Corbus Pharmaceuticals, Inc.

Protocol Number: JBT101-CF-002

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

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Statistical Analysis Plan

Final Version 1.0

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1. LIST OF ABBREVIATIONS AND GLOSSARY OF TERMS

1.1. List of Abbreviations

AE	Adverse event
ARCI-49	Addiction Research Center Inventory 49
ATC	Anatomical Therapeutic Chemical
AUR-Q	Antibiotic Use for Respiratory Signs and Symptoms Questionnaire
BID	Twice per day
BMI	Body mass index
CF	Cystic fibrosis
CFQ-R	Cystic Fibrosis Questionnaire - Revised
CI	Confidence interval
COVID-19	Coronavirus-19 disease
CFRSD	Cystic Fibrosis Respiratory Symptom Diary
CFTR	Cystic fibrosis transmembrane conductance regulator
CRISS	Chronic Respiratory Infection Symptom Scale
CRP	High sensitivity C-Reactive protein
CSR	Clinical Study Report
DMC	Data Monitoring Committee
ECG	Electrocardiogram
ESR	Erythrocyte sedimentation rate
FEV1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
IV	Intravenous
IWRS	Interactive Web Response System
mITT	Modified intent-to-treat
MMRM	Mixed model for repeated measures
PEx	Pulmonary exacerbation(s)
PK	Pharmacokinetic(s)

PP	Per protocol
SAP	Statistical Analysis Plan
SOC	System Organ Class
TEAE	Treatment-emergent adverse event
TMT	Trail Making Test

1.2. Glossary of Terms

Adverse event:	Any untoward medical occurrence in a patient or a clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e., lack of efficacy), abuse, or misuse.
Blinding:	A procedure in which 1 or more parties to the trial are kept unaware of the treatment assignment with the intent to reduce the risk of biased outcomes.
Completed:	Subject who completed the last protocol-defined visit.
Eligible:	Qualified for enrollment into the study based upon adherence to inclusion/exclusion criteria.
Study product:	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial.
Life-threatening:	The term “life-threatening” in the definition of “serious” 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.
Protocol amendment:	As defined by the International Conference on Harmonisation Tripartite Guideline for Good Clinical Practice: “A written description of a change(s) to or formal clarification of a protocol.”
Serious adverse event:	An untoward medical occurrence that at any dose (a) results in death, (b) is life-threatening, (c) requires inpatient hospitalization or prolongation of existing hospitalization, (d) results in persistent or significant disability/incapacity (e) is a congenital anomaly/birth defect (f) results in an important medical event that may jeopardize the patient and may require intervention to prevent one of the other outcomes.
Subject:	Term used throughout the protocol to denote an individual that has been contacted to participate in the clinical study, either as a recipient of the study product or as a control.
Subject Identification Number:	A unique number identifying a treatment to a subject, per the study randomization.

Suspected Unexpected Serious Adverse Reaction:	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 product information in the Investigator's Brochure, and (c) there is reason to suspect that the study product caused the event.
Tolerability:	The incidence of discontinuation of study product or "drop-out" due to a treatment emergent adverse event probably or definitely related to study product.
Treatment:	Term used throughout the protocol to denote the study product or placebo intended to be administered to a subject.
Treatment-emergent adverse event:	Any event 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.

2. INTRODUCTION

This statistical analysis plan (SAP) is being developed in conjunction with the protocol JBT101-CF-002 [Version 3.4 dated 05 NOV 2019 for all countries except France and Version 3.3 dated 05 NOV 2019 for France] sponsored by Corbus Pharmaceuticals Inc. The SAP contains detailed information to aid in the performance of the statistical analysis and reporting of the data for use in the final Clinical Study Report (CSR), including the 28-day safety follow-up period off study product.

This SAP is being written with due consideration of the recommendations outlined in the most recent International Conference on Harmonization E9 Guideline entitled Guidance for Industry: Statistical Principles for Clinical Trials and the most recent International Conference on Harmonization E3 Guideline entitled Guidance for Industry: Structure and Content of Clinical Study Reports.

This SAP describes the data that will be analyzed and the subject characteristics, efficacy, and safety assessments that will be evaluated. This SAP provides details of the specific statistical methods that will be used.

The SAP will be finalized before database lock and unblinding. If FDA requests additional analyses after the SAP is signed, those analyses will be done and added as an amendment to the SAP as additional analyses requested by the FDA. Otherwise, there will be no change to this SAP by the Sponsor after it is signed.

The statistical analysis methods presented in this document will supersede the statistical analysis methods described in the clinical protocol. If additional analyses are required to supplement the planned analyses described in this SAP, then those analyses will be completed and identified in the CSR.

3. STUDY OBJECTIVES

3.1. Primary Efficacy Objective

The primary efficacy objective is to evaluate the efficacy of lenabasum compared to placebo in the treatment of cystic fibrosis (CF) by assessing the event rate per subject per 28 weeks of new pulmonary exacerbations (PEx), using the primary definition of new PEx, comparing lenabasum 20 mg twice per day (BID) and placebo cohorts. The assessment for the primary objective occurs during the treatment period, from Day 1 to Visit 8 (Week 28).

