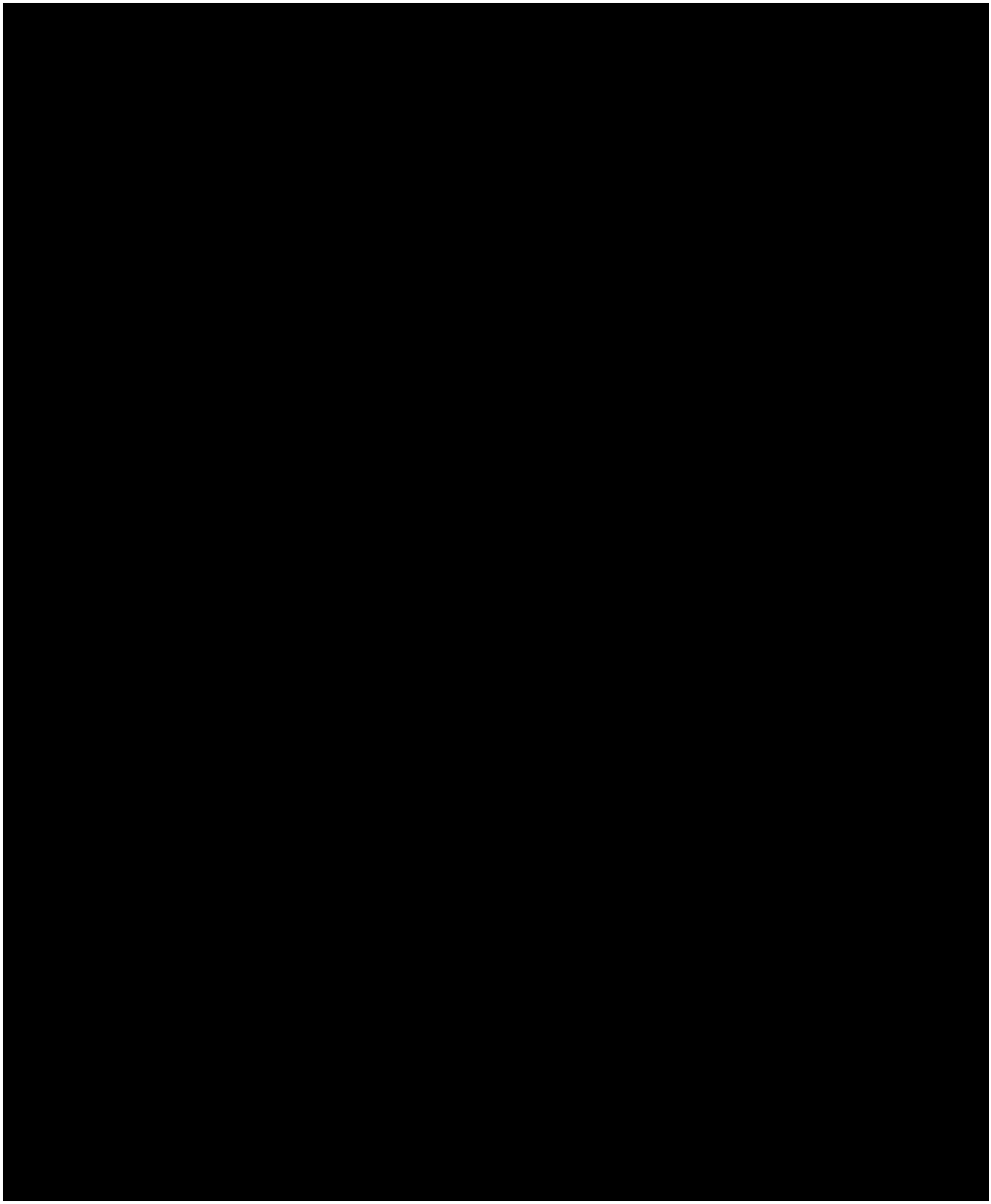

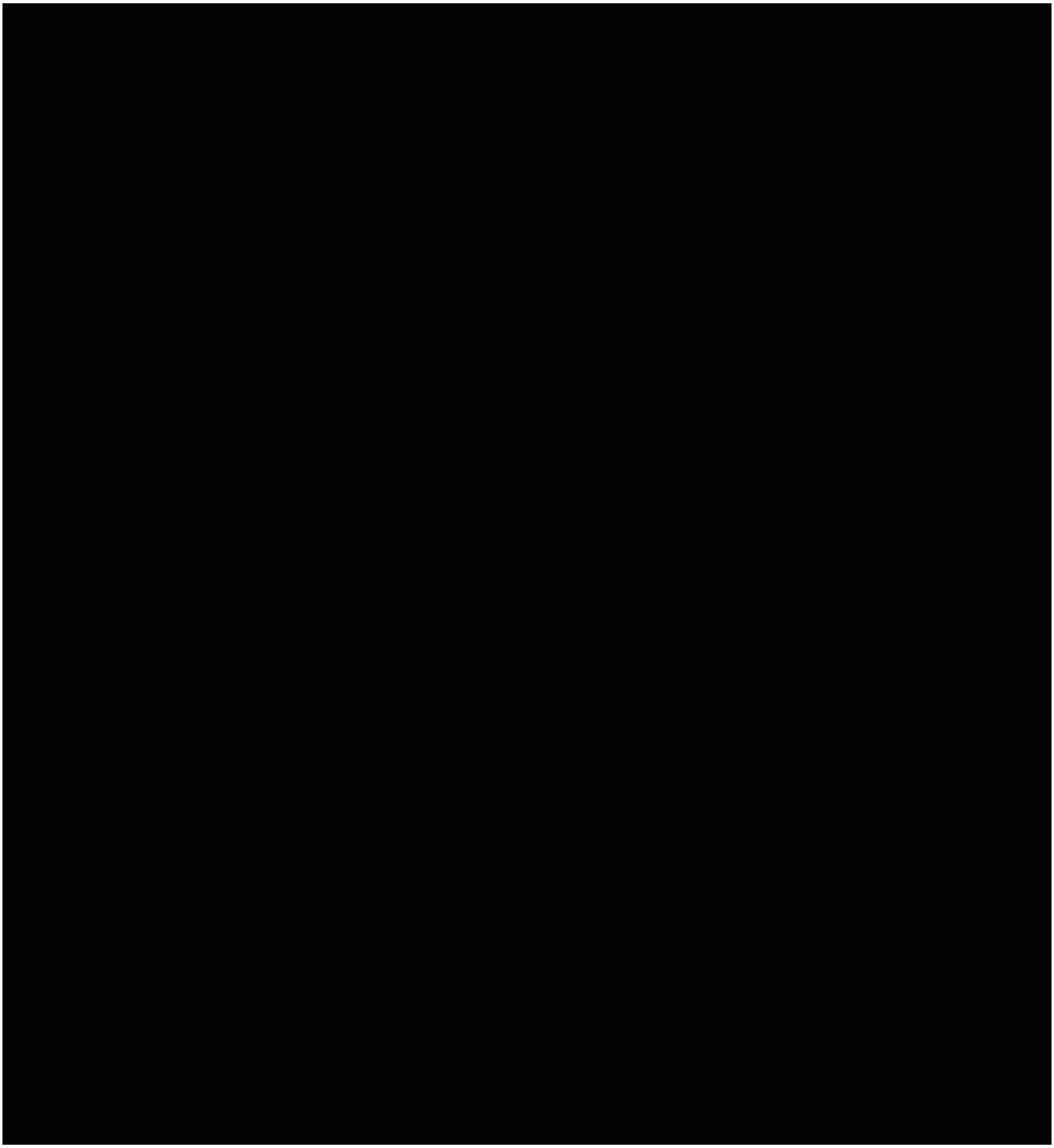

16.3 Appendix C: Protocol Amendment History

Original Protocol	Version 1.0	11 Oct 2017
Amendment 01	Version 2.0	19 Dec 2017
Amendment 02	Version 3.0	14 June 2018
Amendment 03	Version 3.1	15 Oct 2018
Amendment 04	Version 3.2 Version 3.3 France	09 OCT 2019 05 NOV 2019
Amendment 05	Version 3.4	05 NOV 2019

