STUDY PROTOCOL

Protocol Title: A Phase 2, Double-blind, Randomized, Placebo-controlled Study to Investigate the Safety, Tolerability, and Efficacy of JBT-101 in Subjects with Dermatomyositis

Protocol Number: JBT101-DM-001

Identifier: NCT02466243

Study Product:	Lenabasum (formerly known as anabasum, also known as JBT-101)
IND Number:	116313
Indication:	Dermatomyositis
Phase:	2
Name and Affiliation of Principal Investigator:	[redacted]
Name and Address of IND Sponsor:	Corbus Pharmaceuticals, Inc. 500 River Ridge Drive, Second Floor Norwood, MA 02062 Telephone: 617-963-0100
Name and Address of Funding Agency:	[redacted]
Good Clinical Practice Statement:	This study will be performed in compliance with Good Clinical Practice, including the archiving of essential documents.

1. SYNOPSIS

TITLE: A Phase 2, Double-blind, Randomized, Placebo-controlled Study to Investigate the Safety, Tolerability, and Efficacy of JBT-101 in Subjects with Dermatomyositis

STUDY PRODUCT: Lenabasum (formerly known as anabasum, also known as JBT-101)

INDICATION: Dermatomyositis

PHASE OF DEVELOPMENT: 2

INVESTIGATIONAL SITES/LOCATION:

[redacted]

OBJECTIVES: This study will explore the use of lenabasum as a novel, non-immunosuppressive, pharmacologic treatment to resolve pathologic immune responses in dermatomyositis (DM).

Primary Objectives:

1. Evaluate the safety [vital signs, physical examinations including muscle strength, adverse events (AEs), blood and urine laboratory safety tests, electrocardiograms (ECGs) with QT/QTc intervals, psychotropic activity] and tolerability of lenabasum in subjects with skin-predominant DM;
2. Evaluate the efficacy of lenabasum in skin-predominant DM, measuring changes from baseline in the Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI) activity score, a validated measure of skin disease severity.

[redacted]

[redacted]

STUDY DESIGN:

The study has been broken into two parts; Part A and Part B.

Part A. An interventional, double-blind, randomized, placebo-control design will be used. Approximately 33 subjects will be screened to identify 22 eligible males and females ≥ 18 and ≤ 70 years of age (at the time of signing consent) with moderate-to-severely active skin-predominant DM. Subjects will be randomized in a 1:1 ratio to receive:

- Cohort 1: lenabasum 20 mg q a.m. on Days 1-28, then lenabasum 20 mg q a.m. and 20 mg q p.m. on Days 29-84; or
- Cohort 2: Placebo q a.m. on Days 1-28, then placebo q a.m. and placebo q p.m. on Days 29-84.

Screening will be up to 28 days prior to Visit 1 and there will be seven study visits, Visits 1-7 on Days 1, 15 ± 3, 29 ± 3, 43 ± 3, 57 ± 3, 85 ± 3 and 113 ± 3, respectively. Vital signs, adverse events, and blood laboratory safety tests, and CDASI will be assessed on Visits 1-7. Electrocardiograms with QT/QTc intervals will be done on Visits 1, 3, 5, and 6. Tolerability will be assessed on Visits 1-6. C-reactive protein will be assessed on Visits 1-3 and 5-7. Metabolipidomic profiles and lenabasum plasma concentrations will be measured on Visits 1-3, 5, and 6. Urine pregnancy testing for women of childbearing potential, creatine phosphokinase, aldolase, Manual Muscle Testing-8, Physician Global Assessment, Patient Global Assessment, Skindex-29+3, and Patient-Reported Outcomes Measurement Information System (PROMIS)-29 Short Form will be assessed on Visits 1, 3, and 5-7. Additional physical examination will be done on Visits 1, 6 and 7. The Addiction Research Center Inventory – Marijuana (ARCI-M) scale, levels of IFNα, type I IFN gene signature, cytokines levels in the blood, and cytokine production by peripheral blood mononuclear cells will be measured on Visits 1, 3, and 6. Optional punch biopsies of lesional and non-lesional skin will be taken on Visit 1 and repeated for lesional skin at nearby anatomical sites on Visits 3 and 6, for assessment of skin biomarkers and histology. Optional skin photography also will be assessed at Visits 1, 3, and 6.

Part B. An interventional, open-label design will be used. All subjects who complete dosing in Part A without permanent discontinuation of study product for safety reasons or intolerance and who pass repeat safety screening will be eligible for enrollment (n = ~20-22). Subjects will receive lenabasum 20 mg twice a day (bid). Based on safety and tolerability, the dose of lenabasum may be decreased to 20 mg once a day (qd) or less, starting with Visit 1 and anytime thereafter. The dose can be increased up to 20 mg three times a day (tid) starting with Visit 8, or any time thereafter, for consenting OLE subjects that meet pre-specified criteria (Section 7.1).

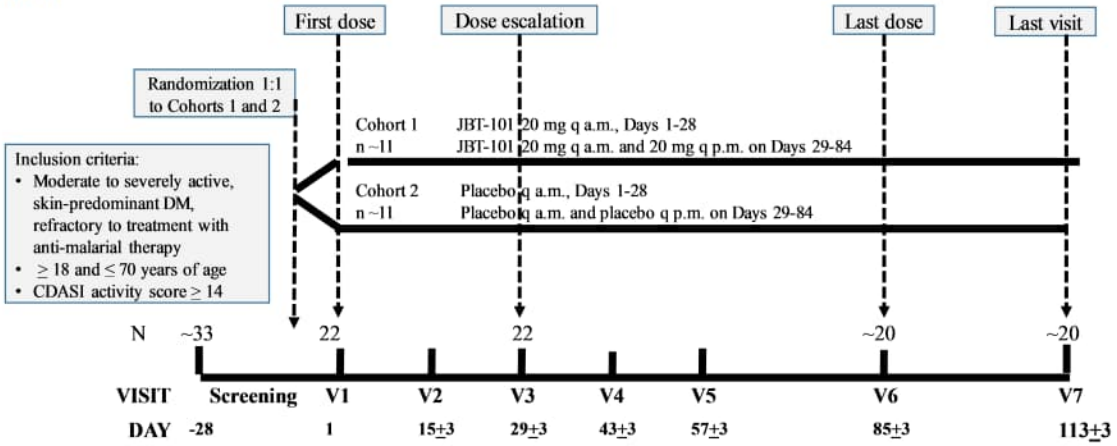
Screening will be up to 28 days prior to Visit 1. In the Year 1 Extension, there will be 8 study visits: Days 1, 29 ± 7, 85 ± 7, 141 ± 7, 197 ± 7, 253 ± 7, 309 ± 7 and, 365 ± 7. For subjects who choose not to participate in the Year 2 Extension, a Follow-up Visit will occur on Day 393 ± 7. Subjects who consent to the Year 2 Extension will have Visits 9-15 on Days 421 ± 7, 477 ± 7, 533 ± 7, 589 ± 7, 645 ± 7, 701 ± 7, and 757 ± 7. Subjects that do not consent to a third year of

open-label treatment (Year 3 Extension) will have a Follow-up Visit on Day 784 ± 7. In the Year 3 Extension there will be 7 study visits and a Follow-up Visit. Visits 16-22 will occur on Days 813±7, 869±7, 925±7, 981±7, 1037±7, 1093±7, and 1149±7. Subjects that do not consent to a fourth year of open-label treatment (Year 4 Extension) will have a Follow-up Visit on Day 1177±7. In the Year 4 Extension there will be 7 study visits and a Follow-up Visit. Visits 23-29 will occur on Days 1205±7, 1261±7, 1317±7, 1373±7, 1429±7, 1485±7, and 1541±7. The Follow-up Visit will occur on Day 1569±7 for subjects completing the study. The open-label extension (OLE) may be extended beyond Year 4. The site will be notified by an administrative memo as to any extension and will inform their IRB. Each year of the extended OLE will include 7 study visits and will follow the same design and procedures as described for the Year 4 Extension. At the investigator's discretion, consenting subjects will rollover at the conclusion of Visit 29. The extension visits will be captured in the electronic data capture (EDC) from Visit 29B in sequential order (e.g., Visit 30B – Visit 36B for Year 5 Extension). Should the OLE be extended, subjects' Follow-up Visit will only occur at the completion of the study.

Unless consent is withdrawn or the subject is lost to follow-up, subjects who are permanently discontinued from study product, or choose not to continue for an additional year in the OLE, as applicable, (e.g., subjects not continuing from Year 3 to Year 4 Extension) will have a Withdrawal Visit approximately 28 days after the last dose of study product, as possible. Assessments performed at study visits will be as noted in the study flow chart.

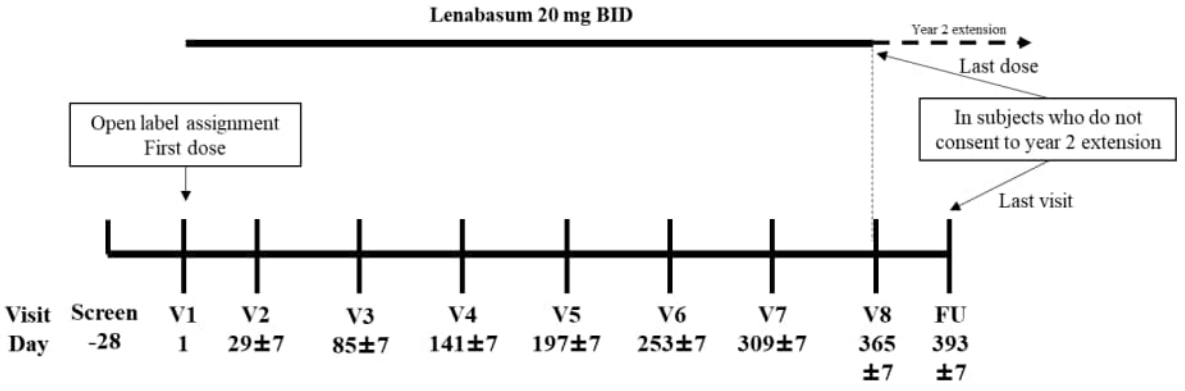
Study Schematics:

Part A:

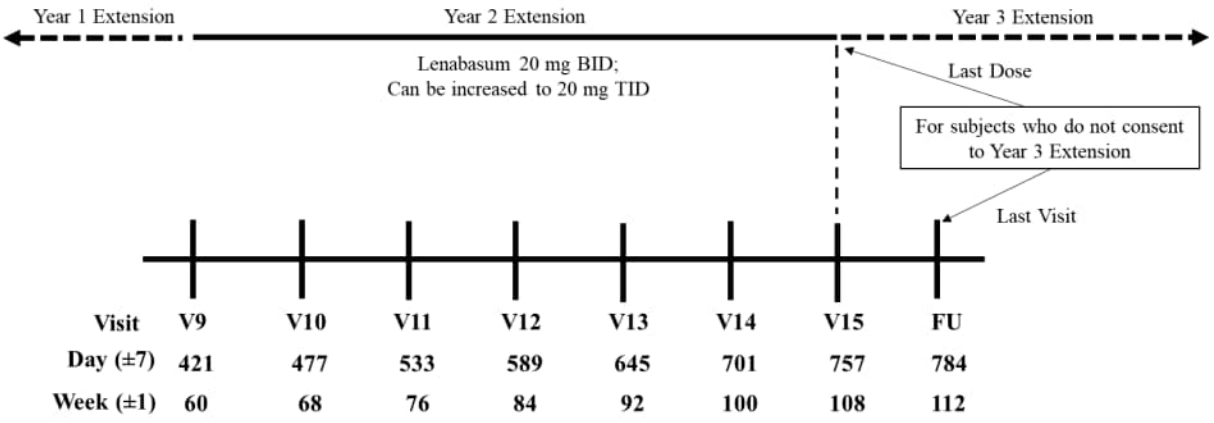


JBT-101 = Lenabasum

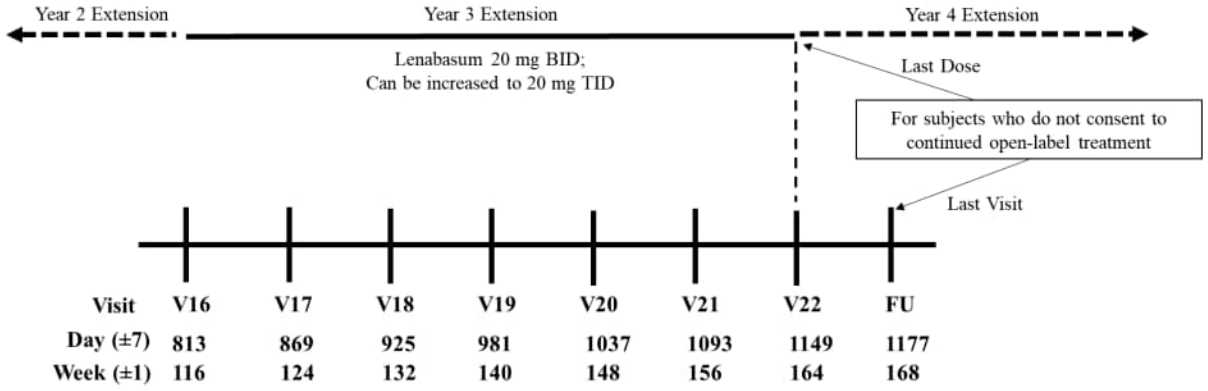
Part B Year 1



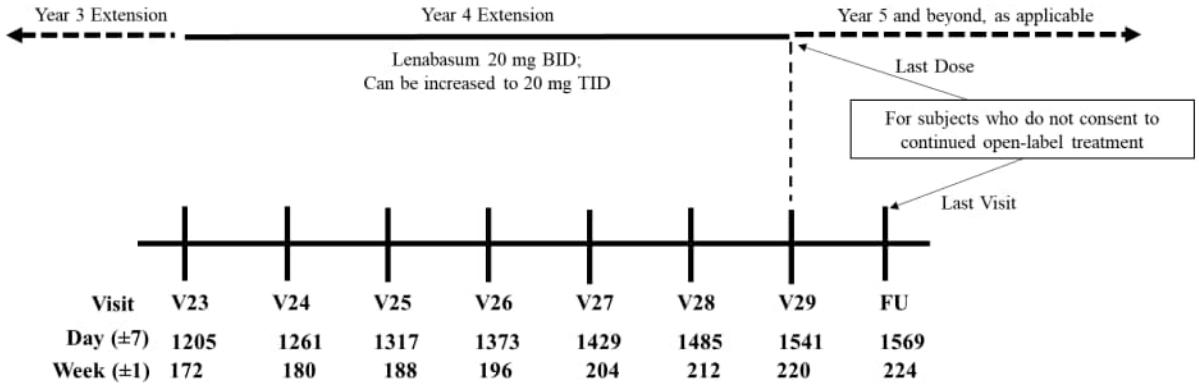
Part B Year 2



Part B Year 3



Part B Year 4



NUMBER OF SUBJECTS PLANNED: Twenty-two subjects to be enrolled into the study from a pool of about 33 screened subjects. Subjects in active screening when the 22nd subject is randomized may enter the trial, if eligibility criteria are met.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION AND EXCLUSION:

The diagnosis criterion is to fulfill Bohan and Peter's or Sontheimer's criteria for classification of DM.

Key inclusion criteria, Part A:

1. ≥ 18 and ≤ 70 years of age at the time the Informed Consent Form is signed;
2. CDASI activity score ≥ 14;
3. No difficulty with lifting or walking, and no more than 1.5 x the upper limit of normal of creatine phosphokinase or aldolase;
4. Failed treatment with hydroxychloroquine;
5. Stable treatment for DM for at least 28 days before Visit 1.

Key inclusion criteria, Part B:

1. Completion of dosing in Part A without permanent discontinuation of study product because of safety or tolerability reasons.

Key exclusion criteria, Parts A and B:

1. Significant diseases or conditions other than DM that may influence response to the study product or safety;
2. Any one of the following values for laboratory tests at Screening:
   a. A positive pregnancy test (or at Visit 1);
   b. Hemoglobin < 10 g/dL;
   c. Neutrophils < 1.0 x 10^9/L;
   d. Platelets < 75 x 10^9/L;
   e. Creatinine clearance < 50 ml/min according to modified Cockcroft-Gault equation;
   f. Aspartate aminotransferase, alanine aminotransferase, or alkaline phosphatase > 2.5 x upper normal limit;
   g. Total bilirubin ≥ 1.5 x upper limit of normal.
3. Any other condition that, in the opinion of the investigator, is clinically significant and may put the subject at greater safety risk, influence response to study product, or interfere with study assessments.

See body of protocol for full list of inclusion and exclusion criteria.

STUDY PRODUCTS, DOSE AND MODE OF ADMINISTRATION:

Lenabasum 20 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 that preferentially binds to and acts as a full agonist of cannabinoid receptor type 2, activating molecular mechanisms to resolve ongoing innate immune responses and inflammation;
- Placebo: Microcrystalline cellulose (no active ingredient), with an appearance and weight matched to lenabasum.

Lenabasum and placebo are packaged as powder-in-capsule in identical no. 2 gelatin capsules. Oral doses are:

Part A:

- Cohort 1: lenabasum 20 mg q a.m. on Days 1-28, then lenabasum 20 mg q a.m. and 20 mg q p.m. on Days 29-84; or
- Cohort 2: Placebo q a.m. (microcrystalline cellulose 10 mg) on Days 1-28, then placebo q a.m. and placebo q p.m. on Days 29-84.

Part B:

- Lenabasum 20 mg q a.m. and 20 q p.m. Treatment may be decreased to 20 mg qd or lower, in the judgment of the investigator for reasons of safety or tolerability, or may be increased to 20 mg tid (starting with Visit 8, or any time thereafter, for consenting subjects that meet pre-specified criteria [Section 7.1]).

Subjects will self-administer study product, which will be taken by the oral route. The first dose of study product on Visit 1 in Parts A and B will be given in the clinic, and the subjects will be observed in the clinic for at least 30 minutes following that dose.

DURATION OF TREATMENT:

Part A: 84 days of treatment with a 28-day follow-up period.

Part B: Approximately 365 days for the first year of OLE then approximately 336 days for each year thereafter

DISCONTINUATION FROM TREATMENT:

Removal of Subjects from Therapy or Assessments:

Interruption of continued dosing in individual subjects may occur for safety reasons and at the discretion of the investigator or the Medical Monitor, if it is felt that interruption of dosing is in the best interest of the subject. An individual subject will not receive any further study product if any of the following occur in the subject in question:

- Withdrawal of consent;
- Pregnancy;
- Any serious or life-threatening AE related to lenabasum;
- Other event that, in the opinion of the investigator or the Medical Monitor, contraindicates further dosing such as repeated failure to comply with protocol requirements, concurrent illnesses or disease complications;
- Subject now meets an exclusion criterion (either newly developed or not previously recognized) that, in the opinion of the investigator or the Medical Monitor, precludes further study participation;
- Subject lost to follow-up.

It is possible that subjects' disease may flare after withdrawal of study product, but there are no foreseen serious health complications predicted with abrupt withdrawal of the study product. Unless consent is withdrawn or the subject is lost to follow-up, subjects who are permanently discontinued from study product, or choose not to continue for an additional year in the OLE, as applicable, (e.g., subjects not continuing from Year 3 to Year 4 Extension), will have a Withdrawal Visit approximately 28 days after the last dose of study product, as possible, in Parts A and B.

Premature Termination or Suspension of Study:

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

- Death in any subject related to lenabasum;
- Any life-threatening clinical event (Grade 4 National Cancer Institute Common Terminology Criteria for Adverse Events criteria) related to lenabasum;
- Determination of unexpected, significant, or unacceptable risks to subjects that contraindicate further dosing of additional subjects, in the opinion of the principal investigator or the Medical Monitor;
- Any new information about the execution of the trial that, in the opinion of the principal investigator or Corbus Pharmaceuticals, Inc. (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 product may continue during the time of review in subjects who are already receiving study product, based on the judgment of the principal investigator and in consensus with the Medical Monitor.

An expedited and cumulative review of safety data and the circumstances of the event(s) in question will be conducted by the Safety Monitoring Committee, with additional external expertise as needed, to make recommendations to the principal investigator and Corbus whether study entry/randomization and dosing 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 terminated permanently by Corbus, in consensus with the principal investigator.

Written notification, documenting the reason for study suspension or termination, will be provided by Corbus to the Food and Drug Administration (FDA). If the study is suspended or prematurely terminated, the investigator will promptly inform the reviewing Institutional Review Board(s) and will provide the reason(s) for the suspension or termination. Review and approval by the reviewing Institutional Review Board(s) will be required for resumption of the study in the event the study is suspended because of one of the above-listed events.