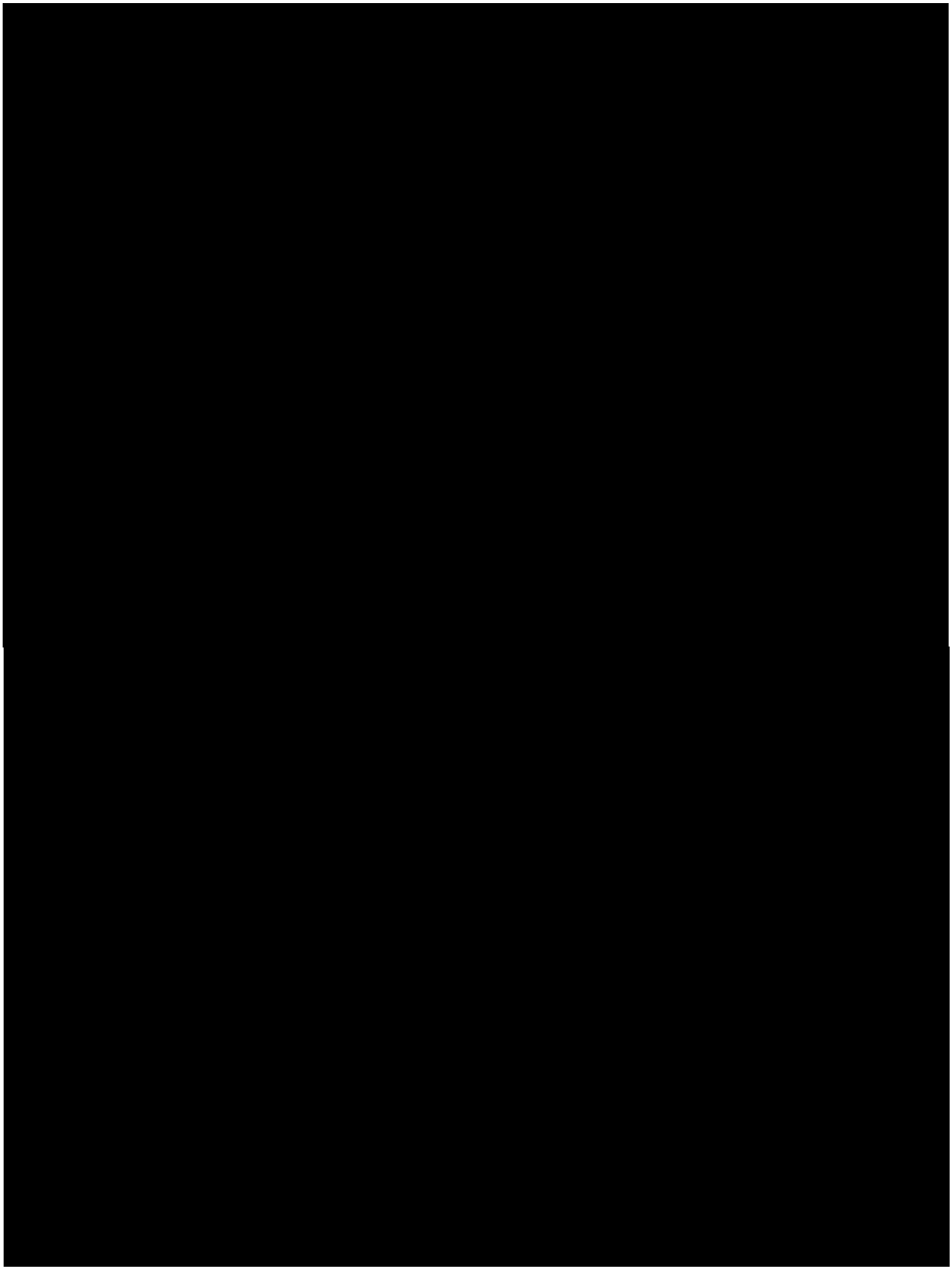
3.2. Secondary Efficacy Objectives

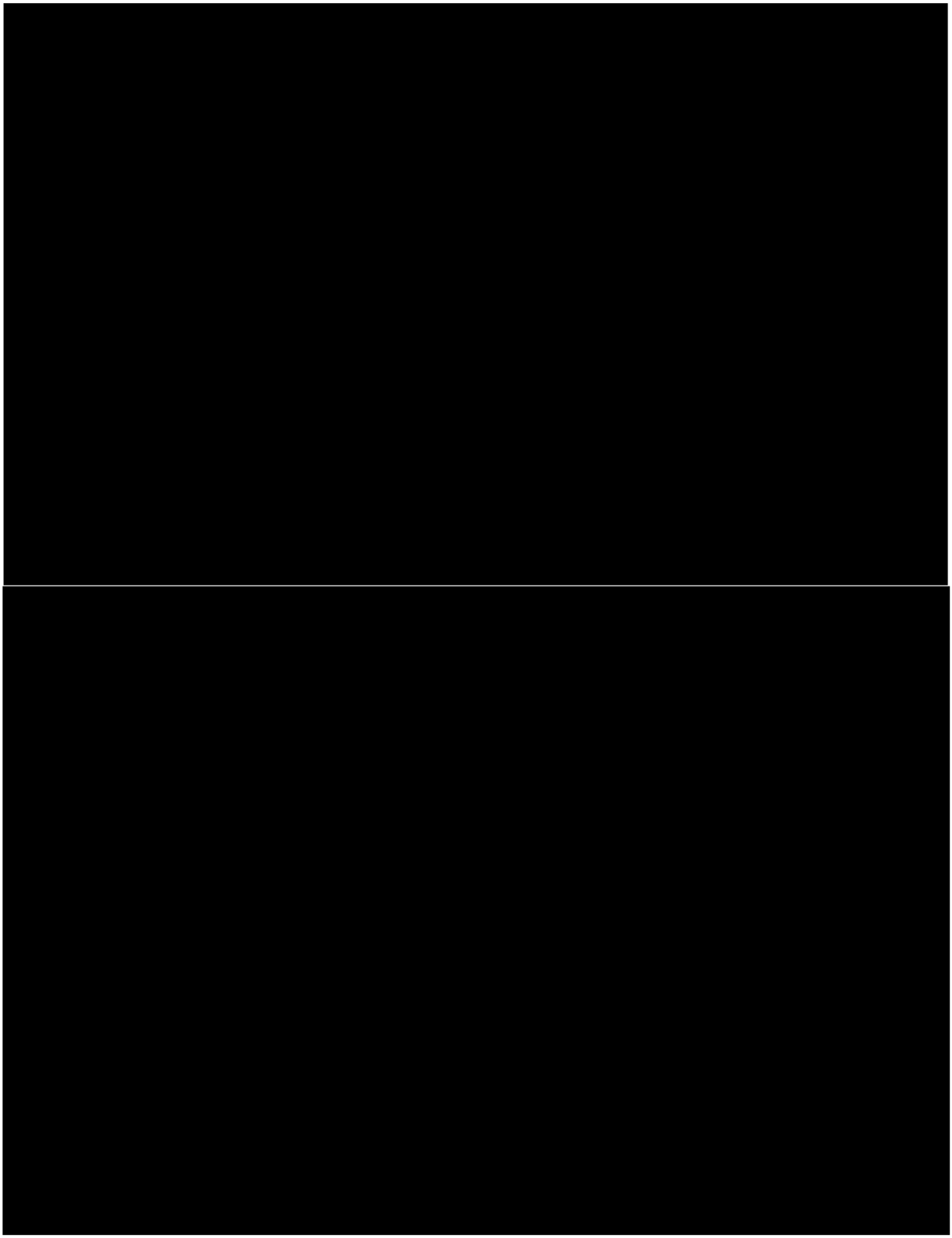
The secondary efficacy objectives are assessed through or at Visit 8, as relevant. The secondary objectives will be assessed in the order below. For all analyses in the SAP, change means change from Baseline, and Visit 8 means Visit 8 or study discontinuation, unless otherwise specified.

The secondary efficacy objectives are to evaluate:

1. Event rate per subject per 28 weeks of new PEx using secondary definition of new PEx, comparing lenabasum 20 mg BID and placebo cohorts
2. Time to first new PEx using primary definition of new PEx, comparing lenabasum 20 mg BID and placebo cohorts
3. Time to first new PEx using secondary definition of new PEx, comparing lenabasum 20 mg BID and placebo cohorts
4. Event rate per subject per 28 weeks of new PEx using the primary definition of new PEx, comparing lenabasum 5 mg BID and placebo cohorts.
5. Event rate per subject per 28 weeks of new PEx using secondary definition of new PEx, comparing lenabasum 5 mg BID and placebo cohorts
6. Time to first new PEx using primary definition of new PEx, comparing lenabasum 5 mg BID and placebo cohorts
7. Time to first new PEx using secondary definition of new PEx, comparing lenabasum 5 mg BID and placebo cohorts
8. Change in Cystic Fibrosis Questionnaire – Revised (CFQ-R) respiratory symptom domain score, comparing lenabasum 20 mg BID and placebo cohorts. [redacted]
9. Change in forced expiratory volume in 1 second (FEV1) % predicted, comparing lenabasum 20 mg BID and placebo cohorts
10. Change in CFQ-R respiratory symptom domain score, comparing lenabasum 5 mg BID and placebo cohorts
11. Change in FEV1 % predicted, comparing lenabasum 5 mg BID and placebo cohorts

[redacted]





3.4. Primary Safety Objective

The primary safety objective will be assessed by treatment cohorts and by combined lenabasum cohort, for TEAEs.

1. TEAEs associated with lenabasum treatment, by treatment cohorts and combined lenabasum cohort

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[redacted]

[redacted]

[redacted]

4. STUDY DESIGN AND PLAN AND STUDY ENDPOINTS

4.1. Study Design and Plan

This is a randomized, double-blind, placebo-controlled, multicenter, interventional, parallel-dose Phase 2b study to assess the efficacy and safety of treatment of CF subjects with lenabasum 20 mg BID and lenabasum 5 mg BID. Subjects will be randomized 2:1:2 to receive blinded study product (lenabasum 20 mg BID, lenabasum 5 mg BID, or placebo BID) for 28 weeks.

Active dosing with study product is 28 weeks. There will be 8 scheduled study visits during active dosing with study product, 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 product will have a Safety Follow-up Visit, labeled Visit 9, at 28 ± 7 days after Visit 8, at all study locations except for those in France.

[redacted]

All subjects who develop acute signs and symptoms of possible worsening respiratory disease will be asked to return to the site, as possible, 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. If a new PEx and associated tests are recorded at an Unscheduled Visit rather than a Possible PEx Visit, that PEx information and any associated efficacy or biomarker assessments done at the Unscheduled Visit will be handled as if the Unscheduled Visit were a Possible PEx Visit.