Summary of Changes for Version 3.4

Synopsis 7.1.6.1	Updated site locations to eliminate Israel and Australia to make consistent with previous change in Synopsis, Study Design (previously made under Global changes)	**Sponsor**
Synopsis	Fixed typo under Statistical Analysis in PKAS description to match body of protocol: “SAF” should read “SS”	**Sponsor**
Synopsis 7.1.4 7.2.8.3 10.2.5 10.2.8	Language was changed from ‘will’ to ‘may’ in regards to being asked to participate in a two-year observational safety follow-up study.	**Sponsor**
Global	Corrected typographical and other minor errors throughout protocol.	**Sponsor**

Amendment 04 (Version 3.2 Effective 09 OCT 2019) Summary of Changes

Section	Description of change	Change requested by
Title Page	Updated contact information for Principal Investigators.	Sponsor
Synopsis	Modified text to align with protocol body.	Sponsor

Section	Description of change	Change requested by
6 Study Objectives and Endpoints	Addition of a second tertiary efficacy objective and corresponding endpoints: To evaluate recovery from PEx in lenabasum 20 mg BID, lenabasum 5 mg BID, and placebo. a. Proportion of early rapid responders b. Proportion of subjects with FEV1 improvement to pre-PEx FEV1 values defined by study baseline and FEV1 prior to PEx by study completion c. Event rate of subsequent PEx d. Time to subsequent PEx e. Sputum granulocytes and neutrophils, actual values and change in number of granulocytes and neutrophils from pre-to post-PEx	Sponsor
3.1 9.1.5	CRISS was updated for clarification. CRISS in this protocol refers to the Cystic Fibrosis Respiratory Symptom Diary (CFRSD) – Chronic Respiratory Symptoms Score (CRISS). The CRISS is a score calculated from the 16-item CFRSD.	Sponsor
7.1.4 10.2.5 10.2.8	Addition of language to indicate subjects will be asked to participate in a 2-year safety follow-up study. Subjects who agree to participate in the follow-up study will be consented under a separate protocol.	Sponsor
7.2.2 9.1.1	Clarification of Definition of Pulmonary Exacerbation: addition of phrase “Physician diagnosis of pulmonary exacerbation” to the primary definition. Language also was added to clarify physicians do not need to count the 28-day gap from last use of antibiotics to the new antibiotics in the definition of PEx. The 28-day gap will be counted centrally.	Sponsor
7.2.2	Addition of definition of Early Rapid Responder: Early rapid responders will be defined in several ways including but not limited to achieving a certain degree of improvement in FEV1, improvement in CRISS score, and improvement of other related measurements within a certain period of time.	Sponsor
Synopsis 7.1.4 10. Schedule of Assessments 10.2.9	Ensure consistency throughout to indicate the Visit 9 safety follow-up visit is to occur 28 (± 7) days after Visit 8.	TMC

Section	Description of change	Change requested by
Introduction 9.2.3. 9.2.5.2 9.2.5.3 9.2.6.8	Update of safety language and removal of language that describes the role of the Sponsor that is not needed in the protocol. Updated lenabasum exposure data Deleted "Discontinuation adverse events (DAEs) - Adverse events leading to discontinuation of treatment will be recorded and narratives will be generated for DAEs" Narratives will be written by the sponsor as part of the Clinical Study Report. Removed language on expectedness of AEs, the determination is made by the sponsor, not the investigator. Streamlined language on reporting of SAEs and AEs to Country Regulatory Agencies to say "The mandatory reporting of safety events to regulatory authorities will be followed as required by applicable regulatory authority, and as per the applicable reporting timelines." Simplified reporting of pregnancy that is classified as SAE to state "the investigator should follow the procedures for expedited reporting of SAEs"	Sponsor
7.1.6 8.1 9.1.6 10.2.6	Update language from "will" to "should" for the following measurements: Ideally doses should be about 12 hours apart and at a minimum there should be at least 8 hours between any 2 doses Ideally, morning and evening doses will be about 12 hours apart. Morning and evening doses must be at least 8 hours apart Sputum specimens should be obtained from each subject at Visit 1, Visit 2, Visit 5 and Visit 8 and any Possible PEx Visit Subjects who experience new or worsening respiratory symptoms or have received a prescription for a new antibiotic from a physician other than a study physician should contact the site staff and return for a Possible PEx Visit if instructed to do so.	Sponsor
Global	Corrected typographical and other minor errors throughout protocol.	Sponsor

Amendment 03 (Version 3.1 Effective 15 October 2018) Summary of Changes

Section	Description of change	Rationale
Synopsis	The number of life-threatening AEs to stop/suspend study was changed in Section 7.2.8.4 from two to one. This change was added to the synopsis.	Synopsis updated to match body of protocol.
Title Page, Protocol Approval	Responsible Medical Officer revised.	Previous Medical Officer has left the company.
Protocol Approval	Removed signatures for Principal Investigators.	Signatures from Principal Investigators are not required for protocol approval.