SAFETY ENDPOINTS:

The main safety parameters that will be assessed are:

- Vital signs;
- Physical examination including Manual Muscle Testing-8;
- Adverse events;
- Blood and urine laboratory safety assessments including:
  - Complete blood count with differential and platelets;
  - Metabolic panel that includes electrolytes, renal function and liver function tests;
  - Urine dipstick;
  - Pregnancy tests for women of childbearing potential;
- 12-lead ECGs, including QT/QTc measurements;

- National Institute of Drug Abuse Addiction Research Center Inventory-Marijuana scale (Part A only).

Tolerability will be assessed by incidence of discontinuation of study product due to adverse events related to study product from Visits 1-6 in Part A and Visit 1-last dose in Part B.

PRIMARY EFFICACY ENDPOINT:

- Cutaneous Dermatomyositis Disease Area and Severity Index activity score

SECONDARY ENDPOINTS:

[redacted]

PHARMACOKINETIC ENDPOINTS:

[redacted]

STATISTICAL ANALYSIS:

The final Statistical Analysis Plan, database lock, data analyses, and generation of Tables, Listings, and Figures will be done separately for Parts A and B. The Statistical Analysis Plan for Part A and Part B will be completed before database locking and data analyses for Part A and Part B, respectively.

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, by Part A or B. 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 one decimal place. Differences between treatment groups will be calculated as active – placebo (Part A only) and change from baseline will be calculated as follow-up visit – baseline. The baseline measure will be defined as the last non-missing measure prior to initiation of study product. In Part A, p-values for the CDASI activity score will be assessed at a 2-sided alpha =

0.05 level and for other efficacy outcomes at a 1-sided alpha = 0.10 level, unless otherwise noted. Adjustments for multiplicity will not be made due to the early phase of the study.

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

DOCUMENT APPROVAL

By my signature, I agree to personally supervise the conduct of this study at my study site and to ensure its conduct is in compliance with the protocol, informed consent, Institutional Review Board (IRB)/Ethics Committee (EC) procedures, instructions from Corbus representatives, the Declaration of Helsinki, ICH Good Clinical Practices Guidelines, and local regulations governing the conduct of clinical studies.

[redacted]

Signature of Investigator **Date**

[redacted]

Printed Name of Investigator

Institution Name: [redacted]

This study will be conducted in compliance with the protocol, Good Clinical Practice and applicable regulatory requirements.

SPONSOR REPRESENTATIVE

[redacted]

Signature **Date**

[redacted]

Printed Name

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2. LIST OF ABBREVIATIONS

AE	Adverse event
ARCI-M	Addiction Research Center Inventory-Marijuana
AUC	Area under the curve
bid	Twice per day
BP	Blood pressure
CB	Cannabinoid
CB1	Cannabinoid type 1 receptor
CB2	Cannabinoid type 2 receptor
CBC	Complete blood count
CDASI	Cutaneous Dermatomyositis Disease Area and Severity Index
CFR	Code of Federal Regulations
C_{max}	Concentration maximum
Corbus	Corbus Pharmaceuticals Inc.
CPK	Creatine phosphokinase
CRF	Case report form
CRP	C-reactive protein
CTCAE	Common Terminology Criteria for Adverse Events
DEA	Drug Enforcement Administration
DM	Dermatomyositis
ECG	Electrocardiogram
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IFN	Interferon
IFNα	Interferon alpha
IFNγ	Interferon gamma
IL	Interleukin
IND	Investigational New Drug Application
IP	Investigational product
IRB	Institutional Review Board
ITT	Intent to treat
LMP	Last menstrual period
LSmeans	Least Squares Means
MAD	Multiple ascending dose
MMT-8	Manual muscle testing-8
MOP	Manual of Procedures

msec	Milliseconds
N	Number
NCI	National Cancer Institute
NIAMS	National Institute of Arthritis, Musculoskeletal, and Skin Disease
NOAEL	No observed adverse effect level
P	Pulse
PBMC	Peripheral blood mononuclear cell
PHI	Protected Health Information
PG	Prostaglandin
PK	Pharmacokinetic(s)
PP	Per protocol
PROMIS	Patient-Reported Outcomes Measurement Information System
qd	Once per day
QTc	Corrected QT
R	Respiratory rate
SAD	Single ascending dose
SAE	Serious adverse event
SID	Subject identification number
SPMs	Specialized Pro-resolving Lipid Mediators
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment emergent adverse event
THC	Tetrahydrocannabinol
tid	Three times per day
TLR	Toll-like receptors
TNFα	Tumor necrosis factor α
US	United States
VAS	Visual analogue scale
WOCBP	Woman (women) of childbearing potential

3. ETHICAL CONDUCT OF THE STUDY AND REGULATORY REQUIREMENTS

3.1. Ethical Conduct of the Study

This study will be conducted in accordance with U.S. 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 (IRBs) (21 CFR 84), and Obligations of Clinical Investigator (21 CFR 312), in compliance with the approved protocol, Good Clinical Practice (GCP) Food and Drug Administration (FDA) Title 21 part 312 and International Conference on Harmonization [ICH] guidelines, applicable government regulations, and institutional research policies and procedures. The site investigator (hereafter called investigator) will ensure, through reporting to Corbus, that the FDA is advised of all changes post initiation that may in any way affect the safety of subjects.

3.2. Institutional Review Board (IRB)

This protocol and any amendments will be submitted to the reviewing central or local IRB (hereafter referred to as IRB) for review and approval before the study is begun. The IRB will review the protocol, the informed consent form, written materials given to the subjects, and other regulatory documents. The IRB's written unconditional approval of the study protocol and the informed consent form will be in the possession of the investigator and Corbus Pharmaceuticals Inc. (hereafter called Corbus, which includes Corbus Pharmaceutics Inc. and its designees), before the study is initiated. The IRB's unconditional approval statement will be transmitted by the investigator or qualified designee to Corbus before shipment of study product supplies to the site. This approval must refer to the study by exact protocol title and number and should identify the documents (date and version) reviewed and the date of review, as well as any updates after initial approval.

All subjects for this study will be provided an informed consent form that describes the study and provides sufficient information for them to make an informed decision about their participation in this study. Separate IRB approved consent form will be signed by the subject for Part A and Part B of the study and witnessed by a member of the research team before any study related procedures are performed. The consent for Part A will be signed prior to any assessments for eligibility for Part A. The consent for Part B will be signed separately and not before Visit 6 in Part A. A subject can participate in Part A and decline participation in Part B. In contrast, a subject cannot participate in Part B without participating in Part A.

The informed consent will include optional consents for skin photography, skin biopsies, storage and use of left-over blood and skin samples for future autoimmunity research, and sharing of and use of left-over samples outside of the site's institution for future autoimmunity research.

Any amendment to the protocol will be written by the principal investigator or Corbus, in consensus with the other. Protocol and/or informed consent modifications or changes may not be initiated without prior written approval by the IRB except when necessary to eliminate immediate hazards to the subjects or when the change(s) involves only logistical or administrative aspects of the study. Such modifications will be submitted to the IRB and written verification that the modification was submitted should be obtained.

The investigator or qualified designee is required to notify the IRB of:

- Revisions of documents originally submitted for review;
- Serious adverse events (SAEs) including Suspected Unexpected Serious Adverse Reaction (SUSARs) occurring during the study [Corbus and the National Institute of Arthritis, Musculoskeletal, and Skin Disease (NIAMS) Safety Monitor also will be notified];
- New information that may affect adversely the safety of the subjects or the conduct of the study (Corbus and the NIAMS Safety Monitor also will be notified);
- Pregnancies occurring in female subjects (Corbus and the NIAMS Safety Monitor also will be notified);
- Annual update and/or request for re-approval;
- Suspension or premature termination of the study. Review and approval by the IRB is required for resumption of the study, in the event the study is interrupted;
- Study completion.

The investigator must keep on file copies of all adverse event (AE) information, including correspondence with Corbus, the Safety Monitoring Committee, and the IRB. All IRB records related to this investigation will be retained by the investigator for at least three years after completion of the research.

This study will be monitored according to guidelines set forth by the governing institution and the IRB. The investigator will permit study-related monitoring, audits and inspections of all study related documents by the IRB or its designated representatives.

The approving IRBs affirm the subject's right to protection against invasion of privacy. Should direct access to medical records require a waiver or authorization separate from the subject's statement of informed consent, the investigator or qualified designee is obligated to obtain such permission in writing from the appropriate individuals.

3.3. Subject Information and Consent

The investigator or designated staff will prepare the informed consent form and Health Insurance Portability and Accountability Act (HIPAA) authorization and provide the documents to Corbus for approval prior to submission to the IRB. The consent form generated by the investigator must be acceptable to Corbus and be approved by the IRB. The written consent document will embody ICH elements of informed consent and will also comply with local regulations. The investigator will send an IRB-approved copy of the informed consent form 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. Informed consent will be obtained in accordance with 21 CFR 50.25 by the investigator or qualified designee. 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 forms must be written so as to be understood by the prospective subject. The explanation of the investigation will be in language that is understandable to the individual. Subjects who so choose

will be given the opportunity to take the consent form home for review with other family members or their medical doctor.

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

Subjects must also be informed of alternative procedures. 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. Subjects must be informed about 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 consent forms must be written in language that is understandable to subjects, and opportunity to ask questions about the study must be given. [redacted]

A subject may agree to participate or decline to participate in any sub-study. The choice will have no effect on eligibility for the main study, and it will not interfere with the benefits to which he/she is otherwise entitled.

The extent of the confidentiality of subject records must be defined. Subjects must be informed that the study will comply with applicable data protection legislation. Health Insurance Portability and Accountability Act authorization 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), the Medical Monitor, the NIAMS Safety Monitor, auditor(s), IRB 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.

Informed consent will be documented by the use of a written consent form approved by the IRB that is signed and dated by the subject, and witnessed by the person who conducted the informed consent discussion. The signature confirms the consent is based on information that has been understood. Each subject's signed informed consent form must be kept on file for possible inspection by regulatory authorities, including regulatory compliance personnel representing Corbus. The subject should receive a copy of the signed and dated written informed consent form and any other written information provided to the subjects.

4. INTRODUCTION

This document is a protocol for a human research study of lenabasum for treatment of skin-predominant DM.

4.1. Background Information

Lenabasum is a Schedule I drug that will be investigated for use in several inflammatory and autoimmune conditions, especially those accompanied by some degree of tissue fibrosis, including dermatomyositis (DM), systemic sclerosis, and cystic fibrosis. Lenabasum is not approved by the FDA or any regulatory body for any indication.

Dermatomyositis is a severe autoimmune disease with distinctive cutaneous symptoms that may be accompanied by inflammatory muscle disease. Dermatomyositis strikes older people, with most common age of onset between 50-60 years (Tansley et al., 2013). The disease may also include lung (classically interstitial lung disease), joint, esophageal, and cardiac findings. Patients with DM have an increased risk of malignancy, most commonly in older patients. Current therapies are frequently ineffective and often include toxic immunosuppressive therapies.

The skin findings in DM are rashes characterized by erythema and often pruritus in the scalp, face, dorsum of the hands, upper back, and photo-exposed areas (Klein et al., 2007). The lesions are obviously visible and disfiguring, having a large impact on patient quality of life. Goreshi et al., (2011) observed that skin-specific quality of life measures for patients with DM were comparable to those of patients with cutaneous lupus erythematosus and vulvodynia, and much higher than those of many other dermatologic diseases. His study also found that the physical symptoms of DM were worse than those of cutaneous lupus erythematosus, Type 2 diabetes, clinical depression, and hypertension. The social and emotional symptoms of DM were worse than those of congestive heart failure, recent myocardial infarction, Type 2 diabetes, and hypertension.

At least 20% of the 60,000 individuals in the U.S. with DM have skin predominant disease, and many more have active skin disease despite successful treatment of their muscle and/or lung disease (Bendewald et al., 2010). The first line treatment for cutaneous DM disease is antimalarial therapy, which frequently is ineffective, or can cause drug reactions (Pelle et al., 2002; Ang et al., 2005). Antimalarial-refractory disease is then treated with systemic therapies that may additionally cause toxicity, including systemic glucocorticoids, immunosuppressive therapies, or long-term intravenous immunoglobulin.

More effective and safer therapeutic approaches for patients with cutaneous DM who are refractory to antimalarial therapy are needed. Relevant to this unmet medical need, it is well established that specific chemical modifications of tetrahydrocannabinol (THC) can increase its potency (Loev et al., 1973) and render it free of central nervous system activity. This strategy was employed to design lenabasum (Burstein et al., 1992) in which the pentyl side chain has been extended from 5 to 7 carbons, with 2 methyl groups added to increase specific receptor affinity and a carboxylic acid added at the 9 position to reduce blood brain barrier penetration. The resulting orally administered compound has little to no psychotropic activity, especially at likely therapeutic doses. A newer formulation of lenabasum, to be used in this trial, has a 12 times greater affinity for the cannabinoid (CB) type 2 receptor (CB2) than the cannabinoid type 1 receptor (CB1), which reduces even further any potential central nervous system effect.

Cannabinoid receptors are G-protein coupled receptors that are part of the primitive endocannabinoid system. 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, myocytes, epithelial cells, fibroblasts, osteoblasts, skin keratinocytes, and the peripheral nervous system (Rom and Persidsky, 2013). CB2 plays a role in modulating and resolving inflammation by, in effect, turning inflammation "off" through the production of Specialized Pro-resolving Lipid Mediators (SPMs) (Serhan et al., 2008), such as lipoxin A4.

Lenabasum binds CB2 which are localized at endolysosomes, where CB2 activation releases Ca^{++} from inositol 1,4,5-trisphosphate-sensitive- and acidic-like Ca^{++} stores and elicits Ca^{++} signaling (Brailoiu et al., 2014). CB2-mediated release of intracellular Ca^{++} in turn releases arachidonic acid from cellular membranes (Hunter and Burstein, 1997, Stebulis et al., 2008). Ordinarily, the release of arachidonic acid would promote inflammation, but lenabasum also induces "class switch" of arachidonic acid metabolism from pro-inflammatory lipid mediators to anti-inflammatory lipid mediators, or SPMs (Levy et al., 2001). Notably, CB2 agonists such as lenabasum cause "class-switch" from inflammatory eicosanoids to lipoxin A4 through effects on 15-lipoxygenase (Zurier et al., 2009) and possibly other lipid metabolizing enzymes. Lipoxin A4 production is followed by the biosynthesis of "Resolvins" and "Protectins" at the inflammatory site (Serhan et al., 2008).

CB2 are found on immune cells where they play a role in modulating and resolving inflammation. Through activation of CB2, lenabasum stimulates the production of anti-inflammatory mediators and causes a concomitant reduction in pro-inflammatory mediators and cytokines. As a non-psychotropic cannabinoid (Karst et al., 2003), lenabasum has been shown to reduce inflammation and joint tissue injury in animal models (Zurier et al., 1998). Experiments suggest the potential of lenabasum to reduce such inflammation and tissue injury may occur in part through increasing production of anti-inflammatory eicosanoids such as prostaglandin (PG) J2 (Stebulis et al., 2008) and lipoxin A4 (LXA4) (Zurier et al., 2009). These eicosanoids facilitate resolution of inflammation and auto-inflammatory response.

Lenabasum activation of CB2 expressed in peripheral tissues and on immune cells, reduces leukocyte infiltration in a murine model of inflammation and fibrosis (Marquat et al., 2010). In addition, lenabasum reduces production by human peripheral blood mononuclear cells (PBMC) of potential mediators of inflammation including IL-1 (Zurier et al., 2003) and IL-6 (Parker et al., 2008), induces apoptosis of T cells (Bidinger et al., 2003), and increases production of PGJ2, an eicosanoid that facilitates resolution of inflammation (Stebulis et al., 2008). Another eicosanoid,

LXA4, serves as a stop signal for inflammation in that it prevents leukocyte mediated tissue injury, antagonizes peptidoleukotrienes and stimulates uptake of apoptotic neutrophils at sites of inflammation, thereby enhancing resolution of inflammation (Zurier et al., 2009). The addition of lenabasum to resting or activated human neutrophils, whole blood, or fibroblast-like synovial cells increases production of LXA4 by these cells.

Inflammation is a primitive, protective response and impaired resolution of inflammation is a problem in diseases such as DM, which are characterized by chronic inflammation, pain, and tissue injury. The inflammatory processes in DM-associated skin disease are likely related to classic mediators of tissue damage such as cytokines and activated immune cells, as the skin is readily accessible to circulating pro-inflammatory molecules. Additionally, the role of pro-inflammatory mediators such as tumor necrosis factor alpha (TNFα), interleukin-1 beta (IL-1β), and interferons (IFNs) in the pathogenesis of DM is well-documented (Wong et al., 2012). Dr. Werth and others have shown up-regulation of type I and II IFN genes in the skin of DM: IFN up-regulated proteins in the skin correlate with an inflammatory signature seen in Gottron's papules, a pathognomonic and particularly visible and refractory manifestation of cutaneous DM (Kim et al., 2012). Dr. Werth and colleagues have similarly demonstrated increased TNFα production by PBMC from subjects with DM (Nabatian et al., 2012).

Like many autoimmune diseases, type I IFNs are implicated in the pathogenesis of DM. Many patients with DM display up-regulation of IFN-inducible genes, referred to as the "IFN signature", with some patients showing elevated serum levels of IFNα. Thus, restraint of IFN production would appear to be a rational approach to the treatment of patients with DM. Dr. Werth and colleagues have similarly demonstrated the presence of a type I IFN signature in the PBMC of patients with specific subsets of cutaneous lupus erythematosus, an autoimmune disease similar to DM, and increased TNFα production by PBMC from these patients (Nabatian et al., 2012). Dr. Werth is currently testing the ability of lenabasum *in vitro* to suppress production of IFNα, IFNγ, TNFα, and IL-1β from PBMC from patients with DM.

Lenabasum is being developed as a new therapy for DM because it potentiates resolution of chronic, active innate immune responses, back to a state of homeostasis. As a potent synthetic full agonist of CB2, lenabasum has a unique spectrum of analgesic, anti-inflammatory and anti-fibrotic activities. The use of oral lenabasum in DM is proposed to facilitate resolution of inflammatory processes underlying DM skin disease. This study will explore the use of lenabasum as a novel, non-immunosuppressive, anti-inflammatory pharmacologic treatment for DM.

The primary goal of the proposed study is to evaluate the safety, tolerability, and efficacy of lenabasum in subjects with skin-predominant forms of DM. Safety assessments including vital signs, AEs, complete blood count (CBC) with cell differential, metabolic panel including electrolytes, liver function tests and renal function tests, urinalysis, and 12-lead electrocardiograms (ECG) for QT/QTc intervals will be monitored throughout both Parts A and B of the study. Improvement in DM skin disease activity will be measured using a validated disease severity tool, the Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI), patient-reported outcomes [the Skindex-29+3, Patient Global Assessment, and Patient-Reported Outcomes Measurement Information System (PROMIS)-29 Short Form], Physician Global Assessment, blood biomarkers of disease activity and inflammation, and optional skin histology and biomarkers of inflammation. Skin photography is optional. Confirmation of the lack of psychotropic

properties of oral lenabasum will be done using the Addiction Research Center Inventory-Marijuana (ARCI-M) scale in Part A. Plasma concentrations and metabolites of lenabasum will be measured in Part A.

The importance of this study is that it is the first-in-DM study of lenabasum. The data from this study will provide information whether the benefit: risk profile in DM supports further clinical development and progression of lenabasum to a larger phase 2 study and phase 3 testing. The data will support selection of optimal dose and dose regimen of lenabasum in additional phase 2 and/or phase 3 studies.

Please see investigator's brochure for detailed background information on lenabasum.

4.2. Rationale for Design and Dose Justification

Studies have shown anti-inflammatory effects of lenabasum on multiple cytokines implicated in the pathogenesis of DM, as demonstrated in the animal models and *in vitro* studies, provide evidence that lenabasum will be a novel orally administered, useful treatment for DM patients with predominant skin disease. Given the low toxicity profile demonstrated with lenabasum at anticipated therapeutic doses proposed for testing and used in the previous clinical trials, compared to the toxicities associated with standard therapies of corticosteroids and immunosuppressive drugs, this novel therapy may have a significant impact on disease morbidity and quality of life. The results from the proposed clinical trial will be used to power a larger phase 2 clinical trial to better characterize the clinical efficacy of lenabasum in DM.

The hypothesis is that lenabasum will provide clinical efficacy in DM subjects by triggering pathways that actively resolve adverse innate immune responses and blunting ongoing pro-fibrotic processes. Based on preclinical data, there is a component of the study to evaluate the expectation that lenabasum increases production of pro-resolving lipids, including but not limited to LXA4, PGD2 and PGJ2, via CB2. Conversely, lenabasum is expected to cause a relative decrease in production in pro-inflammatory eicosanoids, including leukotriene B4. Lenabasum is expected to activate apoptosis in activated immune cells and fibroblasts. Lenabasum is expected to inhibit production of cytokines, especially type I IFNs, and cellular infiltration of tissues in DM subjects. By resolving pathologic innate immune responses in DM, lenabasum is expected to reduce disease activity, including skin manifestations.