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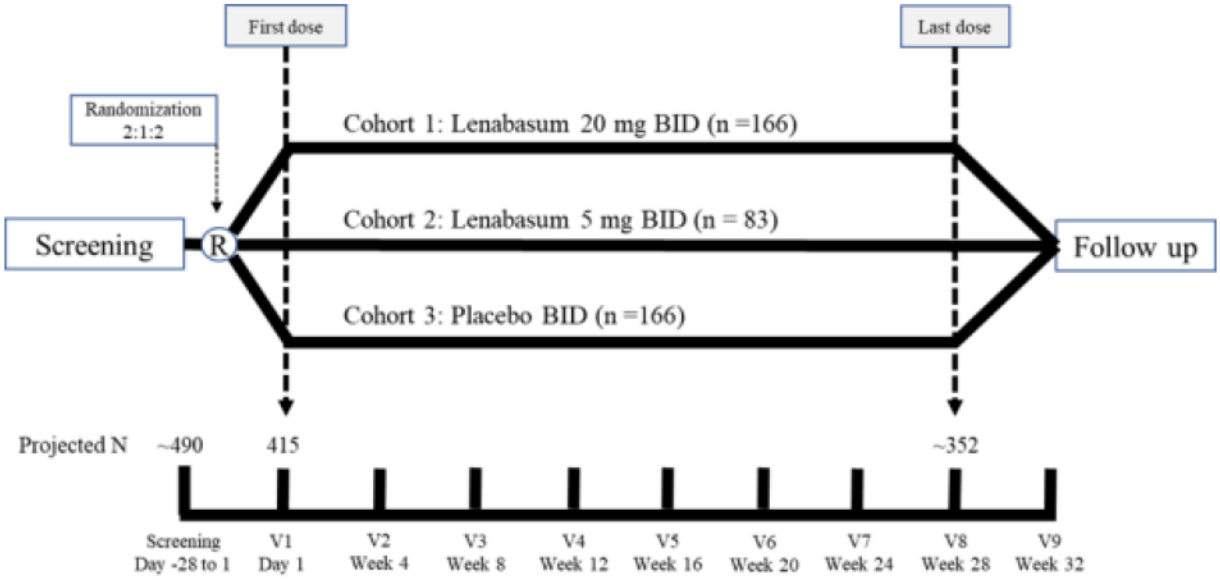
4.1.1. Study Schematic

Figure 1: Study Schematic for JBT101-CF-002



BID = twice per day; N = number of subjects; V = visit

[redacted]

4.1.2. Schedule of Visits and Assessments

Schedule of clinical assessments/procedures for all subjects is presented in Appendix 2. Additional assessments/procedures for France are presented in Appendix 4.

The following will be assessed at all in-person visits:

- Endpoints related to PEx, CRISS, spirometry
- Concomitant medications
- Adverse events
- Study product tolerability
- Vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate, body temperature, height and weight)
- Brief Physical examination

- Contraceptive assessment and pregnancy screening for women of childbearing potential
- Complete blood count with cell differential and platelets; metabolic panel; and urine dipstick

Other assessments will be done less frequently:

- 12-lead ECGs including QT/QTc intervals (Visit 1, Visit 5, and Visit 8)
- CFQ-R questionnaire (Visit 1, Visit 5, and Visit 8)
- CRP and ESR (Visit 1, Visit 2, Visit 5, and Visit 8)
- Plasma concentrations of lenabasum and its metabolites (Visit 1, Visit 2, Visit 5, and Visit 8). Plasma concentrations and metabolites of lenabasum and ARCI-49 questionnaire will be assessed on Visit 1 before and 3.0 ± 0.5 hours after dosing.

4.1.3. Possible Pulmonary Exacerbation Visit

Subjects who experience new or worsening respiratory symptoms or who receive 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
  - CRP, ESR and other inflammatory biomarkers
- Spirometry
- Attempt sputum collection
- Physician assessment of:
  - Brief physical examination
  - Antibiotic Use for Respiratory Signs and Symptoms Questionnaire (AUR-Q)

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

- AE monitoring.
- Record concomitant medications.
- Physician assessment of:
  - AUR-Q

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 site, 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.

4.1.4. Study Population and Background Treatment for CF

The study population is males and females with CF ≥ 12 years of age with FEV1 ≥ 40% predicted and < 100% predicted at least once within 12 months before Screening. Subjects must have 2 to 3 new PEx treated with IV antibiotic therapy within 12 months before Screening or, as an alternative, 1 new PEx treated with IV antibiotics and at least 1 PEx treated with oral antibiotics within 12 months before Screening.

Subjects should be considered stable and on stable medication for treatment of CF prior to Visit 1. For example, subjects are allowed use of prophylactic antibiotics and CFTR-modulating medications if they are on stable doses within 28 days of Visit 1. A subject with an increase in dose or initiation of any new chronic therapy for CF within 28 days of Visit 1 is not eligible for enrollment. Changes in treatment of CF after study start are allowed when those changes are in the subject's best medical interest, as assessed by the treating physician. Sensitivity analyses will be performed to assess potential impact of treatment at Baseline with drugs that might reduce rate of PEx, including concomitant CFTR-targeting medications, azithromycin, prophylactic antibiotics, and dornase alfa on the primary and first secondary efficacy outcome.

4.1.5. Target Enrollment

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.

4.1.6. Screening

Screening can occur up to 28 days before Visit 1. A subject that has screen failed may re-screen later at the discretion of the site investigator. A new subject code will be allocated at re-screening.

4.1.7. Duration of Study

The intended duration of active dosing is 28 weeks (through Visit 8).

4.1.8. Masking, Blinding, and Unblinding

Dosing will be done in a double-blinded, randomized, placebo-controlled manner.

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

All study subjects and the site study staff, including the investigators who will do safety and clinical assessments, qualified designees, study nurses, and study coordinators at the sites, will remain blinded to treatment assignment during the entire study, until after the database is locked. If the treatment allocation for a subject otherwise becomes known to the investigator or other study staff at the site prior to database lock, the investigator or designee must notify Corbus immediately.

In an identical manner, all Corbus medical and clinical operations staff associated with the conduct of this study will remain blinded to treatment assignment during the entire study, until after the database is locked.

Corbus clinical supplies personnel will be unmasked to the study product randomization. They are required not to reveal randomization information to others, unless a formal unmasking of information for a given subject is undertaken for safety reasons.

A limited number of contract laboratory personnel who perform and interpret assays of lenabasum concentrations and metabolites, as well as an independent statistician assigned to the Data Monitoring Committee (DMC), will be unmasked. These unmasked external 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.

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 Interactive Web Response System (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.

4.1.9. Randomization, Stratification Factors, Treatment Cohorts, and Dosing

Before dosing on Visit 1 (Day 1), eligible subjects will be randomly assigned using an Interactive Web-based Response Technology system to one of three treatment cohorts, based on a randomization schedule prepared by an independent biostatistician who was not involved in the day-to-day conduct of the study. The randomization will be stratified by number of previous new PEx requiring IV antibiotics in the previous year (“1 vs 2 or 3”; however, this changed approximately midway of study to “1 or 2 vs 3” , See Section 13), FEV1 % predicted at baseline (< 70; ≥ 70) and location of site (United States; Non-United States).

Subjects will be randomized in a 2:1:2 ratio to 1 of 3 treatment cohorts:

- 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 two doses each day with at least 8 hours between doses. Subjects will self-administer study product, which will be taken by the oral route and with no requirement as to fed or fasting state. Phase 1 data showed little impact of the fed-state on exposure to lenabasum, and subjects in all Phase 2 studies to date have taken lenabasum without regard to fed state.

4.1.11. Dose Reduction

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 product by 1 capsule per day on a temporary or permanent basis. The impact of any temporary or permanent reduction in dose > 30 days will be assessed in sensitivity analyses of the primary and first secondary efficacy outcomes.

4.1.12. Discontinuation from Study Product but Continuation in Study

A subject may discontinue study product and continue in the study. If a subject permanently discontinues study product, they will be asked to continue in the study for efficacy and safety follow-up with Visits 5 and 8 performed off study product, starting with the next one of these visits that occurs after discontinuation of study product. For subjects who do not withdraw consent and agree to return for these visits, an additional 28-day safety follow-up after Visit 8 will not be done. Safety and efficacy data will be collected during these visits and included in analyses of safety and efficacy data. The impact of having these subjects remain in the study will be assessed in sensitivity analyses of the primary and first secondary efficacy outcomes.

4.1.13. Early Discontinuation from Study

Reasons for early discontinuation from the study include: death; AE; lack of efficacy - withdrawal by subject; lack of efficacy – physician decision; physician decision – other; withdrawal of consent by subject; lost to follow-up; non-compliance with study; pregnancy; study termination by sponsor; and other.

Subjects who withdraw consent will not have any efficacy or safety follow-up assessments following withdrawal of consent.

Participants who are discontinued permanently from study product due to an AE will be followed until resolution or stabilization of the event.

4.1.14. Coronavirus Disease 2019 (COVID-19)

Starting in winter 2019/2020, a pandemic of infection with new coronavirus (2019-nCOV) caused national and regional governments to restrict travel and gatherings of multiple people. Access of clinical study subjects to study sites and staff was severely restricted from mid-March 2020, as was access of study monitors to monitor study data at sites and remains restricted at the time of writing this SAP. At the time the restrictions began, all subjects had completed Visit 5 (Week 16) of the study.