Amendment 02 (Version 3.0 Effective 14 June 2018) Summary of Changes

Section	Description of change	Change requested by
Synopsis	Modified text and study schematic to align with protocol body.	Sponsor
4.3	**Subject Information and Informed Consent** Revised text to provide clarity on the use of leftover blood and sputum samples.	Health Canada
5.2.2	**Animal Pharmacokinetics and Metabolism** Removed data regarding human metabolites since section 5.2.2 pertains to animal pharmacokinetic data	Sponsor
5.3.1	**Lenabasum as a Selective Cannabinoid Receptor Type 2 Agonist** Figure 1 Structure of Lenabasum was revised for clarity and minor corrections in the associated text.	Sponsor
5.9.1	**Potential Risk** Handling-induced convulsions, or seizures, occurred in some animal studies and were included as a potential risk. Additionally, the results of an animal study that was specifically designed to assess the seizure potential of lenabasum was added.	FAMHP of Belgium
7.1.1	**Study Schematic** Modified study schematic figure for improved clarity.	Sponsor
7.1.4	**Defined Study Start/Stop** Defined study start and stop dates as the date of first subject's first visit and the date of last subject's last visit, respectively. Included to better clarify the duration of the study.	MPA of Sweden
7.1.10	**Lenabasum exposure** Updated cumulative exposure numbers for lenabasum based on the last DSUR with data lock point of 05 March 2018. Exposure data were updated to reflect the most up to date subject numbers reported to regulatory agencies.	Sponsor
7.2	**Amendment and Administrative Change Summary** Removed summary of changes from Section 7.2 to Appendix C in Section 16.3. Updated summary of protocol changes made from Version 2.0 to 3.0.	Sponsor

7.3.4	**Inclusion Criteria** Updated male subject's requirements pertaining to contraceptive responsibilities (1 highly effective or acceptable method required).	Sponsor
7.3.5	**Exclusion Criteria** • Added: "Subject's with a history of any seizure within the last 2 years" to mitigate a potential risk of seizures identified in animal studies. • Clarified which formula to be used for measurement of creatinine clearance in adolescent subjects – "Schwartz eGFR formula"	FAMHP of Belgium, Health Canada, Sponsor
7.3.8.4	**Premature Termination/Suspension of the Study** Modified study stop/suspension criteria from 2 life-threatening clinical events deemed probably/definitely related to study drug to 1 related event.	UK EC
8.6.2.1	**Emergency Unblinding Procedures** Incorrect text was deleted as it did not accurately reflect the study procedures. Unblinding is carried out and documented in IWRS.	Sponsor
9.1.3	**CFQ-R** Clarification that subjects aged ≥ 14 years of age will take the adolescent/Adult version of the CFQ-R and that subjects aged 12-13 will take the Child version of the CFQ-R and their parent/caregiver will take the Parent/Caregiver version for ages 6-13. Clarification was added about age requirement at the time of consent for use of the correct questionnaire.	Health Canada
9.1.6	**Sputum Evaluation** Added "other biomarkers of inflammation may be analyzed and reported separately". Added a general statement to provide flexibility regarding which biomarkers will be analyzed.	Sponsor
9.1.7	**Blood Biomarkers of Inflammation** Section title changed from "C-reactive Protein and Erythrocyte Sedimentation Rate" to "Blood Biomarkers of Inflammation". Section title was changed to improve consistency with how the endpoint is described throughout the rest of the protocol including the table of objectives and endpoints in the synopsis and Section 6. Added "other biomarkers of inflammation may be analyzed and reported separately". Added a general statement to provide flexibility regarding which biomarkers will be analyzed.	Sponsor
9.2.1	**Adverse Events** Consolidated redundant wording. Added additional clarification on when a report of death or hospitalization will be recorded as an SAE.	Sponsor