This first-in-DM study, proposed for conduct after results in healthy normal and pain were obtained in humans, is designed to assess safety, tolerability, and efficacy of lenabasum in DM subjects. The target population in this phase 2 study is adults $\geq$ 18 and $\leq$ 70 years of age, at the time of signing informed consent form, having skin-predominant DM who have failed standard of care with hydroxychloroquine treatments. Adults have been selected as the target population for this study because neither toxicology studies in juvenile animals nor safety or efficacy assessments in adults with DM have been done yet. The target population is subjects who have active skin-predominant disease who are refractory to standard of care, so that efficacy can be assessed. Active skin-predominant DM is defined for this study as CDASI $\geq$ 14 and minimal muscle disease with no difficulty with lifting or walking, no more than 1.5 x upper limit of normal of creatine phosphokinase (CPK) or aldolase, and no requirement for corticosteroid treatment for muscle disease. QT/QTc intervals will be monitored in all subjects.

To reduce risk to subjects in this first-in-DM study, subjects will be excluded who have an unstable clinical course reflected as a change in DM medications in the 28 days prior to first dose. Lenabasum or placebo will be administered as "add-on" to standard of care, allowing subjects to continue to receive what the investigator or their other treating physicians deem most appropriate baseline therapy for their disease. The proposed duration of lenabasum dosing of 84 days in this study of 22 subjects with DM is covered by 13-week toxicology studies in rat and dog. This study is expected to provide data on safety, tolerability, clinical efficacy, and PK of lenabasum over a longer exposure to than in a shorter study. The feasibility of enrolling 22 subjects into this study within 12-24 months is judged acceptable, based on the investigator's knowledge of their clinical sites.

The lenabasum oral doses selected for this study are 20 mg qd and 20 mg bid, and in Part B there is also an option to increase the dose up to 20 mg tid starting with Visit 8, or any time thereafter, for consenting OLE subjects that meet pre-specified criteria [Section 7.1]). All doses are expected to have an acceptable safety profile, be well tolerated, and provide clinical benefit, based on previous animal or human testing and the nature of the immune-mediated components of DM. Based on preclinical data and early clinical data, it is expected that safety risk and clinical efficacy of lenabasum in humans will be related to exposure. To maximize opportunity to detect an early safety signal and clinical efficacy in this study, subjects will receive lenabasum 20 mg bid on Days 29-84 (Part A). The availability of data from individual subjects who have been exposed to two different doses of lenabasum will increase the robustness of the modeling of relationship between exposure and biomarkers. The lenabasum 20 mg bid dose is expected to provide maximal or near maximal levels of clinical benefit, but dose response is not well known, therefore in Part B there is also an option to increase the dose up to 20 mg tid starting with Visit 8, or any time thereafter, for consenting OLE subjects that meet pre-specified criteria (Section 7.1). It is planned to increase the maximum daily allowed to up to 20 mg tid at the discretion of the investigator, with the higher dose selected in subjects who do not respond fully to the 20 mg bid dose and optimization of treatment per standard of care. With the safe dosing of subjects in open label extension studies in DM and systemic sclerosis at the 20 mg bid dose, and the accumulating safety data set, the 20 mg tid dose would be considered acceptable.

4.3. Potential Risks and Benefits

4.3.1. Potential Risks

Expected AEs in clinical studies with lenabasum include those related to active skin-predominant DM or tissue damage from DM, lenabasum, and common events in the general population. Expected AEs related to active disease (DM) or tissue damage from DM include constitutional symptoms such as fatigue, reduced appetite, and weight loss, progressive skin disease, new types of skin involvement, new or progressive muscle disease including muscle weakness or pain, new or progressive lung fibrosis/ interstitial lung disease with cough, dyspnea, shortness of breath, and reduced exercise tolerance, and pericarditis. Expected AEs related to active disease also include Raynaud's phenomenon, joint inflammation and pain, pain, pruritus, elevations in muscle enzymes and acute phase reactants such as total globulins, C-reactive protein (CRP), sedimentation rate, reductions in complement levels, and mild anemia. Subjects with DM are also at increased risk of malignancy, with reported incidence between 7-30%, with a variety of types, especially ovarian and breast cancer in women and lung cancer in men (Wang et al., 2013).

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, at least in other published clinical trials, 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 and/or 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 potentially be seen with lenabasum exposure.

To date, a number of the AEs associated with CB1/CB2 agonists have been reported in a few of the subjects exposed to lenabasum, such as fatigue, dizziness, decreased concentration, feeling "weird", light-headedness, asthenia, somnolence, nausea, vomiting, mild orthostatic hypotension, and dry mouth.

Psychotropic activity of lenabasum will be formally tested with the National Institute of Drug Abuse Addiction Research Center Inventory-Marijuana (NIDA ARCI-M) questionnaire.

Prolongations of QTc less than 500 msec total and up to 39 msec prolongation from pre-treatment baseline were all judged to be not clinically significant. They were observed in some subjects ≥ 65 years of age exposed to lenabasum at a total daily dose of up to 180 mg for seven days. For this reason, to ensure safety of subjects, the QT/QTc interval will be measured throughout the study.

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

Expected health changes in a general population include events such as mild changes in vital signs, sore throats, mild skin, upper or lower respiratory tract, or genitourinary infections requiring topical or oral antibiotics, asymptomatic bacteriuria, headaches, nausea, mild rashes, minor accidents, and mild abnormalities in laboratory testing of CBC testing, platelets, differential cell counts, metabolic panels including electrolytes, liver function tests and electrolytes, and urinalyses.

Subjects will be reminded to avoid alcohol during the study period to avoid additional enhancement of any sedating effects of the study product. Subjects will be instructed to call the investigator or qualified designee if they experience an AE (whether or not they determine it to be related to the study) and may be evaluated for potential toxicity at an unscheduled visit.

Please see the IB for further information about risk.

4.3.2. Potential Benefits

Lenabasum has not been approved for any indication, and no physical, psychological, social, legal, or any other benefits are claimed for individual DM subjects who chose to participate in this study.

Based on biologic effects of lenabasum and other CB2 agonists in *in vitro* and *in vivo* models of innate immune responses, inflammation, and disease, it is reasonable to test lenabasum for early evidence of efficacy in DM in this study. The information that will come from this study will address effects of lenabasum on safety, tolerability, efficacy, biomarkers of disease activity and inflammation, and PK in DM subjects. This information will be used in decision making about whether to progress lenabasum to phase 2/ phase 3 clinical testing, as a step toward dose determination, safety in patient population and ultimately toward approval by regulatory agencies for treatment of DM.

5. STUDY OBJECTIVES

5.1. Primary Objectives

The primary objectives of this trial are:

1. Evaluate the safety (vital signs, physical examination including muscle strength, AEs, blood and urine laboratory safety tests, ECGs with QT/QTc intervals, and psychotropic activity) and tolerability of lenabasum in subjects with DM;

2. Evaluate the efficacy of lenabasum for the treatment of skin-predominant DM using the CDASI activity score, a validated measure of skin disease severity.

5.2. Secondary Objectives

The secondary objectives of this trial are:

[redacted]

5.3. Exploratory Objective

The exploratory objective of this trial is:

[redacted]

5.4. Optional Future Studies

If the subject agrees, left-over tissue and blood specimens will be frozen and stored in the investigator's or principal investigator's research lab for future autoimmunity research that will include analysis by micro-array and proteomics. If the subject agrees, some of the tissue and blood specimens may be sent outside of the site institution to institutions and companies that collaborate in autoimmune disease research.

6. INVESTIGATIONAL PLAN

6.1. Overall Study Design and Plan – Description

Part A of this study is designed as a randomized, double-blind, placebo-controlled clinical trial to test the safety, tolerability, and efficacy of lenabasum compared to placebo for the treatment of DM skin disease refractory to treatment with antimalarial medications.

The target population in this phase 2 study (Part A) is subjects with DM who have failed or are intolerant to treatment with hydroxychloroquine and who are ≥ 18 and ≤ 70 years of age at the time of signing the informed consent form. Subjects must be on stable medication for DM for at least 28 days prior to Visit 1. The doses of lenabasum that will be tested in Part A are 20 mg qd (Days 1-28) and 20 mg bid (Days 29-84). Subjects who complete dosing in Part A without permanent discontinuation of study product for safety or tolerability reasons comprise the target population for Part B. Part B is an open-label study in DM of safety, tolerability, and efficacy of lenabasum dosed at 20 mg bid, with the option to reduce to 20 mg qd or lower if needed for reasons of safety or tolerability. In Part B there is also an option to increase the dose up to 20 mg tid starting with Visit 8, or any time thereafter, for consenting OLE subjects that meet pre-specified criteria (Section 7.1).

One site in the US is planned, with the option to add a second site if helpful to meet enrollment targets.

In Part A, the target enrollment of about 22 eligible subjects will take place over 12-24 months, for a recruitment rate of about 0.9 to 1.8 subjects per month. Screening will be up to 28 days prior to Visit 1 and there will be seven study visits, Visits 1-7 on Days 1, 15 ± 3, 29 ± 3, 43 ± 3, 57 ± 3, 85 ± 3 and 113 ± 3, respectively. Treatment occurs from Visits 1-6 and Visit 7 is a follow-up visit after treatment ends. The 3 day window on visits in Part A is included in case of holidays or unusual circumstances, and it is expected that most if not all visits will be on the scheduled date, as possible. The total duration of an individual subject's participation in Part A is about 112 days (84 days treatment and 28 days follow-up), plus Screening. As mentioned, the treatment period is 84 ± 3 days, unless an AE occurs that requires discontinuation of treatment or the subject withdraws.

In Part B, the target enrollment is all of the subjects who complete dosing in Part A without permanent discontinuation of study product for safety or tolerability reasons, which is estimated to be 20-22 subjects. Subjects will undergo additional safety screening for Part B up to 28 days prior to Visit 1. In the Year 1 Extension, there will be 8 study visits: Days 1, 29 ± 7, 85 ± 7, 141 ± 7, 197 ± 7, 253 ± 7, 309 ± 7 and, 365 ± 7. For subjects who choose not to participate in the Year 2 Extension, a Follow-up Visit will occur on Day 393 ± 7. Subjects who consent to the Year 2 Extension will have Visits 9-15 on Days 421 ± 7, 477 ± 7, 533 ± 7, 589 ± 7, 645 ± 7, 701 ± 7, and 757 ± 7. Subjects that do not consent to a third year of open-label treatment (Year 3 Extension) will have a Follow-up Visit on Day 784 ± 7. In the Year 3 Extension there will be 7 study visits and a Follow-up Visit. Visits 16-22 will occur on Days 813±7, 869±7, 925±7, 981±7, 1037±7, 1093±7, and 1149±7. The Follow-up Visit will occur on Day 1177±7. In the Year 4 Extension there will be 7 study visits and a Follow-up Visit. Visits 23-29 will occur on Days 1205±7, 1261±7, 1317±7, 1373±7, 1429±7, 1485±7, and 1541±7. The Follow-up Visit will occur on Day 1569±7 for subjects completing the study. The OLE may be extended beyond Year 4. The site will be notified by an administrative memo as to any extension and will inform their IRB. Each year of the extended OLE will include 7 study visits and will follow the same design and procedures as described for the Year 4 Extension. At the investigator's discretion, consenting subjects will rollover at the conclusion of Visit 29. The extension visits will be captured in the electronic data capture (EDC) from Visit 29B in sequential order (e.g., Visit 30B – Visit 36B for Year 5 Extension). Should the OLE be extended, subjects' Follow-up Visit will only occur at the completion of the study.

The 7-day window on visits in Part B is included in case of holidays or unusual circumstances, and it is expected that most if not all visits will be on the scheduled date, as possible. The total duration of an individual subject's participation in Part B is approximately 365 days in the first year of OLE then approximately 336 days per year thereafter, excluding the 28-day follow-up period for discontinuing or completing subjects.

Unless consent is withdrawn or the subject is lost to follow-up, subjects who are permanently discontinued from study product, or choose not to continue for an additional year in the OLE, as applicable, (e.g., subjects not continuing from Year 3 to Year 4 Extension), will have a Withdrawal Visit approximately 28 days after the last dose of study product, as possible. Assessments performed at study visits will be as noted in the study flow chart.

If an AE related to lenabasum prompts discontinuation of treatment or the subject withdraws, the study subject will be followed in the clinic for as long as is necessary to document the resolution or stabilization of the event. For therapeutic stability, the subjects will remain on their current treatment regimen for DM, for the duration of this study. Part A is expected to take between about 21-33 months to complete (about 12-24 months enrollment, up to 1 month Screening, 3 months treatment, 1 month follow-up, and 2-4 months for database lock and generation of data Tables, Listings, Figures, and the Study Report). Part B may be extended beyond Year 4, therefore completion time will be determined at a later stage.).

In Part A, the screening period is up to 28 days. Subjects will be screened prior to Visit 1 by the investigator or qualified designee to assess eligibility for randomization into the study. A master log will be maintained of all consented subjects and will document all screening failures, including the reason for screening failure. The target enrollment is 22 evaluable subjects (subjects who meet

eligibility criteria as defined in the Statistical Analysis Plan and complete Visit 3). The number of subjects enrolled in the study may be expanded if these additional eligible subjects have signed the informed consent form and are actively engaged in the screening process at the time 22 subjects have been randomized into the study.

After successful screening and before Visit 1, each subject will receive a Subject Identification Number (SID), assigned in serial order. That SID will have a corresponding treatment assignment that will have been determined randomly prior to start of the study by Corbus. Randomization will be done in a 1:1 ratio to lenabasum or placebo (See Table 1). There are no stratification criteria that could impact the rate of enrollment.

Table 1. Randomization Cohorts, Part A

Cohort	Target n	Days 1-28	Days 29-84	
		A.M. Study Product	A.M. Study Product	P.M. Study Product
1	11	Lenabasum 20 mg	Lenabasum 20 mg	Lenabasum 20 mg
2	11	Placebo	Placebo	Placebo

Identical to Part A, the screening period in Part B is up to 28 days. Subjects will be screened prior to Visit 1 by the investigator or qualified designee to assess eligibility for the OLE. A master log will be maintained of all consented subjects, and the log will document all screening failures, including the reason for screening failure. The target enrollment is all eligible subjects who successfully complete dosing in Part A. Subjects enrolled in Part B may continue seamless participation in additional extensions beyond year 1 as long as it is approved by the PI or designee and the subject consented to the extension (eg. Year 2, Year 3, etc, as applicable) prior to or at the last dosing visit for each respective year.

The lenabasum 20 mg capsule and placebo capsule are indistinguishable size 2 capsules. In Part A, study product will be administered orally qd on Days 1-28 and bid on Days 29-84, with at least 8 hours between doses. Study product will be administered orally bid throughout Part B, with at least 8 hours between doses. Subjects in Part B may receive a reduced dose of lenabasum 20 mg qd or 20 mg every other day if a reduction is warranted for safety or tolerability reasons in the opinion of the investigator. The dose may increase to 20 mg tid starting with Visit 8, or any time thereafter, for consenting OLE subjects that meet pre-specified criteria (Section 7.1). When taken tid, there should be at least 6 hours between each dose. The first dose of study product in Part A and B will be taken in the clinic, and subjects will be observed in the clinic for at least 30 minutes afterwards, or longer until vital signs and clinical symptoms are acceptable for discharge from the clinic, in the opinion of the investigator, if the subject experiences an AE. Study product can be taken without regard to fed state.

Part A Assessments

Vital signs, blood laboratory safety tests, and CDASI will be evaluated on Screening through Visit 7. Adverse events will be evaluated on V1-V7. The type, nature, severity, expectedness and relationship to study product of AEs that occur from after the time informed consent is signed

through the last visit will be recorded. Urine pregnancy testing will be done in WOCBP at Visits 1, 3 and 5-7. Muscle strength will be assessed using Manual Muscle Testing-8 (MMT-8) on Visits 1, 3, and 5-7, preferably by the same investigator at each visit. Physical examinations will be done on Screening and Visits 1, 6 and 7. Urine dipstick will be evaluated at Screening and Visits 1, 3, 5, and 6.

Tolerability will be evaluated from Visits 1-6, as number and percentage of subjects who discontinue study product because of a related treatment-emergent adverse event (TEAE). Psychoactivity of lenabasum will be assessed using the ARCI-M survey on Visits 1, 3, and 6. Twelve-lead ECGs and QT/QTc intervals will be assessed on Screening and Visits 1, 3, 5, and 6.

Efficacy of lenabasum will be measured at all Visits using CDASI to identify subjects who have had an improvement in disease activity and damage. Efficacy also will be evaluated using the Physician Global Assessment, Patient Global Assessment, Skindex-29+3, PROMIS-29 Short Form (all on Visits 1-3, 5-7 in Part A), and optional skin photography (on Visits 1, 3, and 6 in Part A). Photography will be incorporated on for research purposes only if the subject consents to the photos. The photos will have all identifiers removed to protect the identity and privacy of subjects and be referred to by Subject number. The investigator or qualified designee will complete clinical effectiveness outcomes, with the preference that the investigator complete all of them each visit.

Blood samples will be taken at various visits, depending upon the individual test, for studies of biomarkers of disease activity and inflammation. Optional skin biopsies will be performed for histology and studies of biomarkers of inflammation on Visits 1, 3, and 6. Metabolipidomic profiles and plasma concentrations and metabolites of lenabasum will be obtained on Visits 1-3, 5, and 6.

Data will be collected on Case Report Forms (CRFs). A local clinical laboratory will be used for routine laboratory testing. Measurement of metabolipidomic profiles and lenabasum concentrations will be done at a central contract laboratory. The QT/QTc intervals will be determined by a single reader, either the investigator or a qualified designee.

After the study period, if they so choose, study subjects may continue to be seen in investigator's clinical practice.

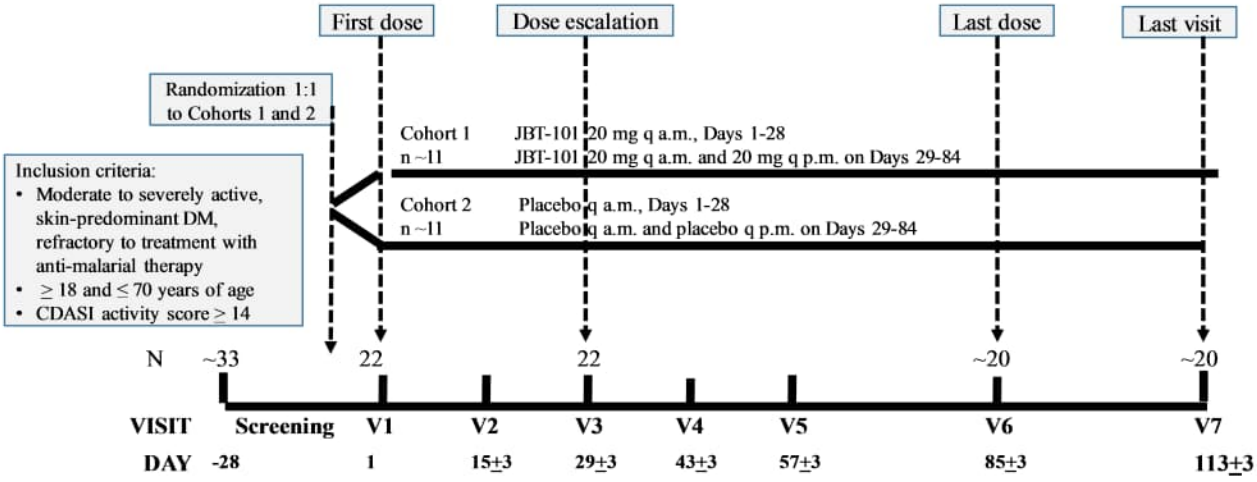
Part B Assessments

Similar efficacy and safety procedures will be conducted in Part B. The timing of assessments is outlined in Section 9.2 for Year 1, Section 9.3 for Year 2, Section 9.4 for Year 3, and Section 9.5 for Year 4. If the OLE is extended beyond Year 4, the same assessments as described for Year 4 will be followed for each year added, as applicable.

Figure 1 provides study schematics for Part A and Part B.