The Sponsor developed and communicated a plan to manage safety and efficacy analyses of study subjects and maintain continuity of supply of study product to subjects, which is consistent with the *FDA Guidance on Conduct of Clinical Trials of Medical Products During COVID-19 Public Health Emergency* (FDA COVID-19 Conduct Guidance, March 2020). This plan was communicated internally first and then to sites during a series of webcasts on March 12 and 13, 2020, just before most restrictions began to take effect. As the Sponsor's management of the impact of COVID-19 evolved, any changes to the plan were communicated to the sites through e-mail or phone calls. The plan was communicated to internal study staff, vendor staff, study site staff, and the DMC. Details of the plan and communication are maintained separately at Corbus.

Approaches to mitigating potential major impact of COVID-19 on performance of study JBT101-CF-002 are summarized in **Table 1**.

Table 1. Summary of Mitigation of Negative Effects of COVID-19 on Study JBT101-CF-002

COVID-19 Negative Effects on Execution of study JBT101-CF-002	Mitigation
Subjects not able to have study visit at site because site is closed, site staff cannot travel, or subject is at high risk of traveling to site • Missed visits • Visits outside study window • No safety assessments on site at Visit 5-8 or safety follow-up visit • Missed efficacy assessments at Visits 5-8 • Subjects unable to get study product at site	Extend visit windows by 1 week, to ± 2 weeks, to increase opportunity for study visits at site and full study evaluation Obtain safety follow-up including use of contraception using interview-based assessments over the phone or computer, between subjects and physicians. Document TEAEs and use of contraception per protocol Obtain safety lab follow-up at local laboratories when possible. Results will be reviewed by study staff, put into source documents, but not study database Obtain concomitant medication history using interview-based assessments over the phone or computer. Document concomitant medications per protocol Obtain information of PEx using interview-based assessments over the over the phone or computer, between subjects and physicians. Document PEx per protocol To maintain continuity of dosing with study product: • Make provisions for sites to ship study product directly to subjects. Obtain a DEA waiver for lenabasum so US sites can ship study product directly to subjects • Allow subjects not to return unused study product to site until end of study and to use that study product if needed to maintain continuity of dosing • Maintain subjects on a reduced dose of study product if direct shipment of study product to subject will not arrive in time to allow subject to continue to take full dose of study product. This approach is preferred to continuing subject on full dose of study product, then temporarily discontinuing study product altogether while waiting for direct shipment of study product to subject to arrive

Study staff not on site or have restricted access to site to enter study data. • Late data entry • Incomplete data entry	Closely monitor site visits and data entry to determine what data will be late versus what will not be obtained. Work with sites to get data entered whenever possible
External monitors unable to travel to or enter study site to monitor data • 100% source document verification will not be possible	Remote data monitoring, as allowed by site/country policies. Perform and document oversite of remote data monitoring Central data monitoring when data cannot be verified on site or by remote monitoring. Perform and document oversite of central data monitoring Resume source document verification on site when travel restrictions and access allow

Treatment assignment does not influence the negative effects of COVID-19 on execution of study JBT101-CF-002 or the plans put into place to mitigate those effects. The COVID-19 pandemic is not expected to introduce bias into the statistical analyses of the data.

A Table listing amendments to study plans to ensure continuity and oversight of the study will be included in the JBT101-CF-002 CSR.

A listing by subject and a table summarizing COVID-19 associated events by treatment cohorts and combined lenabasum cohorts will be provided. This listing and table will include protocol deviations.

Protocol deviations related to COVID-19 are expected to fall mostly into categories of study visits outside of windows, missing efficacy assessments, and short periods of temporary reduction/discontinuation of study drug.

Safety oversight was maintained throughout either with onsite visits or with interview-based safety assessments by the treating physician.

The following effects of COVID-19 on subject disposition are identified before database lock:

- No subject early terminated before Visit 8 because of COVID-19
- All subjects had safety follow-up during COVID-19
- On March 16, 2020, when staff at Corbus began work-from-home policy for COVID-19, 18 subjects (~4%) had not yet completed Visit 6 (Week 20); 48 subjects (~11%) had not yet completed Visit 7; and 67 subjects (~16%) had not yet completed Visit 8. These subjects were in United States (n = 16), and other countries (n = 51).

  Of these subjects, all had interview-based safety assessments and all but 1 had PEx assessments, with <1% of total without adequate assessment for the primary efficacy outcome because of COVID-19.

The adjustments in this SAP for COVID-19-associated events are listed below and only apply when the event was related to COVID-19. None of the approaches are expected to introduce

bias into the results missing efficacy assessments because COVID-19 is unrelated to treatment assignment.

For events related to COVID-19 only, at Visit 6, Visit 7, and Visit 8 only (FDA COVID-19 Statistical Guidance, June 2020):

- Protocol deviations will be identified as COVID-19 related
- Adverse events will be identified as COVID-19 related
- Concomitant medications given for COVID-19 associated illnesses will be identified as COVID-19 related
- Reduction in dose or interruptions in study product will be identified as COVID-19 related
- Safety laboratory test results done at local laboratories will not be included
- Early or late safety and efficacy assessments that are done out of window due to COVID-19 will be included as observed values
- Last post-baseline observation carried forward will be used for missing data at incomplete visits or missed visits due to COVID-19 only (sensitivity analyses will be performed on observed cases without LOCF imputation) for the following efficacy endpoints:
    - FEV1 % predicted
    - FEV1
    - CFQ-R respiratory symptom domain score for adolescents and adults
    - CRISS score
- No biomarker values and no pharmacokinetic (PK) values will be carried forward

4.2. Study Efficacy Endpoints

4.2.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the event rate of new PEx per subject per 28 weeks using the primary definition of new PEx comparing the lenabasum 20 mg BID and placebo cohorts. The event rate is based on the occurrence of new PEx, and the occurrence will be assessed during the treatment phase. It is defined as follows:

The primary endpoint will be calculated by the following for each treatment cohort:

Event rate of PEx (per subject-28 Weeks) for a treatment group is calculated as follows:

Total number of PEx using primary definition during the treatment period / [sum of subject treatment exposure durations in the treatment group (days) / 196]

Event rate of PEx (per subject) for a treatment group (without adjustment of treatment exposure) is calculated as follows:

Total number of PEx using primary definition during the treatment period / number of subjects in the treatment group

4.2.2. Secondary Efficacy Endpoints

The secondary efficacy endpoints include the following, all assessed at or through Visit 8 (treatment phase), as relevant:

- Event rate of new PEx per subject per 28 weeks using secondary definition of new PEx, comparing lenabasum 20 mg BID and placebo cohorts
- Time to first new PEx using primary definition of new PEx, comparing lenabasum 20 mg BID and placebo cohorts
- Time to first new PEx using secondary definition of new PEx, comparing lenabasum 20 mg BID and placebo cohorts
- Event rate of new PEx per subject per 28 weeks, using the primary definition of new PEx, comparing lenabasum 5 mg BID and placebo cohorts.
- Event rate of new PEx per subject per 28 weeks, using secondary definition of new PEx, comparing lenabasum 5 mg BID and placebo cohorts
- Time to first new PEx using primary definition of new PEx, comparing lenabasum 5 mg BID and placebo cohorts
- Time to first new PEx using secondary definition of new PEx, comparing lenabasum 5 mg BID and placebo cohorts
- Change in CFQ-R respiratory symptom domain score for adolescents and adults, comparing lenabasum 20 mg BID and placebo cohorts
- Change in FEV1 % predicted, comparing lenabasum 20 mg BID and placebo cohorts
- Change in CFQ-R respiratory symptom domain score for adolescents and adults, comparing lenabasum 5 mg BID and placebo cohorts
- Change in FEV1 % predicted, comparing lenabasum 5 mg BID and placebo cohorts

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[redacted]

- [redacted]
- [redacted]
- [redacted]

[redacted]

4.3. Study Safety Endpoints

4.3.1. Primary Safety Endpoints

- TEAEs by treatment cohorts and combined lenabasum cohorts

[redacted]

[redacted]

4.6. 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 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 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.

5. ASSESSMENT AND DERIVATION OF EFFICACY AND BIOMARKER ENDPOINTS

5.1. Primary Efficacy Endpoint

The primary efficacy endpoint will be based on the occurrence of new PEx. The occurrence of a new PEx will be assessed throughout the active dosing period. The primary comparison of the

lenabasum 20 mg BID treatment cohort to the placebo cohort will be based on the event rate of PEx per subject per 28 weeks using the primary definition of PEx.