9.2.2	**Serious Adverse Events** Added additional clarification for reporting death.	Sponsor
9.2.6.3	**Safety Reporting Procedures** Added the Sponsor's responsibilities for reporting SUSARs per local country regulatory requirements. Removed a requirement for the investigator to complete a SAE form and provide it to Sponsor in addition to eCRF as both actions are seen as being redundant.	MPA of Sweden, Sponsor
9.3	**Pharmacokinetics** Clarification of the method by which Corbus plans to quantify lenabasum plasma concentrations and investigate lenabasum metabolites.	ANSM of France
10.1	**Schedule of Assessments** Removed change in medical history as an assessment to be conducted from the schedule of assessments table. This was removed as a change in medical history will be detailed as an AE for the subject in question.	Sponsor
10.2	**Visits** General clarification added to all study visits using the schedule of assessments and footnotes to help better detail study visit assessment procedures.	Sponsor
11.6	**Analysis of Pharmacokinetics** Referenced the plan for interim PK analysis and DMC monitoring for adolescents to ensure safety and comparable lenabasum systemic exposure between adults and adolescents.	Health Canada, ANSM of France
12.1	**Data Monitoring Committee** Clarified DMC responsibilities and members: • Members will include not only CF experts but also an expert in the monitoring of CNS AEs. • Responsible to review all AEs in an unblinded manner as well as PK data from the first 20 adolescent and 20 adult subjects to monitor for safety and PK comparability.	Health Canada, ANSM of France and FAMHP of Belgium
13.1.6	**Protocol Deviation and Reporting** Added that any substantial change in the protocol will be submitted to the regulatory agency for approval prior to implementing such change in the clinic per regulators request.	MPA of Sweden
16.1	**Reproductive Potential** Correction and reclassification of the combination of condom and spermicide to an "acceptable method" and not a "highly effective" method of contraception.	BfArM of Germany
16.2	**AUR-Q** Updated with clarification and organized to better align with eCRF.	Sponsor
Global	**Clarifications, error correction, layout improvement**	Sponsor

	Updated study schematic figure throughout protocol Typographical and other minor error correction, and improvement of layout.	

Amendment 01 (Version 2.0 Effective 19 Dec 2017) Summary of Changes

Section	Description of change	Change requested by
6	**Endpoint changes** Order of endpoints changed so that, pulmonary exacerbation rate has been made primary endpoint (instead of secondary endpoint), and time to first exacerbation has been demoted to a secondary endpoint. Moreover, for primary endpoint of pulmonary exacerbation (PEx), the event will need to meet 4/12 symptoms from Fuch's criteria, in presence of antibiotic usage for respiratory signs and symptoms. Order of secondary endpoints changed.	FDA
7	**Sample size change** Sample size changed from 315 randomized subjects to 415 randomized subjects, because of change in primary endpoint	CFF-TDN
7	**ARCI-M removed**	FDA
7	**Adolescent sputum induction** Adolescents may opt out of providing sputum sample as some adolescents may find it challenging	CFF-TDN
7	**Stratification** Scheme changed slightly in terms of number of prior exacerbations	CFF-TDN
7	**PEx collection** Questionnaire for capturing PEx modified based on changed definition of primary endpoint of PEx	Sponsor's responsible medical officer
7	**Justification of dose** Section added to answer potential questions from investigators, ethics committees (information was already present in investigator's brochure)	Sponsor's responsible medical officer
7	**Treatment discontinuation** Clarified in the CSP that treatment discontinuation is not the same as withdrawal from the study, and further details around data collection and reporting added for treatment discontinuations	FDA
10	**Biomarker collection**	CFF-TDN

	Addition of 4-week timepoint, to get earlier readout of any signals of potential efficacy	
9	**Adverse event collection** • Adverse event collection method clarified, and description homogenized between different studies to be conduct by the sponsor • Clarified that potential abuse related events should be recorded as adverse events • Added dizziness as AE of special interest, to capture more details about this AE observed in prior studies • Added that discontinuation adverse events (DAEs) would also have narratives	Sponsor's responsible medical officer
Global	**Clarifications, error correction, layout improvement** Clarified- rescreening is permitted Typographical and other minor error correction, and improvement of layout	Sponsor's responsible medical officer