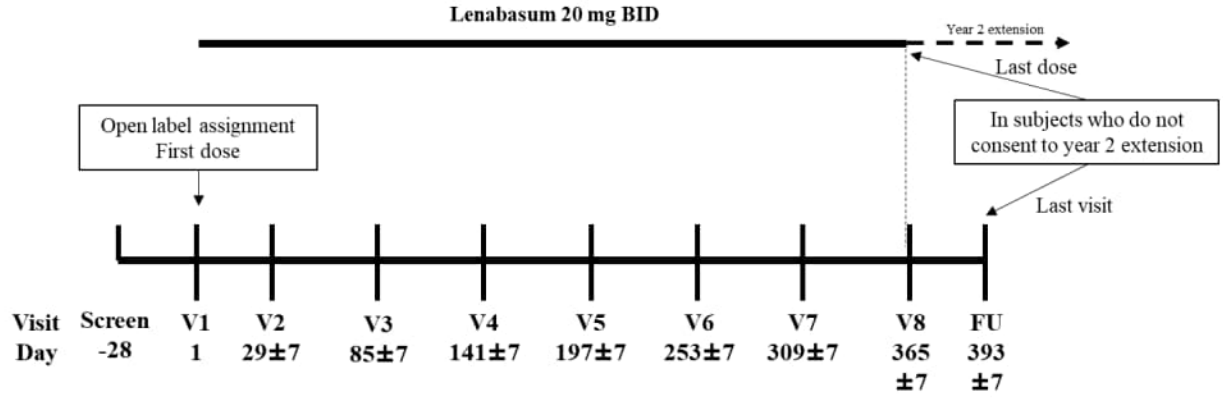
Figure 1. Study Schematic

Part A

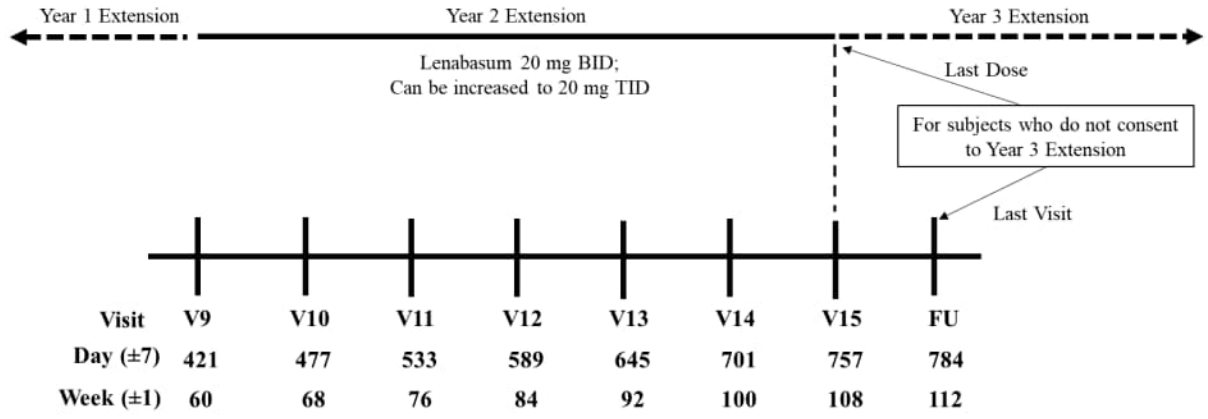


JBT-101 = Lenabasum

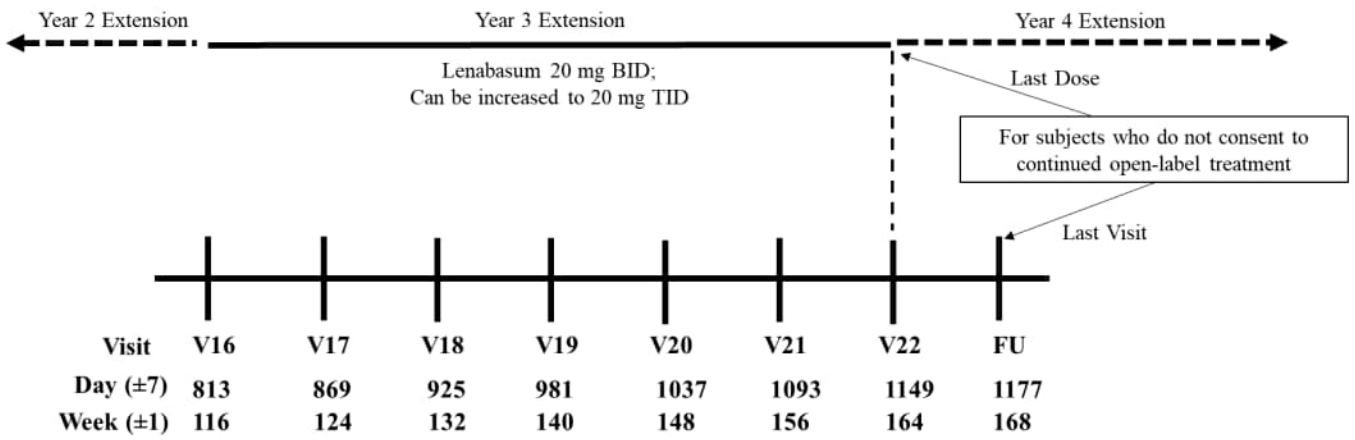
Part B Year 1



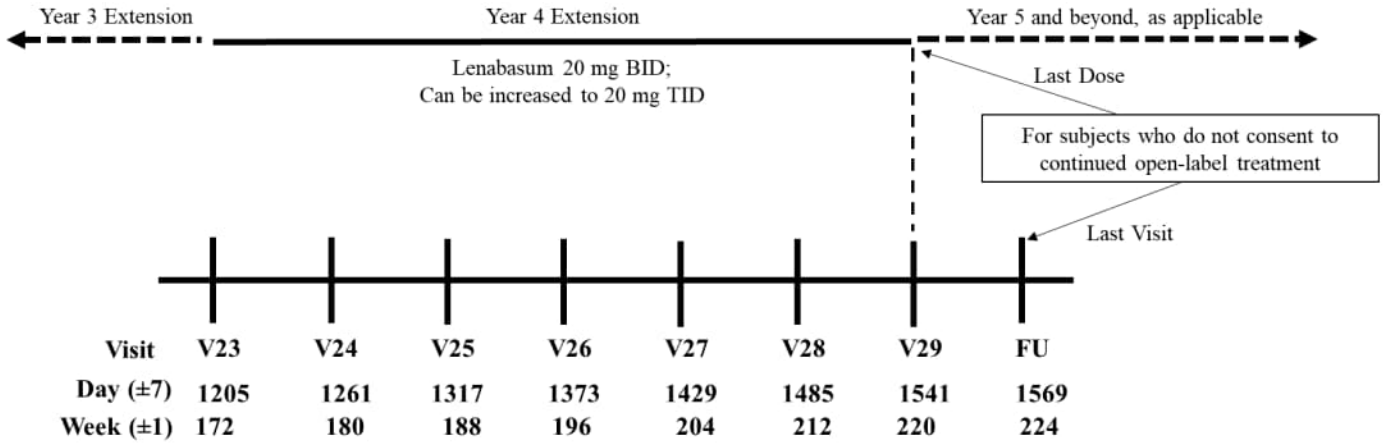
Part B Year 2



Part B Year 3



Part B Year 4



6.2. Discussion of Study Design and Control Group

In Part A, a double-blind, randomized, placebo-controlled design will be used to reduce bias in assessment of safety, tolerability, and efficacy, in order to facilitate the quantitative assessment of these effects of lenabasum in DM. Placebo and lenabasum will be administered in addition to current standard of care treatments that the subject is receiving, to avoid precipitating disease flares.

The lenabasum doses selected for this study are 20 mg qd and 20 mg bid, for oral administration without regard for fed/fasted state, and in Part B there is the option to increase the dose up to 20 mg tid starting with Visit 8, or any time thereafter, for consenting OLE subjects that meet pre-specified criteria (Section 7.1). In Part A, the 20 mg qd dose will be administered for 28 days, then the subjects will receive 20 mg bid for Days 29-84. In Part B, the 20 mg bid dose will be administered throughout, and the investigator will have the option to reduce the dose temporarily or permanently to 20 mg qd or 20 mg every other day for safety or tolerability starting as early as Visit 1. The dose

can increase to 20 mg tid, starting with Visit 8 or any time thereafter, for consenting OLE subjects that meet pre-specified criteria (Section 7.1). These doses are expected to have an acceptable safety profile, be well-tolerated and provide clinical benefit, based on previous animal or human testing.

In support of oral administration without regard to fed/fasted state, lenabasum is well absorbed from the gastrointestinal tract and exhibits dose proportional PK at the doses to be tested in this study. Based on PK results in previous clinical trials at doses between 10-20 mg single doses and first dose of the 20 mg multiple dose cohort, T_{max} is expected to be between 2.7 to 3.5 hours for the 20 mg dose in the current trial, which supports the timing of 3 hours post dosing to estimate maximal plasma concentrations. The average terminal half-life of lenabasum in subjects who received 10 mg or 20 mg qd in previous studies ranges from 3.7 to 4.4 hours, which supports qd and bid testing. Doses to be tested in this study have not shown a significant food effect in a prior clinical study, which supports dosing without regard to fed state.

In support of dose selection for this study, lenabasum has already been in human testing in single and multiple ascending dose studies and a phase 2 study. The lenabasum doses selected for this study are below the dose of 40 mg bid that was well tolerated with a safety profile that would support further clinical testing, as evaluated in the 7 day phase 2 study. Both doses are below the human equivalent doses of 3.2 and 5.4 mg/kg/day of the 13-week NOAEL in rats and dogs, respectively. Based on lenabasum doses that were active in several animal models of inflammatory diseases, the 20 mg qd dose is expected to provide some clinical efficacy, and the 20 mg bid dose is expected to provide near maximal levels of clinical benefit.

In support of dose escalation within the same subject, existing preclinical data do not show a "U" shaped dose response curve within the potential therapeutic range for lenabasum. Based on this information, it is assumed that safety risk and clinical efficacy of lenabasum in DM subjects will be related to exposure, and early safety signals and clinical efficacy will occur at higher rather than lower doses of lenabasum. To maximize opportunity to detect early safety signals and clinical efficacy in Part A of this study, all subjects will receive lenabasum 20 mg bid on Days 29-84. Once daily dosing vs. twice daily dosing in the same individual will provide data to model dosing interval for additional phase 2 and phase 3 testing. The availability of data from individual subjects who have been exposed to two different doses of lenabasum will increase the robustness of the modeling of relationships between lenabasum dose and exposure, and between exposure and biomarkers of disease activity and SPMs measured in metabolipidomic profiling.

A proposed duration of lenabasum dosing of 84 days for this phase 2 study is covered by 13-week toxicology studies in rats and dogs and will provide more useful data on safety, tolerability, and efficacy in humans, as well as PK of lenabasum than a shorter study. A proposed longer duration of lenabasum dosing for Part B is covered by the 26-week rat and 39-week dog toxicology studies, plus additional data in ~100 subjects safely dosed in completed Phase 2 studies with study product up to 20 mg bid, in some cases for >3 years in open label extensions (in subjects with systemic sclerosis and DM). Plasma exposures determined at the NOAEL in repeat dose chronic toxicology studies (i.e., 26-week rat and 39-week dog studies) were at least 1.3× higher than the anticipated clinical exposures with lenabasum 20 mg tid dosing. A higher dose of 60 mg/day is also supported based on the accumulated safety data and prior experience of dosing 40 mg/day in DM and systemic sclerosis patients.

6.3. Selection of Study Population

The target population is adults with active skin-predominant DM. There is no FDA approved medication for improvement in signs and symptoms of skin-predominant DM. These subjects have significant morbidity related to DM, especially those who are refractory to anti-malarial treatments, and need additional treatments to control signs and symptoms of DM. Subjects can be maintained on most baseline medications during this trial, which reduces a risk of disease flare precipitated by discontinuation of baseline medications to meet entry criteria.

6.3.1. Inclusion Criteria for Part A

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

1. ≥ 18 and ≤ 70 years of age when the informed consent form is signed;
2. Understand and voluntarily sign the informed consent and HIPAA forms;
3. Able to adhere to the study visit schedule and other protocol requirements;
4. Meet Bohan and Peter's criteria for DM (Bohan and Peters, 1975a, Bohan and Peters, 1975b) or Sontheimer's criteria for DM (Sontheimer, 2002);
5. Moderate-to-severe DM skin disease with a CDASI activity score ≥ 14;
6. Minimal muscle disease defined as no difficulty with lifting or walking, no more than 1.5 x the upper limit of normal of CPK or aldolase, and no requirement for corticosteroid treatment for muscle disease;
7. Failed standard treatment with hydroxychloroquine, as defined by use of hydroxychloroquine for at least 8 weeks at Screening and at least 12 weeks at Visit 1 without significant improvement in skin disease activity or intolerance to hydroxychloroquine, in the opinion of the investigator or treating physician;
8. Stable treatment for DM for at least 28 days before Visit 1;
9. Not expected by the investigator to require a change in corticosteroid treatments for DM during the study period through Visit 7;
10. Willing not to start or stop any medications or supplements for DM during the study period through Visit 7, unless a change is recommended by the investigator or other treating physicians;
11. Must not have used any cannabinoids during 14 days prior to Visit 1 and must be willing to continue not to use cannabinoids or any illegal substance of abuse during the study through Visit 7;
12. Women of childbearing potential must not be pregnant or breastfeeding, and must be using at least one highly effective method of contraception (failure rate < 1% per year) for at least 28 days before Visit 1 and be willing to continue to use at least one highly effective method

of contraception throughout the study and for at least 28 days after discontinuation of study product (See Section Appendix A, Appendix A);

13. Willing to follow instructions, complete study procedures and attend study visits as required by this protocol.

6.3.2. Inclusion Criteria for Part B

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

1. Complete dosing in Part A without permanent discontinuation of study product for safety or tolerability reasons or voluntary withdrawal from the study.
2. Complete Visit 6 of Part A at or before screening for Part B.
3. Understand and voluntarily sign the informed consent and HIPAA forms;
4. Able to adhere to the study visit schedule and other protocol requirements;

6.3.3. Exclusion Criteria for Parts A and B

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

1. Investigator, site personnel directly affiliated with this study, or their immediate families. Immediate family is defined as a spouse, parent, child or sibling, whether biologically or legally adopted;
2. Treatment with any one of the following:
    a. Anti-TNF agent within 6 months of Visit 1;
    b. Any corticosteroids > 10 mg per day or > 20 mg every other day oral prednisone or equivalent, within 28 days before Visit 1;
    c. Other immunosuppressive agents whose dose has increased within 8 weeks prior to Visit 1;
    d. Prior treatment with B cell-depleting monoclonal antibodies within 6 months of Visit 1;
    e. Narcotic analgesia for more than 14 consecutive days within 6 months of Visit 1;
    f. Any investigational agent other than lenabasum within 1 month or 5 therapeutic half-lives of that agent, whichever is longer, before Visit 1;
3. Significant diseases or conditions other than DM that may influence response to the study product or safety, such as any one of the following:
    a. Bacterial or viral infection requiring systemic treatment within 28 days of Visit 1 or requiring prophylactic antibiotics;
    b. Acute or chronic Hepatitis B or C infection;
    c. Human immunodeficiency virus (HIV), infection;

d. History of active tuberculosis or positive tuberculosis skin or blood test without a completed course of appropriate treatment;

e. Any major surgery within 3 months and any minor surgery within 14 days before Visit 1;

f. Current malignancy. A 5-year cancer-free period is required if previously cured of any malignancy. Exceptions include skin basal or squamous cell carcinoma excised and cured, or cervical carcinoma-in-situ that has been successfully treated with conization/biopsy ≥ 1 year prior to Visit 1;

g. Ascites or pleural effusion, unless completely resolved and not requiring treatment for at least 4 months prior to Visit 1;

h. Significant heart disease as defined by:

i. Uncontrollable congestive heart failure, unstable angina, unstable atherosclerotic cardiovascular disease, or significant arrhythmia, pulmonary arterial hypertension with dyspnea, disability rated as New York heart Association Grade III or higher, severe systemic hypertension or severe peripheral vascular disease;

ii. Marked baseline prolongation of QT/QTc interval (i.e. repeated demonstration of a QTc interval ≥ 450 msec for men and ≥ 470 msec for females);

iii. History of risk factors for torsade de pointes (*e.g.,* heart failure, hypokalemia, family history of long QT/QTc syndrome);

iv. History of severe pericardial disease;

v. Clinically significant confirmed abnormality, as determined by the investigator or qualified designee, on 12-lead ECG at Screening or Visit 1 before dosing;

4. 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 prior to Screening;

5. Breast-feeding or lactating;

6. Any one of the following values for laboratory tests at Screening. Results on screening laboratory tests, except pregnancy tests, may be repeated once at the discretion of the investigator or qualified designee, before Visit 1, to determine eligibility:

a. A positive pregnancy test (also at Visit 1);

b. A positive QuantiFERON test;

c. Hemoglobin < 10 g/dL;

d. Neutrophils < 1.0 x 10^9/L;

e. Platelets < 75 x 10^9/L;

f. Serum creatinine > 1.5 mg/dL (female) or > 1.8 mg/dL (male);

g. Chronic proteinuria > 1+ by dipstick (1+ on dipstick on two measurements 1 month apart);

h. Aspartate aminotransferase, alanine aminotransferase, or alkaline phosphatase > 2.5 x upper limit of normal;

i. Serum bilirubin > 1.5 x upper normal limit;

j. Received B cell depleting monoclonal antibodies six months or less from visit 1;

7. Any other medical, psychiatric or substance abuse condition, concurrent medical therapies, or abnormal laboratory values in the screening panel that, in the opinion of the investigator, are clinically significant and may put the subject at greater safety risk, influence response to study product, or interfere with study assessments. When in doubt, the investigator or qualified designee should discuss with the Medical Monitor.

6.3.4. Women, Minorities, and Children (Special Populations)

Women and minorities will be recruited. It is anticipated that approximately 80-90% of the study population will be women and 10% minorities. Subjects < 18 years of age will be excluded because there are no toxicology studies in juvenile animals and no safety, tolerability, and efficacy data in adults with DM.

[redacted]

6.3.6. Removal of Subjects from Therapy or Assessments

Interruption of Dosing in an Individual Subject

Interruption of continued dosing in individual subjects may occur for safety reasons and at the discretion of the investigator or the Medical Monitor, if it is felt that interruption of dosing is in the best interest of the subject. In the event a subject experiences a clinically significant AE related to study product, a dose interruption for up to 14 days in total will be permitted, at the discretion of the investigator.

If a subject experiences an increase in disease activity of DM during participation in the study, including an increase in muscle disease, he/she should be treated according to standard of care. Any new medication(s) will be recorded and may be considered in analyses of outcomes.

There will be no dose modification in Part A of this study.

Discontinuation of Dosing in an Individual Subject

Subjects are free to withdraw from participation in the study at any time upon request.

An individual subject will not receive any further study product if any of the following occur in the subject in question:

- Withdrawal of consent;
- Adverse events that in the judgment of the investigator may cause severe or permanent harm, or which rule out continuation of the study product; for example, any serious or life-threatening AE related to the study product [Grade 3 or Grade 4 National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE)];
- Other event(s) which in the opinion of the investigator or the Medical Monitor contraindicates further dosing such as, but not limited to, repeated failure to meet protocol requirements, significant concurrent illnesses or disease complications;
- Pregnancy;
- Subject now meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation, in the judgment of investigator or the Medical Monitor;
- Subject lost to follow-up.

Participants who are discontinued permanently from drug therapy due to an AE related to study product will be followed until resolution or stabilization of the event. Subjects withdrawn for any of the above reasons except loss to follow-up will be evaluated at the time of their withdrawal (regularly Scheduled Visit or an unscheduled visit), as well as a Withdrawal Visit approximately 28 days after cessation of the study product, following the plan for the Visit 7 follow-up (Part A) or Follow-Up Visit (Part B). Subjects who withdraw consent will be asked to complete the Withdrawal Visit; however, they will not be required to complete the visit. Subjects who are withdrawn due to pregnancy will be followed according to the procedures outlined in Pregnancies, Section 8.1.10.

If a subject fails to return for scheduled study visits, he/she will be contacted at least three times via phone by a member of the research staff. A certified letter to update him/her on the study status will also be sent. If the subject does not respond to these attempts, he/she will be considered lost to follow up.

Any withdrawal of consent during the study after the first dose of study product requires immediate reporting within 24 hours to the Medical Monitor at the number provided. An individual subject will not receive any further study product after consent is withdrawn.

Abrupt discontinuation of treatment with lenabasum is not known to cause any harmful effects. Therefore, the drug will be stopped without tapering of drug or adding additional treatments. All remaining study product and packaging will be returned to the study staff.

6.3.7. Replacement Policy

Subjects, for reasons other than safety related to study product, may be replaced at the discretion of the principal investigator to maintain a sample size of at least 22 subjects through Visit 3.

6.3.8. Premature Termination or Suspension of Study

This study may be suspended or prematurely terminated by Corbus independently or at the request of the FDA, with sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by Corbus to the FDA. If the study is suspended or prematurely terminated, the investigator will promptly inform the IRB and will provide the reason(s) for the suspension or termination. Review and approval by the IRB (and possibly the FDA) is required for resumption of the study in the event the study is interrupted because of one of the events listed below.