The event rate comparison is calculated as follows:

$$\theta = R_l / R_p$$

where R_l is the event rate of PEx per subject per 28 weeks using the primary definition of PEx for the lenabasum treatment cohort, and R_p is the event rate of PEx per subject per 28 weeks using the primary definition of PEx for the placebo group.

See Section 4.2.1 for the calculation of the event rate of PEx per subject per 28 weeks.

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 should 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 AUR-Q (refer to Case Report Form).

The AUR-Q questionnaire includes Fuchs criteria (Fuchs et al, 1994) and a list of additional signs and symptoms, that may have led a physician to make a diagnosis of pulmonary exacerbation. At least 4 out of 12 Fuchs criteria are required to make a diagnosis of a new PEx by the primary definition, but not by the secondary definition.

5.1.1. Primary Definition of New Pulmonary Exacerbation

The derivation for new PEx by the primary definition is provided below. The rules for defining new antibiotics used for new PEx, including the start and stop days, are also provided below.

Primary definition of new PEx:

- Physician diagnosis of PEx
- Prescription of new antibiotics for PEx
- Start date of new antibiotics for PEx is > 28 days after the stop date of any antibiotics given for any previous PEx. The physician does not need to determine if there is > 28 days from last use of antibiotics to the new antibiotics for PEx analysis purposes. The > 28-day gap will be determined centrally
- A new PEx is not defined by the number of antibiotics prescribed or the order of route of administration of the antibiotics (oral or IV) for that new PEx
- ≥ 4 out of 12 Fuchs criteria are met

New antibiotics for PEx

- Must be given for PEx

- Must be administered by oral or IV route
- Start date is day the physician prescribes that the subject should take this antibiotic treatment for a PEx
- Stop date is the last day the physician prescribes that the subject should take this antibiotic treatment for a PEx
- Start day > Day 1
- Start day ≤ Day of Visit 8 or discontinuation from the study
- Regularly given prophylactic inhaled, oral, or IV antibiotics do not count as new antibiotics unless the dose is increased or given early for a PEx

Start day of a new PEx:

The first day that the physician prescribes that the subject should take any new antibiotic treatment for that new PEx

Stop day of a new PEx:

The last day that the physician prescribes that the subject should take any new antibiotic treatment for that new PEx or day of discontinuation from the study, whichever is sooner

5.2. Secondary Efficacy Endpoints

5.2.1. Secondary Definition of Pulmonary Exacerbation

The following derivation is provided for new PEx by the secondary definition. Definitions of new antibiotics for PEx and start and stop days of new PEx are as outlined in Section 5.1.1.

Secondary definition of new PEx:

- Physician diagnosis of PEx
- Prescription of new antibiotics for PEx
- Start date of new antibiotics for PEx is > 28 days after the stop date of any antibiotics given for any previous PEx
- A new PEx is not defined by the number of antibiotics prescribed or the order of route of administration of the antibiotics (oral or IV) for that new PEx

5.2.2. Cystic Fibrosis Questionnaire-Revised Respiratory Domain Score and Other Domain Scores

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.

Actual values and change from baseline in all CFQ-R domain scores will be calculated centrally. Change in CFQ-R respiratory domain at Visit 8 is a secondary efficacy endpoint.

Actual values and change from baseline in all CFQ-R domain scores at all visits, except change in CFQ-R respiratory domain score at Visit 8, are tertiary efficacy endpoints.

5.2.3. Forced Expiratory Volume in 1 Second

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. The FEV1 results will be calculated as % predicted and L (absolute), and FVC results will be calculated as % predicted and L (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 best FEV1, FVC, and other spirometry values will be reported. Blinded FEV1 and FVC data will be reviewed prior to database lock, and any extreme outliers (implausible values) will be identified and excluded from the analyses but displayed in listings

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

Change from baseline in FEV1 % predicted at Visit 8 is a secondary efficacy endpoint.

Actual values and change from baseline in FEV1, FEV1 % predicted, FVC, and FVC % predicted at all visits are tertiary efficacy endpoints, except change in FEV1 % predicted at Visit 8.

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6. GENERAL STATISTICAL CONSIDERATIONS

6.1. Reporting Conventions

All data analysis will be performed by Statistics & Data Corporation after the study is completed and the database has been locked. The following reporting conventions will be used:

- Outputs will be provided in rich text format for tables and portable document format for tables, listings, and figures using landscape orientation.
- Data from all study centers will be combined for analysis.

- All study data will be listed by subject, treatment, and visit (as applicable) based on all randomized subjects unless otherwise specified. Additional data listings will be provided as described in the sections for the data analyses.
- Summaries for continuous and ordinal variables will include: the number of observations (n) of observations, arithmetic mean, standard deviation (SD), median, minimum (min), maximum (max). Unless specified in the actual table shells, the mean, median, first quartile, second quartile, third quartile, (interquartile range), the upper and lower limits of the confidence interval (CI) will be displayed to one more decimal place than the original data (derived analysis data). Standard deviation and standard error values will be displayed to two more decimal places than the original data. Minima and maxima will be displayed to the same number of decimal places as the original data. Summaries for discrete variables will include frequency counts and percentages. All percentages will be rounded to one decimal place (i.e., XX.X%).
- The number and percentage of responses will be presented in the form XX (XX.X%), where the percentage is in parentheses. The denominator of all percentages will be number of subjects in the analysis population, unless otherwise stated. When count data are presented, the percent will be suppressed when the count is zero in order to draw attention to the non-zero counts. A row denoted "Missing" will be included in count tabulations where necessary to account for dropouts and missing values. Non-zero percentages will be rounded to one decimal place, except 100% will be displayed without any decimal places.
- The day of the first dose of study product will be defined as Day 1, which is the day of Visit 1. All study days before Day 1 will be calculated as (assessment date – first dose date of study product). The study day on or post Day 1 will be calculated as (assessment date - first dose date of study product + 1).
- Baseline value for comparisons to Visit 1 will be defined as the last non-missing value on or before Visit 1 and before the first dose of study product**.**
- Change from Baseline will be calculated as the value at post-dose minus the value at pre-dose (Baseline). Differences between treatment cohorts will be calculated as lenabasum minus placebo.
- Listings will be presented for all randomized subjects unless otherwise specified.
- All analyses will be conducted using SAS Version 9.4 or higher.
- The modified intent-to-treat (mITT) population will be the primary population for the efficacy analyses. In addition, supportive analyses using the per protocol population will be conducted for the primary efficacy endpoints and selected secondary endpoints, if relevant.
- All statistical tests will be two-sided with a significance level of 0.05 ($\alpha = 0.05$), unless otherwise specified. All p-values will be rounded to four decimal places; p-values less than 0.0001 will be presented as "<0.0001"; p-values greater than 0.9999 will be presented as ">0.9999."

6.2. Statistical Hypotheses

Primary Endpoint Hypotheses:

H_0: $\theta = 1$

H_1: $\theta \neq 1$

where $\theta = R_l / R_p$,
R_l is the event rate of PEx per subject per 28 weeks using the primary definition of PEx for the lenabasum treatment cohort, and
R_p is the event rate of PEx per subject per 28 weeks using the primary definition of PEx for the placebo group.

Similar hypotheses will apply to the secondary endpoints, where the null hypothesis is the hypothesis of no difference between the active lenabasum dose and placebo, and the alternative hypothesis is that the active lenabasum group differs from placebo.

6.3. Sample Size and Power Considerations

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 event rate in the control group is 0.80.

This also provides 90% power to detect a significant difference between lenabasum 20 mg BID and placebo BID in the secondary endpoint of 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.

6.4. Analysis Populations

There will be four analysis populations.

6.4.1. Modified Intent to Treat Population

The mITT population will consist of all randomized subjects who received study product. The mITT population will be used for all primary and secondary efficacy analyses and will include subjects under the treatment to which they were randomized, regardless of compliance with the assigned treatment.

6.4.2. Per Protocol Population

The per protocol (PP) population will consist of subjects in the mITT population who complete the study without major protocol violations deemed likely to affect the primary efficacy outcome. These deviations will be classified during a blinded deviation review which will occur before unblinding the study. The PP population will be used for sensitivity analyses of the primary efficacy endpoint, including subjects under the treatment received. If the PP population

does not differ from the mITT population by more than 5%, then the sensitivity analyses with the PP population will not be done.

6.4.3. Safety Population

The safety population will consist of all subjects who received any study product. Analyses performed on the safety population will be per the study product received.