If any of the following events occur during the enrollment, then study entry and randomization of new subjects into the study will be suspended until expedited review of the event in question occurs by the Safety Monitoring Committee:

- Death in any subject judged to be related to lenabasum;
- Any life-threatening clinical event (Grade 4 NCI CTCAE criteria) related to lenabasum;
- Determination of unexpected, significant, or unacceptable risks to subjects that contraindicate further dosing of additional subjects, in the opinion of the principal investigator or the Medical Monitor;
- Any new medical or administrative information about the execution of the trial that, in the opinion of the principal investigator or 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: 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 product may continue during the time of review in subjects who are already receiving study product at the discretion of the principal investigator and in consensus with the Medical Monitor.

An expedited and cumulative review of safety data and the circumstances of the event(s) in question will be conducted by the Safety Monitoring Committee, with additional external expertise as needed, to make recommendations to NIAMS, the principal investigator, and Corbus whether study entry/randomization and dosing 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, in consensus with the principal investigator and with notification of NIAMS.

Review and approval by the site IRB (and FDA) will be required for resumption of the study in the event the study is suspended because of one of the above-listed events.

7. STUDY PRODUCT

7.1. Dosage, Preparation and Administration

The doses of study products available are:

- Lenabasum 20 mg
- Placebo, no dose.

No onsite preparation or masking of clinical supplies is required by site personnel. The study product will be self-administered and taken orally in the following doses in Part A:

- Cohort 1: Lenabasum 20 mg q a.m. on Days 1-28, then lenabasum 20 mg q a.m. and 20 mg q p.m. on Days 29-84;
- Cohort 2: Placebo q a.m. on Days 1-28, then placebo q a.m. and placebo q p.m. on Days 29-84.

In Part B, all subjects will receive lenabasum 20 mg q a.m. and lenabasum 20 mg q p.m. throughout, unless the investigator reduces or increases the dose following the criteria below.

The investigator may reduce the dose to 20 mg qd or 20 mg every other day, temporarily or permanently, for safety or tolerability reasons.

The investigator may increase the dose to 20 mg tid starting with Visit 8, or any time thereafter, for consenting OLE subjects that meet the following pre-specified criteria:

- Less than 5 point improvement in CDASI score from start of treatment in the open label period (Visit V1B) after being on Lenabasum for at least 12 weeks
- A CDASI score >14
- Disease worsening defined as an increase in CDASI score of $\geq$ 4 points from a prior visit, that is sustained over a period of at least 8 $\pm$1 weeks.

Note: Lenabasum dose increase to 20 mg tid will be considered only if the subject is unresponsive or intolerant to optimized treatment per standard of care. In case of continued sustained disease worsening while on lenabasum 20 mg tid, please consult Section 6.3.6 Removal of Subjects from Therapy.

The study medication must be taken according to the following regimen:

1. Lenabasum and placebo capsules should be swallowed whole and should not be broken, chewed or opened. Morning and evening doses should be at least 8 hours apart. When taken tid, there should be at least 6 hours between each dose.
2. If a dose of lenabasum or placebo 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.
3. Doses can be taken without regard to fed state.

4. Subjects who take more than the prescribed dose of lenabasum or placebo should be instructed to contact the study staff immediately and to seek emergency medical care, if needed.

7.2. Study Medication Supply

No clinical supplies will be shipped until 30 days after FDA has reviewed the protocol and has not objected to initiation of the study. The IRB's unconditional approval statement will be transmitted by the investigator or qualified designee to Corbus before shipment of study product supplies to the site.

For each SID for Part A, five bottles of 35 capsules each of the study product corresponding to the treatment assignment will be labeled with that SID and with bottle numbers from 1 through 5. For each SID for Part B, bottles of 35 capsules each of lenabasum 20 mg will be sent to the site. The maximum quantity for any given subject that will be sent to the site in any one shipment is a 4 month supply or maximum of 8 bottles at any one shipment, whichever is least. All bottles in Part B will be labeled as containing lenabasum 20 mg. The bottles will be stored by the Corbus distributor until shipment to the investigator.

In Part A, the investigator will request study product for the first one to four subjects by SID, depending upon how many subjects have been randomized and received SIDs. All five bottles of study product needed to complete Part A for each of these subjects (SIDs) will be shipped to the investigator. Thereafter, for Part A, the investigator or qualified designee will order study product when needed for the next subject by SID and will receive all five bottles for that SID. Each order will include a Drug Enforcement Administration (DEA) Form 222.

In Part A, for any given subject, Bottle 1 will be dispensed at Visit 1 for Days 1-28, and overage will be returned on Visit 3. Next, Bottles 2 and 3 will be dispensed at Visit 3 for Days 29-56, and overage will be returned on Visit 5. Then, Bottles 4 and 5 will be dispensed at Visit 5 for Days 57-84, and the remaining overage will be returned on Visit 6. Should any overage fail to be returned by Visit 6, that overage will be returned on Visit 7.

In Part B, for any given subject, the site also will receive bottles containing lenabasum 20 mg capsules. The number of bottles that the site will receive for any given subject in one shipment will be at least adequate to treat until the next visit, whether it is 28 or 56 days until the next scheduled visit and may be adequate to treat for up to 4 months. If the subject's dose is decreased from 20 mg bid to 20 mg qd or 20 mg every other day, the number of bottles dispensed will be proportionately reduced and instructions for dosing will be provided to the subject by the site. If the dose is increased to 20 mg tid, supplies will be increased accordingly.

For the purposes of due diligence, subjects will be required to bring their medication bottles at every visit for capsule counting. The overage will be collected prior to dispensing the next supply of study product, if applicable. If a subject should fail to return all overage at the designed Visits, that overage should be collected at the next study visit or, if the only possibility, collected at the end of study.

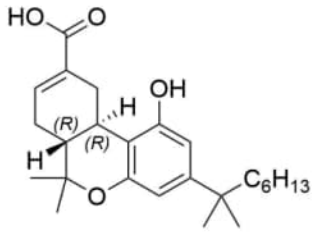
No additional study product will be distributed after the initial distribution, unless the subject returns unused study product at study visits as stipulated in the protocol or the investigator feels the reason for not returning study product is valid.

Detailed instructions will be in the Manual of Procedures (MOP) supplied by Corbus for Part A and in the Investigational Product Manual supplied by Corbus for Part A and Part B.

7.3. Description of Study Product

Lenabasum is (6aR, 10aR)-3-(1,1-dimethylheptyl)-Δ8-tetrahydro-cannabinol-9-carboxylic acid (see Figure 2), also known as JBT-101, Resunab, ajulemic acid, CT-3, IP751 and CPL7075. It is a dimethylheptyl structural analog of THC-11-oic acid, designed and selected on the basis of cannabinoid structure-activity features associated with the reduction of central nervous system penetration and increased affinity for CB receptors. It has preferential binding to CB2 versus CB1 and exhibits preferential cellular activation through CB2. Detailed study product information can be found in the IB.

Figure 2. 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

7.4. Description of Comparator Product

Placebo is microcrystalline cellulose (no active ingredient), formulated to have an appearance and weight matched to lenabasum.

7.5. Packaging and Labeling

Both lenabasum and placebo are powder-in-capsule preparations packaged in identical no. 2 gelatin capsules. Study product will be packaged in bottles of 35 capsules each that will be labeled in accordance with regulatory requirements. The bottles will be made of high density polyethylene with a polypropylene child resistant cap and an induction seal.

Lenabasum will be dispensed to study subjects in the original packaging with a label clearly indicating that the contents are for investigational purposes only. In addition, the label will bear Corbus Pharmaceutical Inc. name, quantity of drug contained, and the following standard statement: Caution: New Drug - Limited by United States Law to Investigational Use Only. The label for Part A will include the SID and bottle number (1 to 5) for that SID. The label for Part B will not include the SID number.

Additional labels must not cover the caution label or the name of the manufacturer. For appropriate drug accountability, it is recommended that each bottle be marked with the IRB protocol number upon receipt.

7.6. Masking and Unblinding

7.6.1. Masking and Blinding Procedures, Part A

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

This study is double-blinded in Part A and open-label in Part B. The blinding of the trial must be maintained throughout Part A until all data entry and processing are complete and the Part A database has been locked. Except for emergency unblinding during Part A (see Section 7.6.2), all Corbus medical and clinical operations staff associated with this study, both internal Corbus staff and contract staff, and including the Medical Monitor, will remain blinded to treatment randomization until the Part A is completed and the Part A database is closed. Study subjects and the study site staff, including the investigator and any co-investigator who will do safety and clinical assessments, qualified designees, study nurses, and study coordinators will be blinded to intervention groups during Part A. The final unblinding of all study participants in Part A will occur only after the data analysis set has been locked. In the event that the treatment allocation for a subject in Part A otherwise becomes known to the clinical site staff, the principal investigator must be notified immediately, and the principal investigator will notify Corbus.

Corbus clinical research pharmacy services personnel will be unmasked to the study product randomization. They are required not to reveal randomization information in Part A 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 will perform and interpret assays of lenabasum concentrations and metabolipidomic profiling may be unmasked during Part A. These results will be provided to Corbus using dummy subject identifications until the database is locked. Certain data management, programming, and a biostatistician may be unmasked. These unmasked 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.

7.6.2. Unblinding Procedures, Part A

Emergency Unblinding Procedures

To maintain the overall quality of data collected during of the study, breaks in blinding during the conduct of Part A should occur only in exceptional circumstances when knowledge of the actual treatment is absolutely essential for further management of the subject. Unblinding of the study product for an individual can be done during the Part A in the case of: a medical emergency where knowledge of the treatment assignment is necessary to treat the subject; a SUSAR when it is necessary for the investigator to know which treatment the subject is receiving before the subject can be treated; in the event of a SUSAR needing expedited reporting; where a child accidentally

takes the study product; or if requested by the Safety Monitoring Committee. Unblinding will occur only in situations that also call for study product discontinuation in an individual subject.

In the event of a safety concern that requires immediate emergency unblinding of treatment assignment for an individual subject in Part A, the investigator will have 24-hour access to break the randomization code for that subject by opening the an individual sealed envelope that is kept on file with other subjects' sealed envelopes in the investigator's secure research office. The sealed envelopes will be labeled on the outside with the subject's SID and inside they will contain the treatment assignment that matches the SID of the individual subjects. In all circumstances other than a medical emergency, unblinding will be done only by the Medical Monitor, and only after discussion with the investigator.

Emergency unblinding in Part A must be reported to the Medical Monitor immediately and to the NIAMS Safety Officer within two business days of the unblinding. When it is necessary to break the blind, the investigator must notify the IRB. Corbus will be notified by the investigator regarding the unblinding. Corbus will notify the other investigator, if any, with the reasons for unblinding.

If the blind is broken for a subject, this must be documented fully on a CRF that will record the date and time, reason for unblinding, name and signature of the person requesting the code break, and name and signature of the person breaking the code.

The subject will have either a routine scheduled visit, if due, or an unscheduled visit as soon as possible after emergency unblinding in Part A, with appropriate testing to evaluate the safety concern that caused the emergency unblinding. As possible, the subject also should have a Withdrawal Visit at 28 $\pm$ 3 days after discontinuation of the study product.

After emergency unblinding in Part A, the investigator will continue to maintain the blind for that subject throughout completion of Part A, as possible. The actual allocation will not be disclosed to the subject and/or other study personnel, including other site personnel, monitors, or project office staff. There will not be any written or verbal disclosure of the code in any of the corresponding subject documents.

Unblinding Procedures at the End of Part A

After study completion of Part A, when all the Part A data are collected, all queries have been resolved, the Safety Monitoring Committee has had its final review of the safety data, and the Part A database has been locked, the statistician will then generate a request to break the treatment code for all subjects, for purposes of data analyses and generation of Tables, Listings and Figures. This will be done to determine the effect of lenabasum in Part A.

After the treatment code has been broken for Part A, the investigator will be given a copy of the treatment code and asked to inform subjects of their blinded treatment allocation, if the subject choses to know.

7.7. Conditions for Storage and Use of Study Products

The study product will be stored in a manner that meets DEA requirements. Bottles of study product are to be stored at room temperature away from temperature and humidity extremes and

under conditions appropriate for small quantities of Controlled Drugs Act Schedule 1 substances. The study product that is returned by the subjects to the site also will be stored under conditions appropriate for small quantities of Controlled Drugs Act Schedule 1, until disposition or return to the manufacturer.

The investigator or qualified designee will maintain accurate logs of drug shipments received, returned to the manufacturer (or sponsor's designated location), or destroyed, to ensure the appropriate amount of study product is kept on site and that it is used for research purposes only. The investigator or qualified designee will perform drug accountability procedures such as checking drug shipments against the shipping contents form, maintaining a log of the amount of study product 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 and reported to Corbus and the DEA.

Subjects will be instructed to store study product at home at room temperature, away from temperature and humidity extremes and in areas that are not accessible to children. All study product will have an expiration date that exceeds the last date when the study product will be administered to that subject. All study product that is not ingested by study subjects will be disposed of according to instructions provided by Corbus to the investigator or returned to Corbus, as requested by the Corbus.

Detailed instructions will be in the Investigational product (IP) manual.

7.8. Method of Assigning Subjects to Treatment Groups

A randomization scheme for serial SIDs randomized 1:1 to lenabasum or placebo will be generated by a Corbus contractor. Based on this randomization scheme, study product vials containing the appropriate treatment for each SID will be labeled with the SID by the manufacturer.

As each new eligible subject is identified, the principal investigator will assign in consecutive order the next unassigned SID to that subject. The principal investigator or qualified designee will maintain a log of subjects, by name, initials, date of birth, SID assigned, and date SID was assigned. This log will be kept in a secure location. An eligible subject is considered randomized into the study upon assignment of the SID by the principal investigator, because that SID is linked to a treatment assignment. The subject does not need to be present for randomization.

7.9. Dispensing, Compliance and Accountability

7.9.1. Dispensing

The study product will be dispensed from the DEA-approved locked storage cabinet. The cabinet will be securely locked after study product has been added or removed. In Part A, the study product dispensed to the subject will be based on matching the subject's SID with the SID on the study product bottle(s). No more than a single, 28-day (Part A) or 56-day (Part B) supply of study product plus packaged overage in the bottle(s) may be provided to the subject at one time of dispensing. Detailed instructions will be in the IP manual.

7.9.2. Compliance

The number of unused capsules of study product will be counted and recorded as a measure of compliance at every visit. After unblinding for Part A, for subjects receiving lenabasum, lack of compliance with study product administration 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.

7.9.3. Accountability

A central repository of study product will be held at the manufacturing site. Study product distributed to the pharmacy or investigator will be sent by express mail and tracked until assurance of receipt.

Depending upon the arrangements at the individual site, either site investigator or qualified designee or the designated site pharmacist is responsible for maintaining accountability records for the receipt, dispensing, and return of all study medication. Procedures for tracking shipment, receipt, distribution, and collection of unused study product are in the IP manual.

7.10. Prior and Concomitant Therapy

The intent is that each study subject is maintained on all his/her baseline medications for DM from Screening through the last visits in Part A and Part B, unless the investigator or other treating physician judges that 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 CRFs.

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, unless medically indicated to optimize care. In Part B, given the duration of the subjects' participation in the study, it is expected that a subject's course may vary over the open label period and the investigator may need to adjust standard of care medications to provide best medical care for the subject. As noted in Section 7.1, treatment must be optimized to prevailing standard of care prior to any increase in lenabasum dose in the open label part of the study.

During the study, concomitant medications and new medications should be administered at the discretion of the investigator or the treating physician in order to provide the subject with the best possible medical care. However, due to the unavailability of toxicology data or clinical experience of 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, unless medically indicated to optimize care. The benefit-risk of adding new medications during the study period should be carefully assessed.

Among the permitted concomitant medications for DM during the study include stable doses, including stable doses of as needed (prn) medications, of any of the following. Visit 1 refers to the relevant Visit 1 in Part A or Part B:

- Antimalarial medications at stable doses for at least 28 days prior to Visit 1, including:
  - Hydroxychloroquine (Plaquenil);
  - Quinacrine (Atabrine);
  - Chloroquine (Aralen);
- Immunosuppressants including, but not limited to:
  - Corticosteroids ≤ 10 mg qd or ≤ 20 mg every other day oral prednisone or equivalent corticosteroid at stable doses for at least 28 days prior to Visit 1;
  - Methotrexate, mycophenolate, azathioprine, or cyclosporine at stable doses for at least 8 weeks prior to Visit 1;
- Topical therapy at stable doses for at least 28 days prior to Visit 1, including:
  - Corticosteroids;
  - Immuno-modulatory therapy, such as tacrolimus (Protopic)

Disallowed medications in Part A and Part B are listed in Table 2.

Table 2. Disallowed Medications

Drug Class	Requirements
Corticosteroids > 10 mg per day or > 20 mg every other day oral prednisone or equivalent	Prohibited in the **28 days** before Visit 1
Anti-TNF agents	Prohibited in **6 months** before Visit 1
B-cell depleting biological agents	Prohibited for **6 months** before Visit 1
Intravenous immunoglobulin	Prohibited after Screening
Investigational agents	Prohibited in **30 days** or 5 therapeutic half-lives before Visit 1, whichever is longer
Narcotic analgesia	Prohibited for ≥ 14 days in 6 months before Visit 1

8. EFFICACY AND SAFETY ASSESSMENTS

8.1. Safety Variables

Assessments of safety and tolerability will be done in Parts A and B. The Visit 1 Part A assessments will be used as baseline for Part A, and Visit 1 Part B assessments will be used as baseline for Part B.

8.1.1. Medical History and Use of Contraception

At Screening for Part A, a medical history will be performed and include subject demographics, documentation of history of DM, organ involvement with DM, and current treatment for DM. The medical history will also include concurrent illnesses, other current medications, past

medical history, child-bearing potential and confirmation of last menstrual period (LMP) for women, family history of DM or prolonged QT interval, and review of systems. At Screening for Part B, this medical history will be updated. Use of highly effective methods of contraception will be assessed at Screening through Visit 7 for WOCBP (Part A) and Screening and Visits 1 through Follow-Up Visit (Part B) for WOCBP.

8.1.2. Concomitant Medication and Treatment History

A list of current prescription and over-the-counter medications, supplements, treatments and devices for DM will be obtained. Assessment of eligibility should include a review of permitted and prohibited medications. Concomitant medications will be recorded on the concomitant medication CRF from Screening through Visit 7 (Part A) or Visit 1 through Follow-Up Visit (Part B). The medication, dose, frequency, route, start date, stop date, and indication will be captured.

8.1.3. Physical Examination

Physical examinations will be done at Screening and at Visits 1, 6 and 7 (Part A) and as outlined in Sections 9.2 – 9.5 for Part B. At Screening, a physical examination is performed to assist in determining the subject's eligibility for the study. The physical exam will include an assessment of alertness and orientation, general appearance, skin, eyes, ears, nose, throat, heart, lungs, abdomen, muscle strength, reflexes, lymph nodes, spine, and extremities. Breast and genitourinary examinations are not required. Details will be provided in the MOP (Part A of study).

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

8.1.4. Vital Signs, Height and Weight Measurements

Systolic and diastolic BP, pulse (P), respiratory rate (R), and temperature will be recorded on Screening and all study visits. Blood pressure will be measured with the subject seated and will be recorded twice after at least 5 minutes of rest. The same arm will be used for the measurement throughout the study. The mean values of both measurements will be used. Pulse will also be measured with the subject seated at rest for at least 5 minutes. Body temperature will be measured on the skin or in the mouth. These vital sign measurements will be obtained prior to taking samples for the laboratory testing at the applicable study visits.

Weight will be measured on Visits 1, 6, and 7 (Part A) and as outlined in Sections 9.2 – 9.5 in Part B with outerwear, such as coats and jackets, and footwear removed. Standing height is to be measured at Visit 1 of Parts A and B with footwear removed.

8.1.5. Adverse Events

Adverse Events and Serious Adverse Events

The incidence of all AEs, and all SAEs will be assessed from the time of informed consent.

An AE is any symptom, sign, illness or experience or untoward medical occurrence that develops or worsens in severity in a subject administered study product and which does not necessarily have to 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 product, whether or not considered related to the

study product. Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Intercurrent illnesses or injuries will be regarded as AEs.

This definition also includes accidental injuries, reasons for any change in medication (drug 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. Any laboratory abnormality assessed as clinically significant by the investigator must be recorded as an AE.

Abnormal results of diagnostic procedures will be considered to be AEs if the abnormality has any one 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;
- Is considered by the investigator to be of clinical significance.

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. 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 qualified designees 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 AEs, 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 product, and the outcome of the event.

Serious Adverse Events

SAEs are a subset of AEs. A SAE is defined as any AE that meets any one of the following criteria:

- Results in death;
- Is life-threatening;
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity;

- Is a congenital anomaly or birth defect;
- Is an important medical event.

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.

Medical and scientific 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 the course of a treatment should be considered as medically important.

An AE caused by an overdose or medication error is considered serious if a criterion listed in the definition above is fulfilled.

All SAEs will be reported by the Corbus regulatory representative to FDA, in accordance with 21CFR312.

Events of Special Interest

The following events will be captured as events of special interest:

- QTc prolongation > 500 msec total duration or > 60 msec from baseline;
- Worsening of muscle disease so that treatment with oral corticosteroids > 10 mg/day or > 20 mg every other day, or equivalent dose, is indicated;
- Aspartate aminotransferase or alanine aminotransferase ≥ 3 x upper limit of normal, with total bilirubin > 1.5 x the upper limit of normal, present on repeat testing.

Disease Flare

Any medically significant worsening in DM, as judged by the investigator, will be recorded as an AE.

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

Throughout the duration of the study, the investigator or qualified designees will closely monitor each subject for evidence of drug intolerance and for the development of clinical or laboratory evidence of AEs. All AEs which occur during the course of the study, whether observed by the investigator or reported by the subject, and whether or not thought to be drug-related, will be recorded. The description of the AEs as recorded on the CRF will include description of event, start date, stop date, intensity, if it was serious, relationship to study product, if the subject died, what actions were taken with respect to the study product, if treatment was required, and the outcome of the event.

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

The investigator will appraise 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 product and about the subject's outcome.

Time Period 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 held approximately 28 days after study product is stopped or at the Withdrawal Visit. Subjects will be followed at least every 28 ± 3 days in Part A and 56 ± 7 days in Part B during the study.

The investigator or qualified designee will record all adverse events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Serious adverse events will be followed for outcome information until the event resolves or is considered by the principal investigator to be clinically stable.

Characteristics of an Adverse Event

Severity of Adverse Events

Severity of AEs will be described by the following criteria:

- Mild: asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Moderate: minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living
- Severe: Medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
- Life-threatening: urgent intervention indicated
- Death

Relationship to Study Product

A TEAE is an AE for which the start date is on or after the date that the subject received study product.

To assess relationship of an event to study product, the following guidelines are suggested:

1. **Related** (Possible, Probable, Definite)
    - The event is known to occur as a class effect with the study product.
    - There is a temporal relationship between the intervention and event onset.

- The event abates when the intervention is discontinued.
- The event reappears upon a re-challenge with the intervention.

2. **Not Related** (Unlikely, Not Related)

- There is no temporal relationship between the intervention and event onset.
- An alternate etiology has been established.

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

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

Expectedness of Adverse Events

Corbus will retain detailed records of all AEs reported by the investigator or qualified designees and perform an evaluation with respect to seriousness, causality and expectedness. Corbus will determine expectedness of an AE. Expected/unexpected is defined from the perspective of previously observed, not on the basis of what might be anticipated from the pharmacological properties of a medicinal product. An "unexpected" adverse reaction is one for which the nature or severity is not consistent with information in the relevant source document(s), including the IB, the general investigational plan in the Investigational New Drug (IND) Application or the study protocol.

Unexpected AE or unexpected suspected AE: An AE or suspected AE will be considered "unexpected" if it is not listed in the Investigator's Brochure or is not listed at the specificity or severity that has been observed; or is not consistent with the risk information described in the general investigational plan or protocol (see Section 4.3.1 above). "Unexpected" also refers to AEs or suspected adverse reactions that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug but are not specifically mentioned as occurring with the particular drug under investigation.

Reporting Procedures

The conduct of the study will comply with all FDA, DEA, and IRB-specific safety reporting requirements.

Investigational New Drug Annual Reports

An annual report will be provided by Corbus to the FDA within 60 days of the IND anniversary date. The Annual Report should be filed in the study's Regulatory Binder.

Investigator Reporting to the Drug Enforcement Administration

The investigator or qualified designee will keep a copy of all completed DEA 222 forms, indicating the amount of substance ordered, and a log of all substance received, placed in the secure storage area and removed from storage for dispensing to subjects. If the substance is contaminated, the investigator or qualified designee will complete DEA Form 41, which requires the signature of a witness. If the substance is lost or stolen, the investigator or qualified designee will notify the Philadelphia DEA immediately and submit DEA Form 106 within 24 hours.

Unanticipated Problem Reporting to IRB

Incidents or events that meet the criteria for unanticipated problems that need to be reported to the IRB (as per FDA Guidance for Clinical investigator, Sponsors, and IRBs. Adverse Event Reporting to IRBs – Improving Human Subject Protection) require the completion of an unanticipated problem CRF by the investigator or qualified designee, which will be sent by e-mail or FAX to the Medical Monitor within 24 hours of learning of the event. Through this mechanism, the Medical Monitor will receive an alert that the report has been or is being filed with the reviewing RB. The investigator will follow the reviewing IRB's procedures when reporting an AE or any other incident, experience, or outcome as an unanticipated problem to that IRB.

To satisfy the requirement for prompt reporting, unanticipated problems will be reported using the following timeline:

- SUSARs will be reported to the IRB within 7 days of the investigator becoming aware of the event and to FDA according to the timeframes of 21CFR312;
- Any other unanticipated problem will be reported to the IRB 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.

Reporting of SAEs and AEs to Corbus

All AEs will be reported to Corbus through AE CRFs.

SAEs must be reported immediately to the Corbus Medical Monitor (no more than 24 hours after becoming aware of the event). The investigator must FAX or e-mail the initial SAE report immediately to the Medical Monitor who in turn will contact the Corbus Regulatory Representative for contacting the FDA and the principal investigator for reporting to NIAMS. Any AE that meets the specified SAE criteria will be recorded on an SAE CRF, by the investigator or qualified designee. Follow-up information on the SAE will be provided in a timely manner to the Medical Monitor.

Reporting of SAEs and AEs to NIAMS

The principal investigator will report all AEs, both serious and non-serious, semi-annually to NIAMS and the NIAMS Safety Monitor. All SAEs require expedited reporting by the principal investigator to NIAMS and the NIAMS Safety Monitor within 48 hours of becoming aware of the event.

Reporting of SAEs and AEs to FDA

This study will be conducted under an IND application (IND 116313) with the FDA. The mandatory reporting of safety events to the FDA will be followed, as outlined in 21 CFR 312.32 by the Regulatory Affairs consultant to Corbus.

Adverse drug reactions that are serious, unlisted/unexpected, and at least possibly associated to the drug, and that have not previously been reported in the Investigator's Brochure, or reference safety information document will be reported promptly to the FDA in writing by Corbus. A clear description of the suspected reaction will be provided along with an assessment as to whether the event is drug or disease related.

Corbus shall, via their regulatory representative, notify the FDA by telephone or by fax of any unexpected fatal or life threatening experience associated with the use of the drug as soon as possible and within 24 hours of receiving notification and then follow-up with an FDA report no later than 7 calendar days after the initial receipt of the information.

Adverse Event Updates/ Investigational New Drug Safety Reports

Corbus is responsible for notifying the investigator via an IND Safety Report of the following information:

- Any AE associated with the use of study product in this study or in other studies that is both serious and unexpected;
- Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

The investigator should notify the IRB promptly of new serious and unexpected AE(s) or significant risks to subjects. The investigator must keep copies of all AE information on file, including correspondence with Corbus, the Safety Monitoring Committee, and the IRB.

8.1.6. Blood and Urine Laboratory Safety Measurements

Blood and urine laboratory safety tests will be performed throughout the study. The results of all safety tests will be reviewed by the investigator or qualified designee, who will make judgments on the medical significance of any new or worsening abnormal value. The results of clinical laboratory tests at Screening for Part A and Part B will assist in identifying subjects who are not suitable for trial due to some biochemical or hematological abnormalities not detectable by clinical examination. Subjects with abnormal screening results that are clinically significant will not be enrolled.

The results of clinical laboratory tests on Visit 1 in Parts A and B prior to study product administration will provide a baseline reference against which any fluctuations in these indices during the treatment phase of the trial can be compared. If any previously normal indices become abnormal and medically significant, then they will be recorded as AEs. The clinical significance of any changes will be assessed by the investigator or qualified designee.

The laboratory safety tests will be performed in licensed, local clinical laboratories, to provide appropriate longitudinal and cross-site comparisons. The following laboratory safety tests will be performed, according to the study schedule:

- Pregnancy tests: Serum βHCG and urine pregnancy tests, the latter of which may be performed using a certified test (dipstick);
- Follicle Stimulating Hormone;
- HIV screening test;
- Hepatitis B core antibody, Hepatitis B surface antigen and Hepatitis C antibody;
- QuantiFERON;
- Complete blood count with differential cell count and platelets;
- Metabolic panel including glucose, urea nitrogen, creatinine, estimated glomerular filtration rate, blood urea nitrogen/creatinine, sodium, potassium, chloride, carbon dioxide, calcium, protein total, albumin, bilirubin total, alkaline phosphatase, aspartate aminotransferase, and alanine aminotransferase;
- Urine dipstick for blood, albumin/protein, and glucose.

8.1.7. Electrocardiograms and QT/QTc Intervals

Twelve-lead ECGs are to be recorded at Screening and Visits 1, 3, 5, and 6 (Part A) and as outlined in Sections 9.2 – 9.5 for Part B, and they will be evaluated for medically significant abnormalities and QT/QTc intervals. An ECG will be recorded with the subject in a rested supine position for at least 10 minutes prior to performing the test. Food and drink should not be consumed by the subject within the 30 minutes before the ECG is recorded. The investigator or qualified designee will review and provide a reading if the ECG is normal or abnormal, and if abnormal, whether the abnormality is clinically significant, and calculate the QT/QTc interval. The same individual will determine QT/QTc intervals on all ECGs. Any medically significant change from the Visit 1 ECG will be recorded as an AE.

8.1.8. ARCI-M

The ARCI-M questionnaire will be completed by subjects at Visits 1, 3, and 6 in Part A. This is a 12-item yes-no questionnaire developed by the National Institute on Drug Abuse, designed to detect the full range of subjective responses experienced by marijuana users and has been validated by subjects following marijuana smoking (Huestis et al., 2007). The subject will be asked to fill out the ARCI-M prior to other interactions with study staff. Evidence of psychotropic effects of the investigational drug in study subjects as measured by increases in the ARCI-M scale assessed longitudinally.

8.1.9. Manual Muscle Testing-8

The MMT-8 is a partially validated tool that assesses muscle strength. A 0 - 10 point scale and an abbreviated group of 8 proximal, distal, and axial muscles will be used.

8.1.10. Pregnancies

The effect of lenabasum in pregnancy is unknown. Pregnancies occurring while the subject is on lenabasum or within 28 days after the subject's last dose of lenabasum are considered expedited reportable events. 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 discontinue the study product and instruct the subject to return any unused portion of study product to the study staff. 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 and send it to the Medical Monitor within 24 hours after learning of the pregnancy, using either a designated fax number or e-mail address. The pregnancy must be reported to the IRB 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 counseling. The investigator or qualified designee will follow the subject until completion of the pregnancy and for 30 days after the birth, and report follow-up findings to the IRB.

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 via the Corbus Regulatory representative to FDA and to the IRB within 24 hours of knowledge of the event. All neonatal deaths that occur within 30 days of birth should be reported as SAEs without regard to causality.

8.1.11. Tolerability

Tolerability is defined as subject discontinuation of study product from Visits 1-6 in Part A and Visit 1-last dose in Part B because of TEAEs related to study product.

8.2. Efficacy Variables

The same assessments of efficacy will be done in Parts A and B. The Visit 1 Part A assessments will be used as baseline for Part A. Visit 1 Part B assessments will be used as baseline for Part B. In secondary analyses, the Part A Visit 1 assessments may be used as baseline for Part B.

8.2.1. Primary Efficacy Variable

Efficacy will be assessed using CDASI activity score in Parts A and B, comparing change from baseline between the treatment and the placebo groups (Part A) and the change from baseline (Part B). The CDASI will be assessed at Screening through Visit 7 (Part A), and Screening through Follow-Up Visit (Part B). Physician assessments of CDASI should preferably be done by the same investigator and preferably by the principal investigator.

The CDASI is a validated outcome measure that systematically quantifies cutaneous DM disease activity (Klein et al., 2008; Yassaee et al., 2010). In the CDASI, DM skin disease activity is scored from 0 to 100 based on the physician's evaluation of erythema, scale, and erosion or ulceration at fifteen anatomic locations as well as alopecia, Gottron's sign or papules on the hands, and

periungual changes. A four point or greater decrease in the CDASI activity score indicates clinically relevant improvement based on statistical analysis using a receiver operating characteristic curve to maximize sensitivity and specificity (Anyanwu et al., 2013). Data collected at the principal investigator's clinic resulted in a cutoff of 20 points to differentiate mild from moderate and severe disease activity.

[redacted]

[redacted]

[redacted]

9. STUDY PROCEDURES AND FLOW CHART

9.1. Flow Chart, Part A

STUDY ACTIVITY	Visit and Study Day					
	Screening	1	2	3	4	5
	Up to 28 Days Prior to Visit 1	Day 1	Day 15 ± 3	Day 29 ± 3	Day 43 ± 3	Day 57 ± 3
ELIGIBILITY						
Written informed consent	X					
Verify eligibility criteria	X	X				
Medical history (including LMP for WOCBP[a])	X					
Record concomitant medications	X	X	X	X	X	X
Contraceptive assessment, for WOCBP	X	X	X	X	X	X
Physical examination	X	X				
Human immunodeficiency virus, Hepatitis B core antibody, Hepatitis B surface antigen and Hepatitis C antibody	X					
QuantiFERON	X					
Follicle stimulating hormone, if applicable	X					
Serum β human chorionic gonadotropin, for WOCBP	X					
Urine β human chorionic gonadotropin, for WOCBP		X		X		X
RANDOMIZATION						
Randomization, prior to		X				
STUDY PRODUCT ADMINISTRATION						
Dispense study product for home administration		X[b]		X[b]		X[b]
Administer study product in clinic		X[c]				
Count capsules of unused study product			X	X	X	X
SAFETY ASSESSMENTS						
Blood pressure[d], pulse, respiratory rate, temperature	X	X	X	X	X	X
Weight		X				
Height		X				
Adverse event monitoring		X	X	X	X	X
Complete blood count with differential and platelets	X	X	X	X	X	X

STUDY ACTIVITY	Visit and Study Day					
	Screening	1	2	3	4	5
	Up to 28 Days Prior to Visit 1	Day 1	Day 15 ± 3	Day 29 ± 3	Day 43 ± 3	Day 57 ± 3
Metabolic panel[e]	X	X	X	X	X	X
Urine dipstick[f]	X	X		X		X
12 lead electrocardiograms with QT/QTc intervals	X	X		X		X
Addiction Research Center Inventory-Marijuana		X		X		
Manual Muscle Testing-8		X		X		X
PRIMARY EFFICACY ASSESSMENT						
Cutaneous Dermatomyositis Disease Activity and Severity Index	X	X	X	X	X	X
SECONDARY EFFICACY ASSESSMENTS						
[redacted]						
MECHANISM OF ACTION						
Metabolipidomic profile		X	X	X		X
PHARMACOKINETICS						
Lenabasum plasma concentrations and metabolites		X	X	X		X
BIOMARKERS						
[redacted]						

[a] Abbreviation: WOCBP; women of childbearing potential.
[b] Study product will be dispensed in WOCBP only if urine pregnancy test is negative.
[c] The first dose of study product on Visit 1 will be taken in clinic from the dispensed study product. Afterwards, subjects will be observed in cl
minutes, or until stable, if longer.
[d] Seated or reclining (≥ 5 minutes) blood pressure and pulse.
[e] Metabolic panel includes glucose, urea nitrogen, creatinine, estimated glomerular filtration rate, blood urea nitrogen/creatinine, sodium, potass
dioxide, calcium, protein total, albumin, bilirubin total, alkaline phosphatase, aspartate aminotransferase, and alanine aminotransferase.
[f] Includes blood, albumin/protein, and glucose.

[g] One 4 mm punch biopsy will be obtained from an area of non-lesional skin on Visit 1 (optional). One 4 mm punch biopsy will be obtained fr
skin on Visits 1, 3, and 6 (optional).

9.2. Flow Chart, Part B Year 1

STUDY ACTIVITY	Visit and Study Day							
	Screening[a]	1	2	3	4	5	6	7
	Up to 28 days Before Visit 1	Day 1	Day 28 ± 7	Day 85 ± 7	Day 141 ± 7	Day 197 ± 7	Day 253 ± 7	Day 309 ±
ELIGIBILITY								
Written Informed Consent	X							
Verify eligibility criteria	X	X						
Medical history (including LMP for WOCBP[b])	X							
Record concomitant medications	X	X	X	X	X	X	X	X
Contraceptive assessment, for WOCBP	X	X	X	X	X	X	X	X
Physical examination	X	X		X		X		
Serum β human chorionic gonadotropin, for WOCBP[c]	X							
Urine β human chorionic gonadotropin, for WOCBP		X	X	X	X	X	X	X
STUDY PRODUCT ADMINISTRATION								
Dispense study product for home administration[d]		X	X	X	X	X	X	X
Administer study product in clinic		X[e]						
Count capsules of returned study product			X	X	X	X	X	X
SAFETY ASSESSMENTS								
Blood pressure[f], pulse, respiration, and temperature	X	X	X	X	X	X	X	X
Height		X						
Weight		X		X		X		
Adverse event monitoring		X	X	X	X	X	X	X
Complete blood count with differential cell count and platelets	X	X	X	X	X	X	X	X
Metabolic panel[g]	X	X	X	X	X	X	X	X
Urine dipstick[h]		X		X		X		
Twelve-lead electrocardiograms with QT/QTc intervals	X	X		X		X		
Manual Muscle Testing-8		X		X		X		
Safety phone call to subject 3-5 weeks post visit				X	X	X	X	X

STUDY ACTIVITY	Visit and Study Day							
	Screening[a]	1	2	3	4	5	6	7
	Up to 28 days Before Visit 1	Day 1	Day 28 ± 7	Day 85 ± 7	Day 141 ± 7	Day 197 ± 7	Day 253 ± 7	Day 309 ±
PRIMARY EFFICACY ASSESSMENT								
CDASI	X	X	X	X	X	X	X	X
SECONDAY EFFICACY OUTCOMES								
[redacted]								
[redacted]								
[redacted]								
[redacted]								
[redacted]								
BIOMARKERS								
[redacted]								
[redacted]								

[a] May overlap with Visit 6 for Part A
[b] Abbreviation: WOCBP; women of childbearing potential.
[c] Urine βHCG may be substituted is subject had prior negative urine βHGC within 28 ± 3 days in Part A.
[d] Study product will be dispensed in WOCBP only if urine pregnancy test is negative.
[e] The first dose of study product on Visit 1 will be taken in clinic from the dispensed study product. The subject will be observed for 3
whichever is longer.
[f] Seated or reclining (≥ 5 minutes) blood pressure and pulse.
[g] Metabolic panel includes glucose, urea nitrogen, creatinine, estimated glomerular filtration rate, blood urea nitrogen/creatinine, sodiu
carbon dioxide, calcium, protein total, albumin, bilirubin total, alkaline phosphatase, aspartate aminotransferase, and alanine aminotran
[h] Includes blood, albumin/protein, and glucose.
[i] For subjects who do not consent to participate in year 2 extension of open label part of the study.
[j] Subjects continuing into year 2 extension will be re-consented at Visit 8, can be done at any Visit prior to Visit 8.
[k] Only for subjects who sign the consent and chose to participate in year 2 extension of open label part of the study.

9.3. Flow Chart, Part B Year 2

STUDY ACTIVITY	Visit and Study Day						
	9	10	11	12	13	14	15
	Day 421 ± 7	Day 477 ± 7	Day 533 ± 7	Day 589 ± 7	Day 645 ± 7	Day 701 ± 7	Day 757 ± 7
ELIGIBILITY							
Written Informed Consent							X[f]
Verify eligibility criteria							
Medical history (including LMP for WOCBP[a])							
Record concomitant medications	X	X	X	X	X	X	X
Contraceptive assessment, for WOCBP	X	X	X	X	X	X	X
Physical examination			X		X		X
Serum β human chorionic gonadotropin, for WOCBP							
Urine β human chorionic gonadotropin, for WOCBP	X	X	X	X	X	X	X
STUDY PRODUCT ADMINISTRATION							
Dispense study product for home administration[b]	X	X	X	X	X	X	
Administer study product in clinic							
Count capsules of returned study product	X	X	X	X	X	X	X
SAFETY ASSESSMENTS							
Blood pressure[c], pulse, respiration, and temperature	X	X	X	X	X	X	X
Height	X						
Weight	X		X		X		X
Adverse event monitoring	X	X	X	X	X	X	X
Complete blood count with differential cell count and platelets	X	X	X	X	X	X	X
Metabolic panel[d]	X	X	X	X	X	X	X
Urine dipstick[e]			X		X		X
Twelve-lead electrocardiograms with QT/QTc intervals			X		X		X

STUDY ACTIVITY	Visit and Study Day						
	9	10	11	12	13	14	15
	Day 421 ± 7	Day 477 ± 7	Day 533 ± 7	Day 589 ± 7	Day 645 ± 7	Day 701 ± 7	Day 757 ± 7
Manual Muscle Testing-8			X		X		X
Safety phone call to subject 3-5 weeks post visit	X	X	X	X	X	X	
PRIMARY EFFICACY ASSESSMENT							
CDASI	X	X	X	X	X	X	X
SECONDARY EFFICACY OUTCOMES							
[redacted]							
[redacted]							
[redacted]							
[redacted]							
[redacted]							
BIOMARKERS							
[redacted]							
[redacted]							

[a] Abbreviation: WOCBP; women of childbearing potential.
[b] Study product will be dispensed in WOCBP only if urine pregnancy test is negative.
[c] Seated or reclining (≥ 5 minutes) blood pressure and pulse.
[d] Metabolic panel includes glucose, urea nitrogen, creatinine, estimated glomerular filtration rate, blood urea nitrogen/creatinine, so
chloride, carbon dioxide, calcium, protein total, albumin, bilirubin total, alkaline phosphatase, aspartate aminotransferase, and alan
[e] Includes blood, albumin/protein, and glucose.
[f] Subjects continuing to the Year 3 extension should sign an ICF by Visit 15 and preferably earlier than Visit 15, if possible.