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6.5. Subject Disposition

The disposition of all subjects over the course of the trial will be presented for treatment cohorts, combined lenabasum cohorts, and all subjects, using number of subjects and percentages. All percentages will be based on the number of subjects randomized.

Information will be presented on subjects who were or had: screening failures with reasons for screening failures; randomized; subjects randomized but withdrawn before dosing with reasons for withdrawal; in each analysis population; excluded from analysis populations with reasons; completed the study; discontinued from study product but continued in the study with reasons; and discontinued from study with reasons.

6.6. Protocol Deviations

Protocol deviations will be recorded in a deviation log. A blinded review of all protocol deviations will be done prior to database lock to classify the deviations into various categories and determine if they are major or minor protocol deviations, and to determine the subject exclusions from the PP analysis population.

Major protocol deviations for this study include, but are not limited to, any one of the following:

- Failure to comply with Good Clinical Practice guidelines
- Failure to meet major eligibility criteria at randomization
- Use of a prohibited concomitant medication

The number and percentage of subjects with protocol deviations will be summarized by deviation category and type (major/minor) for all treatment cohorts and the combined lenabasum cohort for the mITT population. Protocol deviations with the deviation type of “Major Protocol Violation” or “Minor Protocol Deviation” flagged will be presented in a listing.

7. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

7.1. Demographics and Baseline Characteristics

The demographic and baseline characteristics variables include age (years), sex, race, ethnicity, country (United States; Non-United States), height (cm), weight (kg), BMI (kg/m^2), FEV1 actual value, FEV1 % predicted value, and the number of previous PEx requiring IV antibiotics in the previous year (1; 2; 3). Subjects who record more than one race will be grouped into a single category denoted as Multi-racial. Demographic and baseline characteristics variables will be summarized by treatment cohort, the combined lenabasum group, and all subjects for the mITT, PP, and safety populations, separately. The data will also be summarized by age group (< 18 years; ≥ 18 years) for the mITT population.

7.2. General Medical History

General medical history will be coded using Medical Dictionary for Regulatory Activities, Version 22.1. The number and percentage of subjects with any general medical history will be summarized overall and by coded system organ class and preferred term. A summary table will be presented for treatment cohorts and for combined lenabasum cohort for the safety population. The data will also be presented in a listing.

If a subject reports the same preferred term multiple times within the same system organ class (SOC), the subject will only be counted once for the SOC. As with the preferred term, if a subject reports multiple conditions within the same preferred term, that subject will only be counted once for the preferred term.

7.3. CF Medical History

CF medical history data will be captured at Screening visit. Details of the CF medical history will be summarized for the safety populations in a table and presented in a listing.

The following CF medical history will be summarized for the mITT:

- Age at diagnosis (years)
- Method of diagnosis – sweat test
- CFTR genotype (mutation allele #1, mutation allele #2)
- Previous infections (*Aspergillus*, *Burkholderia cepacia*, *Mycobacterium abscessus*)
- Primary pathogenic species present (yes; no) in sputum cultures at Baseline (*Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Aspergillus fumigatus*, *B. cepacia*, *M. abscessus*, *Streptococcus pneumoniae*)
- Lowest FEV1 % predicted in the last year
- Highest FEV1 % predicted in the last year
- Hemoptysis in the last year
- Number of acute PEx in the last year
- Number of acute PEx treated with IV antibiotics in the last year
- Time since last PEx requiring IV antibiotics (days), calculated as:
  First dose date of study drug – date of the last PEx requiring IV antibiotics + 1
- Antibiotic(s) used prophylactically
- Other organ involvement (Pancreatic insufficiency, diabetes, sinusitis, nasal polyps)

8. TREATMENTS AND MEDICATIONS

8.1. Prior/Concomitant Medications

Concomitant medications will be coded using World Health Organization Drug Dictionary (B3, September 2019) and summarized to the therapeutic drug class (Anatomical Therapeutic Chemical [ATC] 4 classification) and preferred name. If the ATC 4 classification is not provided, the next lowest classification that is provided in the coding dictionary will be used. The preferred name will be defined as the active ingredient; if the active ingredient is not provided or includes more than two ingredients (e.g., multivitamins) then the drug name will be summarized as the preferred name. Any uncoded terms will be summarized under the ATC classification and preferred name of "Uncoded."

Concomitant medications will be summarized using the safety population. Medications will be tabulated for each treatment cohort using number of subjects and percentages. Subjects may have more than one medication per ATC text. At each level of subject summarization, a subject will be counted once if he/she reports one or more medications.

8.2. Study Treatments

8.2.1. Extent of Exposure

Treatment exposure duration will be defined as the number of days that the subject was exposed to study treatment as calculated using the formula:

Exposure duration (days) = date of last dose – date of first dose + 1.

Last dose date will be imputed using last contact date during active treatment for the subjects lost to follow up and as the date of the last visit seen, excluding safety follow-up visit, for subjects missing last dose date.

The duration of exposure will be summarized for treatment cohorts and combined lenabasum cohort. All summaries will be based on the safety population. Summary statistics will be presented for treatment exposure.

8.2.2. Treatment Compliance

Study product compliance during the 28-week treatment period will be calculated for each subject by whether a subject takes all doses of study product as instructed. The number of capsules taken will be calculated by subtracting the number of capsules returned from the number of capsules dispensed during the treatment period.

The study product compliance (%) will be calculated by dividing the total number of capsules taken by the total number of capsules prescribed and then multiplying by 100. For calculations of compliance, the number of capsules prescribed will be adjusted downward if the subject was instructed not to take study capsules on certain days. Reduced dosing after Visit 8 will be excluded from the compliance calculation and summary. The formula below will be used.

Compliance (%) = [(number of capsules dispensed – number of capsules returned) / (number. of days in study for which capsules were prescribed x number of capsules prescribed per day)] x 100

Study product compliance will be presented in a listing by individual and treatment cohort, with compliance presented as continuous variable. A subject will be considered compliant if the study product compliance is ≥ 80% to ≤ 120% of prescribed dose.

The overall study product compliance will be summarized by treatment cohorts and combined lenabasum cohort, with compliance presented as a continuous variable and as number of subjects and percentage of subjects in different categories of compliance (< 80%, 80 – 120%, > 120%), for Visits 2-8.

9. EFFICACY ANALYSES

All efficacy variables will be summarized descriptively by treatment and scheduled visit as applicable using the mITT population. Unscheduled visits including unscheduled Possible PEx visits will be excluded from the efficacy by visit analyses, unless otherwise specified for these visits.

9.1. Handling of Missing Data

Missing data will not be imputed for efficacy and safety analyses unless specified otherwise. See Section 4.1.14 for handling data during COVID-19 pandemic.

If start or end date of antibiotics is incomplete:

- Missing start day only: If month and year are the same as first dose date of study product, impute the antibiotics start date using first dose date of study product, impute the missing day using '01'
- Missing start day and month, but year not missing: If year is the same as first dose date of study product, impute the antibiotics start date using first dose date of study product. If year is not the same as first dose date, impute the missing day using '01' and the missing month using 'Jan'
- Start date missing completely: impute the missing date using first dose date of study product
- Missing end day only: impute the missing end day using the last day of the month
- Missing end day and month, but year not missing: impute the missing day using '31' and missing month using 'Dec'
- Missing end date completely: impute using last visit date

9.2. Discontinuations, Lost to Follow-up, and Unscheduled Visits

All assessments of efficacy and safety done after discontinuation of study drug will be included in primary efficacy and safety analyses, for subjects who permanently discontinue study product, do not withdraw consent, and continue in the study.

If a subject withdraws consent, their last regularly scheduled study visit before withdrawing consent will be their last visit for efficacy and safety assessments.

If a subject is lost to follow-up, their last regularly scheduled study visit that they attended will be considered their last visit.

Efficacy assessments done at Unscheduled Visits and Possible PEx visits will be counted in efficacy analyses, only if AUQ-R at that visit indicates that the subject is having a PEx that meets primary or secondary definitions of a new PEx. Otherwise, efficacy assessments done at unscheduled visits and Possible PEx visits will be included only in listings.

9.3. Adjustments for Multiplicity

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 primary efficacy endpoint will be assessed first. If this comparison yields statistically significant results at two-sided alpha level of 0.05, then the secondary outcomes will be assessed in a hierarchical order for statistical significance.

The Type I error will be controlled for secondary efficacy outcomes with hierarchical assessments of efficacy at a two-sided alpha level of 0.05. If the assessment is not significant, then the analysis of the rest of endpoints will be exploratory. The order for tests for treatment effect in secondary efficacy endpoints is listed in Section 4.2.2.

9.4. Primary Efficacy Analysis

9.4.1. Event Rate of New Pulmonary Exacerbations per Subject per 28 Weeks by Primary Definition

The primary efficacy endpoint is the event rate of new PEx per subject per 28 weeks using the primary definition (Sections 4.2.1 and 5.1), for the comparison of lenabasum 20 mg BID cohort to the placebo cohort, in the mITT population, through Visit 8 (Week 28) which is the treatment period.

The event rate per subject per 28 weeks of new PEx will be compared between the lenabasum and placebo cohorts using a Poisson regression model with effects of treatment and log (subject treatment exposure duration), adjusting for baseline subject characteristics of site location (United States; other countries), number of new PEx requiring IV antibiotics in the previous year (1; 2; 3); FEV1 % predicted (< 70; ≥ 70); and baseline CFTR-targeting medications use (Yes; No – taken concomitantly on Day 1, baseline), and based on the mITT population.

9.4.2. Sensitivity Analyses of Primary Endpoint Analysis

The following sensitivity analyses will be performed using the same statistical method as the primary endpoint analysis, including adjusting for baseline subject characteristics of site location (United States; other countries), number of new PEx requiring IV antibiotics in the previous year (1; 2; 3); FEV1 % predicted (< 70; ≥ 70); and baseline CFTR- targeting medications use (Yes; No):

- The event rate per subject per 28 weeks of PEx will be compared between the lenabasum 20 mg BID and placebo cohorts using a Poisson regression model with effects of treatment and log (subject treatment exposure duration), based on the PP population.

- The event rate per subject per 28 weeks of PEx will be compared in the lenabasum 20 mg BID and placebo cohorts using a negative binomial model with effects of treatment and log (subject treatment exposure duration), based on the mITT population. Negative binomial regression is a generalization of Poisson regression which loosens the restrictive assumption that the variance is equal to the mean made by the Poisson model.
- The event rate per subject per 28 weeks of PEx will be compared in the lenabasum 20 mg BID and placebo cohorts using a negative binomial model with effects of treatment and log (subject treatment exposure duration), based on the PP population.

9.5. Secondary Efficacy Analyses

The secondary efficacy endpoints (Section 4.2.2) will be summarized by treatment cohort. Actual values at each visit for each secondary outcome and changes from Baseline will be analyzed. The analyses and summaries of secondary efficacy endpoints will be performed on the mITT population. All secondary analyses will be at or through Visit 8, whichever is relevant, and will be done on observed values only. Two-sided p-values will be presented.

9.5.1. Event Rate per Subject per 28 Weeks of New Pulmonary Exacerbations by Secondary Definition

Analysis of endpoints for various event rates of PEx will be performed using the same method as the primary analysis in Section 9.4.1.

9.5.2. Sensitivity Analyses of First Secondary Endpoint Analyses

Sensitivity analyses will be done for the first secondary efficacy endpoint only. The lenabasum cohort 20 mg BID will be compared to the placebo cohort. The same sensitivity analyses that are applied to the primary efficacy endpoint (Section 9.4.2) will be done for the first secondary efficacy endpoint.

9.5.3. Time to New Pulmonary Exacerbations

Time to first new PEx (days) for subjects with a new PEx is calculated as:

Date physician initiates antibiotic(s) for first new PEx – first dose date of study drug + 1

Time to first PEx for subjects without a new PEx (days event free) is calculated as:

Date of last dose of study product during the 28-Week treatment period – first dose date of study drug + 1

For time to first new PEx analyses, a Cox-proportional hazards (regression) model will be used for comparing the covariate-adjusted difference in event-time distributions between the active and placebo cohorts. Covariates in the model will include site location (United States; Non-United States), number of new PEx requiring IV antibiotics in the previous year (1; 2; 3); FEV1 % predicted (< 70; ≥ 70); and baseline CFTR-targeting medications use (Yes; No). Hazard ratios will be provided.

A life-table method will be used to estimate survival probabilities in 14-day intervals between Day 1 to 182 plus a final interval of ≥ 183 days. Subjects at risk, number of PEx, number of

censored in each time interval and overall, survival probability in each time interval, Kaplan-Meier estimated first quartile, median and third quartile of time, hazard ratios (lenabasum/placebo) and associated 95% CI, and log-rank p-values will be provided.

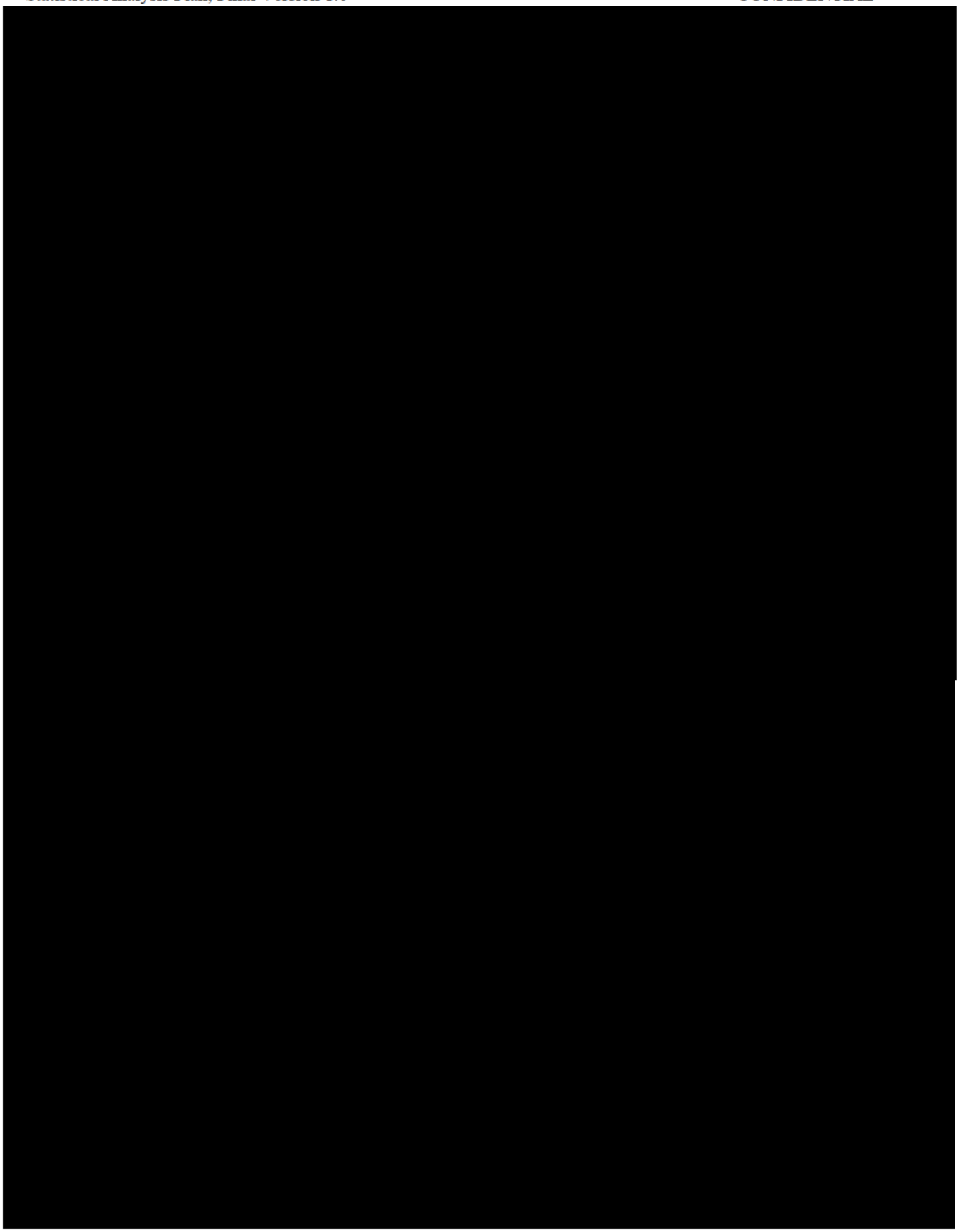
The time to PEx will be evaluated using a Kaplan Meier method. The homogeneity of event time distribution will be tested between each and overall active treatment cohorts as compared to placebo using a log-rank or a weighted log-rank test (Fleming-Harrington) in case of non-parallel curves across groups.