9.4. Flow Chart Part B, Year 3

STUDY ACTIVITY	Visit and Study Day						
	16	17	18	19	20	21	22
	Day 813 ± 7	Day 869 ± 7	Day 925 ± 7	Day 981 ± 7	Day 1037 ± 7	Day 1093 ± 7	Day 1149 ± 7
ELIGIBILITY							
Written Informed Consent							X[f]
Record concomitant medications	X	X	X	X	X	X	X
Contraceptive assessment, for WOCBP[a]	X	X	X	X	X	X	X
Physical examination			X		X		X
Urine β human chorionic gonadotropin, for WOCBP	X	X	X	X	X	X	X
STUDY PRODUCT ADMINISTRATION							
Dispense study product for home administration[b]	X	X	X	X	X	X	
Count capsules of returned study product	X	X	X	X	X	X	X
SAFETY ASSESSMENTS							
Blood pressure[c], pulse, respiration, and temperature	X	X	X	X	X	X	X
Height	X						
Weight	X		X		X		X
Adverse event monitoring	X	X	X	X	X	X	X
Complete blood count with differential cell count and platelets	X	X	X	X	X	X	X
Metabolic panel[d]	X	X	X	X	X	X	X
Urine dipstick[e]			X		X		X
Twelve-lead electrocardiograms with QT/QTc intervals			X		X		X
Manual Muscle Testing-8			X		X		X
Safety phone call to subject 3-5 weeks post visit	X	X	X	X	X	X	
PRIMARY EFFICACY ASSESSMENT							
CDASI	X	X	X	X	X	X	X

STUDY ACTIVITY	Visit and Study Day						
	16	17	18	19	20	21	22
	Day 813 ± 7	Day 869 ± 7	Day 925 ± 7	Day 981 ± 7	Day 1037 ± 7	Day 1093 ± 7	Day 1149 ± 7
SECONDARY EFFICACY OUTCOMES							
Physician Global Assessments	X	X	X	X	X	X	X
Patient Global Assessments	X	X	X	X	X	X	X
SkinDex-29+3	X	X	X	X	X	X	X
PROMIS-29 Short Form	X	X	X	X	X	X	X
Photography of skin lesions (optional)			X				X
BIOMARKERS							
C-reactive protein			X		X		X
Creatine phosphokinase and aldolase			X		X		X

[a] Abbreviation: WOCBP; women of childbearing potential.
[b] Study product will be dispensed in WOCBP only if urine pregnancy test is negative.
[c] Seated or reclining (≥ 5 minutes) blood pressure and pulse
[d] Metabolic panel includes glucose, urea nitrogen, creatinine, estimated glomerular filtration rate, blood urea nitrogen/creatinine, so chloride, carbon dioxide, calcium, protein total, albumin, bilirubin total, alkaline phosphatase, aspartate aminotransferase, and alan
[e] Includes blood, albumin/protein, and glucose
[f] Subjects continuing to the Year 4 extension should sign an ICF by Visit 22 and preferably earlier than Visit 22, if possible.

9.5. Flow Chart Part B, Year 4

STUDY ACTIVITY	Visit and Study Day						
	23	24	25	26	27	28	29
	Day 1205 ± 7	Day 1261 ± 7	Day 1317 ± 7	Day 1373 ± 7	Day 1429 ± 7	Day 1485 ± 7	Day 1541 ± 7
ELIGIBILITY							
Written Informed Consent							X[f]
Record concomitant medications	X	X	X	X	X	X	X
Contraceptive assessment, for WOCBP[a]	X	X	X	X	X	X	X
Physical examination			X		X		X
Urine β human chorionic gonadotropin, for WOCBP	X	X	X	X	X	X	X

STUDY ACTIVITY	Visit and Study Day						
	23	24	25	26	27	28	29
	Day 1205 ± 7	Day 1261 ± 7	Day 1317 ± 7	Day 1373 ± 7	Day 1429 ± 7	Day 1485 ± 7	Day 1541 ± 7
STUDY PRODUCT ADMINISTRATION							
Dispense study product for home administration[b]	X	X	X	X	X	X	
Count capsules of returned study product	X	X	X	X	X	X	X
SAFETY ASSESSMENTS							
Blood pressure[c], pulse, respiration, and temperature	X	X	X	X	X	X	X
Height	X						
Weight	X		X		X		X
Adverse event monitoring	X	X	X	X	X	X	X
Complete blood count with differential cell count and platelets	X	X	X	X	X	X	X
Metabolic panel[d]	X	X	X	X	X	X	X
Urine dipstick[e]			X		X		X
Twelve-lead electrocardiograms with QT/QTc intervals			X		X		X
Manual Muscle Testing-8			X		X		X
Safety phone call to subject 3-5 weeks post visit	X	X	X	X	X	X	
PRIMARY EFFICACY ASSESSMENT							
CDASI	X	X	X	X	X	X	X

STUDY ACTIVITY	Visit and Study Day						
	23	24	25	26	27	28	29
	Day 1205 ± 7	Day 1261 ± 7	Day 1317 ± 7	Day 1373 ± 7	Day 1429 ± 7	Day 1485 ± 7	Day 1541 ± 7
SECONDARY EFFICACY OUTCOMES							
[redacted]							
[redacted]							
[redacted]							
[redacted]							
[redacted]							
BIOMARKERS							
[redacted]							
[redacted]							

[a] Abbreviation: WOCBP; women of childbearing potential.
[b] Study product will be dispensed in WOCBP only if urine pregnancy test is negative.
[c] Seated or reclining (≥ 5 minutes) blood pressure and pulse
[d] Metabolic panel includes glucose, urea nitrogen, creatinine, estimated glomerular filtration rate, blood urea nitrogen/creatinine, so chloride, carbon dioxide, calcium, protein total, albumin, bilirubin total, alkaline phosphatase, aspartate aminotransferase, and alan
[e] Includes blood, albumin/protein, and glucose
[f] Should the OLE be extended, continuing subjects should sign an ICF by the last visit of each respective year, as applicable, and p possible.

9.6. Study Visits

All subjects who are assigned a SID and receive any study product will be followed according to the protocol regardless of the amount of study product administered, unless consent for follow-up is withdrawn. The sponsor must be notified of all deviations from protocol visits or evaluations and these evaluations, if applicable, must be rescheduled or performed at the nearest possible time to the original schedule.

If a subject is withdrawn from the study or discontinues the study on or before Visit 1 in either Part A or B, no additional procedures should be done. If withdrawal or discontinuation is after Visit 1 and at the time of a scheduled visit, the procedures scheduled for that visit should be done and a Withdrawal Visit should be done approximately 28 days after the last dose of study product, unless consent is withdrawn. If withdrawal or discontinuation is after Visit 1 and not at the time of a scheduled visit, then an unscheduled visit should be done as soon as possible and include laboratory safety testing, and a Withdrawal Visit should be done approximately 28 days after the last dose of study product, unless consent is withdrawn.

Subjects will be instructed to call study personnel to report any abnormalities during the intervals between study visits and to come to the study site if medical evaluation is needed. An unscheduled visit will be made, if necessary, for medical issues that arise between study visits. For emergency and other unscheduled visits to a medical facility other than the study site, medical records will be obtained by the investigator or qualified designee.

Specific procedures for sample collection, processing and time requirements for processing, aliquots of specimens, labeling, storage, required temperatures, and shipment can be found in the MOP (Part A of study).

9.6.1. Study Screening, Part A (up to 28 days Prior to Visit 1)

The following procedures will be performed:

- Consent presentation and consent signing
- Verify eligibility criteria
- Medical history, including confirmation of last menstrual period, for WOCBP
- Record concomitant medications
- Assess use of highly effective method of contraception, for WOCBP

- BP, P, R, and temperature
- Physical examination
- Blood and urine tests
  - Human immunodeficiency virus test
  - Hepatitis B core antibody, Hepatitis B surface antigen and Hepatitis C antibody
  - [redacted]
  - Follicle stimulating hormone, for women > 45 and ≤ 55 years of age with no menses for < 2 years
  - Serum βHCG, WOCBP
  - CBC with differential cell count and platelets
  - Metabolic panel
  - [redacted]
  - Urinalysis
- Twelve-lead ECG for medically significant abnormalities and QT/QTc interval
- Physician assessment
  - CDASI

9.6.2. Visit 1, Part A (Day 1)

The following procedures will be performed:

- Verify eligibility criteria
- Patient-reported outcomes, before other interactions with study staff
  [redacted]
- Record concomitant medications
- Assess use of highly effective method of contraception, for WOCBP
- Physical examination
- Height, weight, BP, P, R, and temperature
- AE monitoring
- Blood and urine tests before study product administration
  - CBC with differential cell count and platelets

  - Metabolic panel
  - [redacted]
  - [redacted]
  - [redacted]
  - Lenabasum plasma concentration
  - Urine βHCG for WOCBP, dispense study product to WOCBP only if negative
  - Urinalysis
- Twelve-lead ECG for medically significant abnormalities and QT/QTc prior to study product administration
- Physician assessments
  [redacted]
- [redacted]
- Dispense study product according to randomization schedule
- Administer one dose of newly dispensed study product in clinic
- Observe subject in clinic for 30 minutes after study product administration or until stable, if longer

9.6.3. Visit 2, Part A (Day 15 ± 3)

The following procedures will be performed:

- Record concomitant medications
- Assess use of highly effective method of contraception, for WOCBP
- BP, P, R, and temperature
- AE monitoring
- Blood tests
  - CBC with differential cell count and platelets
  - Metabolic panel
  [redacted]

[redacted]

- Lenabasum plasma concentration

- Physician assessment
  - CDASI

- Count capsules of unused study product

9.6.4. Visit 3, Part A (Day 29 ± 3)

The following procedures will be performed:

- Patient-reported outcomes, before other interactions with study staff
  [redacted]
- Record concomitant medications
- Assess use of highly effective method of contraception, for WOCBP
- BP, P, R, and temperature
- AE monitoring
- Blood and urine tests
  - CBC with differential cell count and platelets
  - Metabolic panel
  - [redacted]
  - Lenabasum plasma concentration
  - Urine βHCG for WOCBP, dispense study product to WOCBP only if negative
  - Urinalysis
- Twelve-lead ECG for medically significant abnormalities and QT/QTc interval
- Physician assessments
  [redacted]

[redacted]

- Collect unused study product and count capsules
- Dispense study product according to randomization schedule, after subject returns unused study product

9.6.5. Visit 4, Part A (Day 43 ± 3)

The following procedures will be performed:

- Record concomitant medications
- Assess use of highly effective method of contraception, for WOCBP
- BP, P, R, and temperature
- AE monitoring
- Blood tests
  - CBC with differential cell count and platelets
  - Metabolic panel
- Physician assessment
  - CDASI
- Count capsules of unused study product

9.6.6. Visit 5, Part A (Day 57 ± 3)

- Patient-reported outcomes, before other interactions with study staff

  [redacted]
- Assess use of highly effective method of contraception, for WOCBP
- Record concomitant medications
- BP, P, R, and temperature
- AE monitoring
- Blood and urine tests
  - CBC with differential cell count and platelets

- Metabolic panel

[redacted]

- Lenabasum plasma concentration
- Urine βHCG for WOCBP, dispense study product to WOCBP only if negative
- Urinalysis

- Twelve-lead ECG for medically significant abnormalities and QT/QTc interval
- Physician assessments

[redacted]

- Collect unused study product and count capsules
- Dispense study product according to randomization schedule, after subject returns unused study product

9.6.7. Visit 6, Part A (Day 85 ± 3)

The following procedures will be performed:

- Patient-reported outcomes, before other interactions with study staff

[redacted]

- Record concomitant medications
- Assess use of highly effective method of contraception, for WOCBP
- Weight, BP, P, R, and temperature
- Physical examination
- AE monitoring
- Blood and urine tests

- CBC with differential cell count and platelets
- Metabolic panel

[redacted]

- Lenabasum plasma concentration
- Urine βHCG for WOCBP
- Urinalysis
  - Twelve-lead ECG for medically significant abnormalities and QT/QTc interval
  - Physician assessments

[redacted]

- Collect unused study product and count capsules

9.6.8. Visit 7, or Withdrawal Visit Part A (Day 113 ± 3)

The following procedures will be performed:

- Patient-reported outcomes, before other interactions with study staff

  [redacted]

- Record concomitant medications
- Assess use of highly effective method of contraception, for WOCBP
- Weight, BP, P, R, and temperature
- Physical examination
- AE monitoring
- Blood and urine tests
  - CBC with differential cell count and platelets
  - Metabolic panel
  - [redacted]
  - Urine βHCG for WOCBP
- Physician assessments

  [redacted]

[redacted]

- Collect any remaining unused study product and count capsules

Visit 7, Part A and Screening, Part B can be done at the same visit. If so, relevant procedures done for Visit 7, Part A also can be used as Screening, Part B procedures, although additional procedures will need to be done to complete the requirements for Screening, Part B (See Section 9.5.9).

9.6.9. Screening, Part B (up to 28 Days Prior to Visit 1)

Some subjects may have a break between Part A and Part B. All subjects should make a decision whether to be screened for Part B, within three months of Part B being open for enrollment at the site or their completion of Visit 7, Part A, whichever is later. Screening can then be done at the earliest convenience of the subject and investigator.

If there is a break between Visit 7, Part A and Screening, Part B, then all Screening procedures for Part B need to be done. If Screening, Part B is at the same time as Visit 7, Part A, then any overlapping procedures for Screening, Part B do not need to be duplicated. Among the procedures listed below that will be done at Screening, Part B, those procedures that are not overlapping with Visit 7, Part A procedures are indicated.

The following procedures will be performed.

- Consent presentation and consent signing (does not overlap with Visits 7, Part A)
- Verify eligibility criteria (does not overlap with Visit 7, Part A)
- Medical history (does not overlap with Visit 7, Part A)
- Patient-reported outcomes, before other interactions with study staff:

  [redacted]
- Confirm date of LMP in WOCBP
- Record concomitant medications
- Assess birth control status, if applicable
- Weight, BP, P, R, and temperature
- Physical examination
- Blood and urine tests:

- Serum βHCG, for WOCBP, or urine βHCG if the last negative urine βHCG was within 28 ± 3 days (serum βHCG does not overlap with Visit 7, Part A);
- CBC with differential cell count and platelets;
- Metabolic panel

- 12 lead ECG for medically significant abnormalities and QT/QTc interval (does not overlap with Visit 7, Part A).
- Physician assessments:
  - CDASI
  - [redacted]

Tests for HIV, hepatitis, and tuberculosis do not need to be repeated for Screening, Part B.

9.6.10. Visit 1, Part B (Day 1)

The following procedures will be performed.

- Verify eligibility criteria
- Patient-reported outcomes, before other interactions with study staff:
  - [redacted]
- Assess birth control status in WOCBP
- Record concomitant medications
- Height, weight, BP, P, R, and temperature
- Physical examination
- AE monitoring
- Blood and urine tests before study product administration:
  - CBC with differential cell count and platelets
  - Metabolic panel, [redacted]
  - Urine βHCG in WOCBP (must be negative before study product is dispensed);
  - Urine dipstick

- 12 lead ECG for medically significant abnormalities and QT/QTc interval prior to study product administration
- Physician assessments:
  - [redacted]
  - CDASI
  - [redacted]
  - [redacted]
- Dispense study product
- Administer study product in clinic and observe for at least 30 minutes or until subject is clinically stable.

9.6.11. Visits 2-29, Part B

The following procedures will be performed:

- Consent presentation and consent signing (Visits 8, 15, and 22)
- Patient-reported outcomes, before other interactions with study staff:
  - [redacted]
  - [redacted]
  - [redacted]
- Contraceptive assessment in WOCBP
- Record concomitant medications
- Height (Visits 9, 16, and 23only)
- Weight (Visits 3, 5, 8, 9, 11, 13, 15, 16, 18, 20, 22, 23, 25, 27, and 29 only)
- BP, P, R, and temperature
- Physical examination (Visits 3, 5, 8, 11, 13,15, 18, 20, 22, 25, 27, and 29 only)
- AE monitoring
- Blood and urine tests before study product administration:
  - CBC with differential cell count and platelets
  - Metabolic panel
  - [redacted]

- Urine βHCG in WOCBP (must be negative before study product is dispensed);
- Urine dipstick (Visits 3, 5, 8, 11, 13, 15, 18, 20, 22, 25, 27, and 29)

- 12 lead ECG for medically significant abnormalities and QT/QTc interval (Visits 3, 5, 8, 11, 13, 15, 18, 20, 22, 25, 27, and 29 only)
- Physician assessments:

  [redacted]

  - CDASI

  [redacted]

  [redacted]
- Dispense study product (Visits 2-28 only)
- Collect any returned study product and count capsules
- Safety phone call will be made by the investigator or qualified designee to the subject between 3-5 weeks post visit, to assess whether any AEs have occurred that would require follow-up evaluation prior to the next visit, assess compliance with medication, and provide any necessary follow-up education to the subject (Visits 3-28 only).

Should the OLE be extended beyond Visit 29, the same assessments as described for Year 4 (Section 9.5) will be followed for each year added, as applicable.

9.6.12. Follow-Up Visit or Withdrawal Visit, Part B (28 ± 7 Days after Discontinuation of Study Product, as Possible)

The following procedures will be performed:

- Patient-reported outcomes, before other interactions with study staff

  [redacted]

  [redacted]

  [redacted]
- Assess use of highly effective method of contraception, for WOCBP
- Record concomitant medications
- Weight, BP, P, R, and temperature
- Physical examination
- AE monitoring
- Blood and urine tests
  - CBC with differential cell count and platelets
  - Metabolic panel

- Urine βHCG for WOCBP

- Physician assessments
  - CDASI

[redacted]

- Collect any remaining unused study product and count capsules

9.6.13. Unscheduled Visit

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

- Record concomitant medications;
- BP, P, R, and temperature;
- Medical history for changes relevant to the reason for the unscheduled visit;
- Physical examination as relevant to the reason for the unscheduled visit;
- AE monitoring;
- Laboratory testing as relevant to the reason for the unscheduled visit.

[redacted]

10. STATISTICAL METHODS PLANNED AND SAMPLE SIZE

Part A of this study is a small-scale, pilot study designed to examine the safety and tolerability of lenabasum and its effectiveness on the disease course of skin-predominant DM. To evaluate mechanism of action of lenabasum in DM, the effects of JBT-1101 on metabolipidomic profiles and biomarkers of disease activity and inflammation will be assessed. Part B of this study is an

open-label extension study to examine the safety, tolerability, and efficacy of lenabasum in subjects who completed dosing in Part A without permanent discontinuation of study product for safety or tolerability reasons.

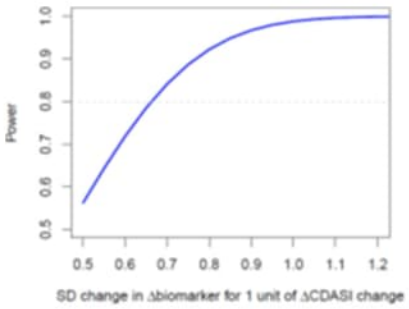
[redacted]

10.1. Determination of Sample Size for Part A

Sample size has been set to detect a clinical meaningful difference of 5 or more points in CDASI change between the two treatment groups. Given the standard deviation in CDASI of 5.8 among eligible study subjects and an inter-person correlation of CDASI of 0.68 in the principal investigator's preliminary data, the standard deviation of CDASI change is 3.45, which corresponds to a 1.35 effect size in standard deviation units. For a two-sided 0.05 level test, 11 study subjects per group is needed to achieve 80% power to detect a significant difference. A total of at least 22 subjects will participate in the study. Given that approximately 20 study subjects will finish the study, the power of detecting a significant difference in biomarker change using a two-side test is shown in Figure 3. The study will have 80% power to detect a significant

difference between two treatment groups for an effect size of 1.33 standard deviations and larger at an α level of 0.05.