9.5.4. Continuous Variable Secondary Endpoints

Continuous variable secondary efficacy endpoints other than PEx event rate per subject per 28 week endpoints, (change from baseline in CFQ-R respiratory symptom domain score for adolescents and adults, and change in FEV1 % predicted, change in CRISS score) will be analyzed using a parametric mixed model repeated measures (MMRM). The MMRM model will include treatment, site location (United States; other countries), number of new PEx requiring IV antibiotics in the previous year (1; 2; 3); FEV1 % predicted (< 70; ≥ 70); Baseline CFTR-targeting medications use (Yes; No), visit, and treatment-by-visit interaction as fixed effects, and baseline of response variable as a covariate. The parametric MMRM will use unstructured covariance matrix. Least squares means, least squares mean differences and associated 95% CI, and 2-sided p-values will be provided.

If the data are not normally distributed, then nonparametric MMRM analyses will be performed using a ranking strategy that relaxes the assumption of normality. The ranks will be assigned by a visit such that the same rank will be assigned across all treatment cohorts and placebo for a dependent variable measurement. The rank transformed nonparametric model will be analyzed including the fixed and random effects similar to the parametric MMRM model. The nonparametric MMRM model will use unstructured covariance matrix. Least squares means, least squares mean differences and associated 95% CI, and 2-sided p-values will be provided.

Two-sample t-test will be used to compare means for change from Baseline within the same group. Wilcoxon rank sum test analyses will be used to compare medians for change from baseline within the same group, in case of shift from the central tendency. Two-sided p-values will be provided.



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11. SAFETY ANALYSES

All safety summaries will be based on the safety population. No formal statistical testing will be performed to compare the safety in different treatments. Unscheduled and PEx visits will not be included in safety by visit tables, but will be included in a listing, by subject.

11.1. 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.

AEs will be coded using Medical Dictionary for Regulatory Activities, Version 22.1.

Treatment-emergent AEs include all AEs onset between first dose and last dose of the study product, inclusive. TEAEs and AE onset during the 28-day follow-up will be summarized separately. Any AEs that occur before first dosing will be summarized in a table as Pre-Treatment AEs.

An overall summary by treatment cohort will be presented that includes the number and percentage of subjects who experienced at least one TEAE, serious TEAE, TEAEs by maximum severity, TEAEs by strongest relationship to study product, TEAEs leading to study product withdrawal, TEAE of dizziness (Section 11.2), and death. The total number of TEAEs will also be presented. The overall summary of TEAEs will also be presented by age group (< 18 years and ≥ 18 years).

The number and percentages of subjects with the TEAEs listed below will be summarized by SOC, preferred term, and treatment separately. The TEAEs listed below will also be summarized by age group (< 18 years and ≥ 18 years). If a subject reports the same preferred term multiple times within the same SOC, that subject will only be counted once for the SOC. As with the preferred term, if a subject reports multiple conditions within the same preferred term, that subject will only be counted once for the preferred term.

- TEAEs
- Serious TEAEs
- TEAEs leading to study product withdrawal
- TEAEs of dizziness (AE of special interest)
- TEAEs by maximum severity
- TEAEs by strongest relationship to study product
- TEAEs in ≥ 2% of subjects in lenabasum 20 mg BID cohort
- TEAEs of abuse potential; relevant preferred terms include the following:

Anxiety, apathy, bradykinesia, bradyphrenia, cognitive disorder, confusional state, depressed level of consciousness, depressed mood, depression, derealization, disorientation, dissociation, disturbance in attention, dizziness, dyskinesia, dysphoria, elevated mood, euphoric mood, feeling abnormal, feeling drunk, feeling jittery, feeling of relaxation, hallucination, hyperflexia, hypersomnia, hypoaesthesia, hypoflexia, inappropriate affect, insomnia, lethargy, malaise, mental disorder, mental impairment, mobility decreased, mood altered, nervous system disorder,

nervousness, neuralgia, panic attack, paraesthesia, restlessness, sleep disorder, sluggishness, somnolence, stupor, thinking abnormal, vision blurred, visual disturbance, visual impairment, sensory disturbance, amnesia, irritability, memory impairment, agitation, and any other related terms

The total number of TEAEs by SOC and preferred term will also be presented.

Similar to TEAEs tables, another set of tables for follow-up AEs will be provided.

In addition to an overall AE listing, serious AEs, AEs leading to study product withdrawal, fatal AEs, and AEs of special interest will also be presented in subject data listings.

11.2. Adverse Event of Special Interest of Dizziness

The adverse event of special interest of dizziness will also be recorded in detail, and narratives will be generated for this AE of special interest with Grade 2 or above. The additional information that will be collected for AEs of dizziness are noted in Table. The AEs of dizziness will be characterized in a summary table, by treatment cohorts and combined lenabasum cohorts, cumulatively through Visit 8 and during the 28-day safety follow-up period. The characteristics will include age, gender, race, past history of dizziness, dizziness AEs that lead to permanent study product or study discontinuation, maximum severity, strongest relationship to study product, day or onset, duration, number of subjects with recurrent AEs of dizziness, and occurrence period while receiving active treatment drug (all, ≤ Day 30, > Day 30 to ≤ Day 90, ≥ Day 90 through Visit 8) and during the safety follow-up period).

Table 2 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)

11.3. Clinical Laboratory Tests

For serum chemistry and hematology, the results for each parameter in the International System of Units will be summarized by treatment and visit using continuous summaries. Change from baseline and shift tables will also be provided comparing post-baseline visits with baseline.

For urine dipstick tests, the results for each parameter will be summarized by treatment at each visit using number of subjects and percentages for each result category.

Serum and urine pregnancy test results will be provided in a data listing only.

11.4. Vital Signs

Vital signs will include systolic blood pressure, diastolic blood pressure, pulse rate, respiratory rate, body temperature, oxygen saturation, weight, and height as safety endpoints. BMI is an efficacy endpoint and the analysis of BMI is included as a tertiary efficacy outcome (Sections 5.3.3 and 9.6.3).

The actual values and change from baseline for every post-baseline visit in each parameter will be summarized by treatment and visit.

11.5. Physical Examination

Physical examination results will be presented in a listing only. A listing of medically significant abnormal physical examination results will also be provided.

11.6. Twelve-Lead Electrocardiogram

Electrocardiogram (ECG) parameters include heart rate, RR interval, QRS duration, PR interval, QT interval, QT interval correction by Fridericia's formula, and if needed by Bazett's formula. In addition, ECG evaluation of abnormality and interpretive statements will also be reported.

The actual values and change from baseline for every post-baseline visit/time point in each ECG parameter will be summarized by treatment and visit/time point.

Electrocardiogram evaluation of abnormality (normal versus abnormal) will be summarized by treatment and visit/time point using number and percentage of subjects in each result category.

11.7. Analyses of Safety Endpoints for Subjects at Sites in France Only

Safety endpoints derived from questionnaires answered by subjects at sites in France only (Section 4.3.3) will be provided in subject data listings and summarized descriptively by treatment cohort and the combined lenabasum cohort. The analyses will be based on the safety population in France and done at the visits at which the data are collected for the relevant endpoint.

[redacted]

[redacted]

13. CHANGES FROM PROTOCOL-STATED ANALYSES

- The randomization schedules were initially set up stratified by 1 or 2 versus 3 number of previous PEx requiring IV antibiotics in the previous year as per protocol version 1. Protocol version 3.1 states that the randomization is stratified by 1 versus 2 or 3 number of previous PEx requiring IV antibiotics in the previous year. However, the IWRS was not updated to reflect this change until after 185 subjects had been randomized. Therefore, the number of previous PEx is treated as a continuous variable in the model for the primary and secondary efficacy endpoints.

- The efficacy and safety analyses will generally be based on on-treatment, from start of treatment to end of the treatment period at Week 28. For subjects discontinuing the study early, the treatment period will end at time of discontinuation. The safety follow-up period will be summarized separately for the AEs.

- Additional analyses and methods for handling missing data due to COVID-19 have been incorporated as described in Section 4.1.14, according to recommendations from the FDA COVID-19 related Guidance dated March 2020 and June 2020.

- Additional detail has been added to the SAP regarding the tertiary objectives to facilitate programming and analyses.

- Baseline CFTR-targeting medications use (Yes; No) was added to applicable statistical models.

14. CHANGES FROM STATISTICAL ANALYSIS PLAN

Changes from this statistical analysis plan will be described in the statistical analysis section of the CSR.

15. REFERENCES

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