Figure 3. Power Calculation for Change in CDASI



Additionally, for secondary efficacy analyses, with this sample size of 22 subjects, 11 subjects within an active group and 11 subjects within the placebo group yields 80% power to detect a statistically significant difference in an efficacy endpoint assuming a 1-sided alpha = 0.10 and an effect size (difference in means/common standard deviation) of 0.93.

10.2. Subject Populations

The subject populations for Parts A and B are defined in the same manner, unless otherwise specified.

The modified intent to treat (ITT) population will consist of all randomized subjects who have received at least one dose of study product. Analysis of the modified ITT population will be used as the primary efficacy analyses and will analyze subjects under the treatment to which they were randomized, regardless of compliance with assigned treatment.

The per protocol (PP) population will consist of subjects who complete the study without major protocol violations deemed likely to affect the efficacy outcomes of interest (these deviations will be classified during a blinded deviation review meeting prior to unblinding the study in Part A). Analysis on the PP population will be used as secondary efficacy analyses, analyzing subjects under the treatment actually received.

The safety population will consist of all subjects who received any study product. Analysis performed on the safety population will be according to the treatment actually received.

Inclusion in the analyses of lenabasum PK will be based upon the frequency and timing of the samples obtained for lenabasum plasma concentration.

The number and percent of subjects in each patient population (modified ITT and PP) will be displayed. Details will be given regarding the reasons for exclusion from each population.

10.3. Statistical Hypotheses

H_0: The mean change from baseline to Day 85 in CDASI activity score between the active group and placebo in Part A (lenabasum group – placebo) at Day 85 = 0.

H_1: The mean change from baseline to Day 85 in CDASI activity score between the active group and placebo in Part A (lenabasum group – placebo) at Day 85 ≠ 0, with superiority of active to placebo claimed if the mean change from baseline to Day 85 in CDASI activity score > 0.

10.4. Subject Disposition

The disposition of all subjects over the course of the trial in Parts A and B will be presented. This presentation will include the number of subjects who completed the study, the number who discontinued early, as well as the reason for study discontinuation. The number and percent of subjects, by treatment group and overall, who discontinue will be summarized by reason for discontinuation. The reasons for discontinuation include:

- Adverse events;
- Withdrawal of Consent;
- Lost to follow-up;
- Other.

10.5. Unit of Analysis

The unit of analysis in this study will be the subject.

10.6. Handling of Missing Data (Imputation Methods)

Missing data will be primarily imputed using last observation carried forward. To check robustness of results, secondary analyses will include analyses of observed data only.

10.7. Methods of Analysis

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 groups. 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 one decimal place. Differences between treatment groups will be calculated as active – placebo and change from baseline will be calculated as follow-up visit – baseline. The baseline measure will be defined as the last non-missing measure prior to initiation of study product. P-values for CDASI activity score will be assessed at a 2-sided alpha = 0.05 level. Other P-values will be assessed at a 1-sided alpha = 0.10 level, unless otherwise noted. Adjustments for multiplicity will not be made due to the early phase of the study.

The subjects' disease activity trends will be compared to their baseline scores and overall improvement will be analyzed. In addition to the change from baseline analyses described, additional analyses of the change from Visit 1 to Visit 3 and from Visit 3 to Visit 7 may be

completed for the analyses of lenabasum and placebo cohorts. Prior to analysis, all data will be examined for missing, outlying, and unrealistic values using both graphical methods and summary statistics.

In Part B, summary statistics will be presented by treatment group (assigned in Part A) and all subjects combined as one group.

Additional statistical approaches may be applied to better understand the efficacy data, such as repeated measures and analysis of variance.

10.8. Demographics and Baseline Characteristics

Subject gender, race, ethnicity, and age will be presented using discrete summary statistics. Age at the time of Visit 1 will also be presented using continuous summary statistics.

Medical history will be summarized by treatment group using discrete summaries.

10.9. Safety Analysis

Safety in both Parts A and B will be assessed by evaluation of vital signs, AEs, blood and urine laboratory tests, ECGs results, including QT/QTc intervals, ARMI-M scores (Part A only), and MMT-8 results. The safety data will be entered into a pharmacovigilance database, and, as part of that database, will be subject to repeated, cumulative meta-analyses of safety data obtained from studies conducted throughout the clinical development of lenabasum.

10.9.1. Vital Signs, Weight and Height

Vital signs (BP, P, R, and temperature), weight, and height will be summarized using continuous summary statistics (mean, standard deviation, minimum, median, and maximum) by visit, and time point including change from baseline summaries.

10.9.2. Adverse Events

The primary outcome is an assessment of safety of lenabasum from Visit 1 through Visit 7 (Part A) and Visit 1 through Follow-up Visit (Part B), using Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class preferred terms to classify AEs. No formal statistical testing will be performed to compare safety in different cohorts.

Safety of lenabasum will be assessed primarily by summarizing treatment emergent AEs and SAEs. Treatment emergent AEs are those AEs that start or worsen after the first dose of study product. The occurrence of AEs and SAEs will be captured from the time the informed consent form is signed through the last completed study visit, for example, the Withdrawal Visit or Visit 7 (Part A) or Follow-up Visit (Part B). Treatment emergent AEs and SAEs will be summarized by system organ class and preferred terms. Similar analyses will be presented by AE severity for related TEAEs, as well as incidence of AEs causing withdrawal. For Part A, the AEs and SAEs will be summarized for placebo, each of the lenabasum doses, and for all lenabasum cohorts combined. For Part B, the AEs and SAEs will be summarized by treatment group assigned in Part A and for all subjects combined. Regarding severity and attribution summaries, the most extreme outcome (highest severity and closest to study product related) will be used for those subjects who experience the same adverse event on more than one occasion.

Safety analyses will be done separately for Part A and Part B, after the separate Part A and Part B databases are locked, and also combined for all subjects who received lenabasum in both Part A and Part B.

Events of special interest will be listed separately in the summary tabulations.

Written narratives will be provided for all serious, unexpected or other significant AEs that are judged to be of special interest because of their clinical importance.

Tolerability will be assessed primarily by numbers and percentages of subjects who discontinue study product, from Visit 1 through Visit 6 in Part A and Visit 1 through last dose in Part B, secondary to a related TEAE. The TEAEs associated with discontinuation of study product will be listed. Tolerability will be summarized for placebo, each of the lenabasum doses, and for all lenabasum cohorts combined.

10.9.3. Blood and Urine Laboratory Safety Tests

Results of laboratory safety tests, including CBC with cell differential and platelets, metabolic panel, and urinalysis will be summarized by visit and for change from baseline to the visit using continuous summary statistics. The number of subjects with low, normal, and high values by visit will also be presented. Shift tables will be presented summarizing the shift from baseline to the visit within the low, normal, and high categorization. Results of pregnancy test will be presented by visit and treatment group.

10.9.4. Electrocardiograms and QT/QTc Intervals

Electrocardiogram results will be described as medically significant abnormalities present or absent at Screening and the specified visits in Parts A and B. Medically significant abnormalities will be tabulated by subject, at Screening and specified visits. QT/QTc intervals will be summarized by visit and change from baseline to the visit using continuous summary statistics. The number of subjects with an increase in QTc to > 500 msec and prolongation of QTc > 60 msec from baseline will be presented by visit, as an event of special interest, for placebo and lenabasum cohorts.

[redacted]

10.10. Efficacy Analysis

10.10.1. Primary Efficacy Analysis

The CDASI activity scores will be summarized by visit and cohort, and for change from baseline to the visit using continuous summary statistics and number and percentage of subjects with ≥ 5,

≥ 8, and ≥ 10 points improvement in CDASI activity score. Comparison of change from baseline in the primary efficacy outcome CDASI (ΔCDASI) activity score between treatment and placebo groups will be performed.

For Part A, an analysis of covariance model for each post-baseline visit will be used with change from baseline the response variable, treatment group as a fixed effect, and baseline as a covariate. The initial analysis will compare lenabasum versus placebo. Least squared means (LSMeans) and standard errors will be presented for each treatment group (lenabasum; placebo) as well as the difference in LSmeans, two-sided 95% confidence interval around the difference, and t-test p-value comparing the difference in LSmeans to 0 to test the primary hypotheses of no difference between the lenabasum group and the placebo group in the mean CDASI activity score.

[redacted]

10.13. Final Analysis Plan

A detailed Statistical Analysis Plan will be compiled before the database lock for Part A. A separate Statistical Analysis Plan will be written to cover Part B, and completed before the database lock for Part B. The Statistical Analysis Plans, for Part A and Part B, will specify all planned analysis in detail.

11. STUDY OVERSIGHT

Corbus is responsible for providing the investigator with the information needed to conduct the investigation properly, including any safety information that would impact the study, ensuring proper monitoring of the study, ensuring conduct is in accordance with investigational plan and protocol, and ensuring all pertinent regulations are followed including maintenance of IND.

The investigator is responsible for ensuring the investigation is conducted according to the signed investigator statement, investigational plan, and applicable regulations; for protecting the rights and safety and welfare of subjects under the investigator's care; and for the control of clinical supplies under investigation. The investigator is responsible for maintaining records of disposition of test articles, accurate case histories of subjects, sending safety reports to Corbus, and for assurance of IRB review at their sites.

11.1. Safety Monitoring Committee

Study progress and oversight of subject safety in this trial will be provided by a Safety Monitoring Committee that will advise Corbus and the principal investigator. The voting members of the Safety Monitoring Committee will include the principal investigator, the Medical Monitor, and an independent expert in DM, who will chair the committee. The voting members will be supported by a blinded biostatistician, who will be a non-voting member. Additional experts in areas related to DM, safety, or regulatory requirements or practices can be added as needed.

The Safety Monitoring Committee will meet according to the following circumstances (whichever occurs sooner): occurrence of the first two Grade 3 SAEs related to study product occurs; enrollment of seven (one third) of the subjects in Part A; one month prior to any scheduled safety review by the NIAMS (Part A only); or 6 months after the first subject is enrolled. The Safety Monitoring Committee will meet every 6 months thereafter, through completion of the study requirements by the last subject. The Safety Monitoring Committee will review blinded interim/cumulative data (Part A) and unblinded data (Part B) for evidence of study-related AEs and factors external to the study such as scientific or therapeutic developments that may impact participant safety.

In addition, if any one of the following events occur during the enrollment, then the Safety Monitoring Committee will review, in an expedited manner, all cumulative safety information and the event(s) of interest:

- Death in any subject related to lenabasum;
- Any life-threatening clinical event (Grade 4 NCI CTCAE criteria) related to lenabasum;

- Determination of unexpected, significant, or unacceptable risk to subjects, in the opinion of the principal investigator or the Medical Monitor.

The Safety Monitoring Committee will conclude each review with written recommendations within 24 hours to Corbus and the principal investigator as to whether the study should continue without change, be modified, or terminated. Recommendations regarding modification of the design and conduct of the study could include study entry/randomization, whether dosing should be discontinued, whether the protocol should be modified, or whether the study should be discontinued permanently.

11.2. Medical Monitoring

Corbus will provide a Medical Monitor for this study. The Medical Monitor has the responsibility to review and evaluate information relevant to the product safety throughout the development 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 Monitor will provide recommendations, as appropriate, to the principal investigator and members of the clinical study team, Corbus and the Safety Monitoring Committee.

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

The investigator is responsible for all clinical trial-related medical decisions at their 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.

The investigator will oversee the day-to-day safety of subjects. In conjunction with study staff, the investigator will review all AEs and SAEs, laboratory results, safety data regarding the study subjects' clinical course and side effect profiles. The principal investigator will regularly assess the number and type of SAEs, if any. Corbus will oversee the construction and implementation of a site data and safety-monitoring plan.

12. DATA QUALITY

12.1. Source Data and Record Keeping

The investigator will keep accurate records of study activities and subject data to ensure that the conduct of the study is fully documented. The investigator or qualified designee will ensure that the source documents and participant study files are legible and complete for each participant. The investigator will be responsible for regularly reviewing 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.

12.1.1. Data Handling, De-identification and Source Records

The investigator or qualified designees will maintain appropriate medical and research 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 documents 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 investigator, both the medical record and the research records will be considered the source documents for the purposes of auditing the study.

Source data/records are: 1) original records; 2) certified copies of original records; 3) observations; 4) laboratory reports; and 5) CRFs 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.

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

Consented subjects who meet eligibility for the study will receive a unique SID which will be used to de-identify subject data for storage in study files. This number will be linked only through a SID log that connects each subject to his/her data. The ID log book will be securely locked in the research offices of the principal investigator and will be accessible to a limited number of study staff members.

12.1.2. Privacy and Confidentiality of Subject Information

Privacy and confidentiality of subjects will be respected throughout the study. As described above, each subject will be assigned a SID and these numbers, rather than subjects' names, will be used during collection, storage, and reporting of participant information.

Information about subjects will be kept confidential and managed according to the requirements of HIPAA. These regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) 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 PHI.

In the event that a subject revokes authorization to collect or use PHI, the principal investigator and Corbus, by regulation, will retain the ability to use all information collected prior to the

revocation of subject authorization. For subjects who have revoked authorization to collect or use PHI, attempts will be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

The IRB(s) affirms the subject's right to protection against invasion of privacy. 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.

Access to the laboratory space used for specimen storage will be restricted by locked portals and/or special access identification badges.

12.1.3. Data Management Responsibilities at the Site

Data collection and accurate documentation are the responsibility of the investigator and study staff under the supervision of the investigator, who will ensure that the data are collected and maintained correctly and in compliance with GCPs. 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. Corbus will ensure the data are collected and maintained correctly and in compliance with GCPs.

12.1.4. Data Capture Method

Data capture on CRFs will be used. It is expected that the CRFs will be completed coincident with the subject visit or within 24 hours, except for laboratory safety data that are not available within that time-frame.

[redacted]

12.1.6. 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 IRB, 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)].

The investigator and study staff are responsible to follow the written protocol as approved by the IRB. The investigator or qualified designee shall prepare and maintain complete, accurate, and timely reports of all protocol deviations.

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

Protocol Deviations that Constitute Unanticipated Problems Involving Risks

A protocol deviation that constitutes an unanticipated problem involving risks to subjects or to others must be reported promptly to Corbus and the IRB, as follows:

1. **Emergency deviations**: This is a deviation that occurs in an emergency situation, such as when a departure from the protocol is required to protect the life or physical well-being of a participant. Corbus and the IRB must be notified as soon as possible, but not later than 5 days after the emergency occurred. Corbus will be notified by e-mail or telephone.

2. **Major, non-emergent deviations without prior approval**: This is a planned deviation that is non-emergent and represents a major change in the protocol as approved by the IRB. If a major, non-emergent deviation occurs, the event will be considered non-compliance. Non-compliance must be reported to the IRB and Corbus promptly. A failure to report promptly any major, non-emergent deviation for which the investigator did not obtain prior approval is itself an incident of non-compliance.

Major protocol deviations must be reported to Corbus within 5 days of first time the investigator or study staff becomes aware of the deviation and must be reported to the IRB within that IRB's guidelines. An investigator's failure to report promptly any major protocol deviation is itself an incident of non-compliance.

The Medical Monitor, in consultation with investigator, will determine if an emergency or major protocol violation should result in early discontinuation of study treatment for a subject. 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 IRB in accordance with their IRB's reporting requirements.

Protocol Deviations that are Only Minor or Administrative

Minor or administrative protocol deviations are defined as those which do 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. These minor or administrative deviations will be captured by the investigator or qualified designee in the CRF system within 28 days after their occurrence.

12.1.7. Schedule and Contents of Reports

Reports will be generated for Corbus and the Safety Monitoring Committee to monitor enrollment and study conduct. Blinded safety monitoring reports will be generated for the Medical Monitor and Safety Monitoring Committee.

Final study reports for Parts A and B will be generated separately and only after the database is locked for each part. The final study reports that will be generated will be stipulated in the final statistical analysis plans for Parts A and B, which will be finalized prior to locking of the Part A and Part B databases, respectively.

12.2. Original Records

Clinical trial data will be entered by the investigator or qualified designees onto CRFs. Changes to the clinical trial data can only be performed by the investigator or qualified designees through a change management methodology that is subject to an audit trial.

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

12.3. Certified Copies of Original Data

In the event there the CRFs change from paper to electronic during the course of the study, the original data on paper CRFs must be entered into the EDC system. If these original data then are designated as Certified Copies within the EDC, the paper records may be discarded if both of the following occur:

- This process is supported by written procedures;
- The study staff is trained on these procedures, including instructions to check the transcribed data prior to certification.

12.4. Quality Control and Quality Assurance

12.4.1. 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 IRB, when applicable. The investigator will allocate adequate time to monitor data quality on a regular basis throughout the study.

The investigator or qualified designees must enter study data, including data concerning occurrence of AEs, into source documents and other data collection systems. The investigator or qualified designees will maintain investigational product storage, dispensing, and accountability of study product. All aspects of the study will be carefully monitored for compliance with the protocol, applicable government regulations, Good Clinical Practice, and the site's standard operating procedures. In addition, the clinical research team will meet regularly to discuss the clinical course of the study. The investigator will allocate adequate time for these 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 or other site staff.

Data quality will be monitored by Corbus on a regular basis throughout the study period. A site monitor representing Corbus will visit the study facility at periodic intervals, in addition to maintaining necessary contact through telephone, e-mail, and letter. The monitor will assess:

informed consent procedures; investigational product storage, dispensing, administration and accountability; compliance with protocol procedures; completeness and accuracy of data entered onto the paper CRFs; 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 other site staff. The investigator must cooperate with the monitor to ensure that any problems noted in the course of the monitoring are resolved.

12.4.2. Audit and Inspection of Site

Participation by the investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable institutional compliance and quality assurance offices. The investigator will maintain a comprehensive and centralized filing system of all study-related documentation that is suitable for inspection by regulatory agency representatives. The investigator will permit study-related audits and inspections of all study related documents (e.g. source documents, regulatory documents, data collection instruments, and study data) by the IRB, and government regulatory bodies. The investigator will facilitate inspections of applicable study-related facilities (e.g., diagnostic laboratory).

Government regulatory authorities may perform inspections either during or after the study. In the event of an inspection by any regulatory authority, the investigator will promptly notify Corbus and will allow Corbus representatives to be present during the audit, if permitted by the regulatory authority. The investigator agrees 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.

12.5. Data Management

A Clinical Data Monitoring Plan will be created to specifically identify how data management will be performed for the study.

The investigator will regularly review trial CRFs for completeness and accuracy and query study staff for corrections, as needed. If the query is due to a data entry error, the investigator or qualified designees can immediately make the corrections in the applicable CRF pages. If the query needs clarification, the investigator and the study staff will work together for resolution, and if indicated, the correct value will be entered on the CRF.

Results from data monitoring by Corbus will be discussed with the investigator. When necessary to maintain data quality, the investigator will implement corrective actions.

12.6. Trial Master File

The Trial Master File will be maintained by Corbus, with the assistance of the principal investigator and study staff.

12.7. Record Retention

The investigator must ensure that the following records and documents pertaining to the conduct of the study and the distribution of study product are retained for as long as needed to comply with national and international regulations (generally two 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 product accountability, and original signed informed consents). All IRB records related to this investigation will be retained by the investigator for as long as required by the IRB or at least three years after completion of the research.

In the event the investigator retires, relocates or for any other reason withdraws from the responsibility for maintaining records for the period of 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 prior to 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.

12.8. Confidentiality of Subject Data

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

[redacted]

[redacted]

13. REPORTING AND PUBLICATIONS

The investigator and Corbus will conduct this clinical study in an ethical and rigorously scientific manner. They will facilitate publication of the clinical data from this study in a timely, objective, accurate, and balanced manner. The principal investigator and 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. 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 www.clinicaltrials.gov, as stipulated by the FDA. A synopsis of the clinical results will be submitted on that same site within 12 months after the last subject's last visit.

The principal investigator will be the lead author of the publication of the final study results and any interim analyses. Any plans to publish parts of the study or complete study results must receive prior approval from the principal investigator and authorization by Corbus.

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, the FDA, and other regulatory agencies as required in the future.

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15. APPENDICES

APPENDIX A. REPRODUCTIVE POTENTIAL AND HIGHLY EFFECTIVE METHODS OF CONTRACEPTION

Women are considered to have "no reproductive potential" if they meet any one of the following criteria:

- Hysterectomy;
- bilateral oophorectomy;
- bilateral tubal ligation;
- > 45 and ≤ 55 years of age with no menses for ≥ 2 years, with follicle stimulating hormone level indicative of menopausal state, or ≥ 55 years of age.

Highly effective methods of contraception are those that result in a low failure rate (i.e., less than 1 percent per year) when used consistently and correctly. Examples of highly reliable methods of contraception when used consistently and correctly are given.

- Abstinence
- Intrauterine device
- Contraceptive implants
- Contraceptive patch
- Birth control shot
- Birth control pill - for subjects using a hormonal contraceptive method, information regarding the specific product used and its potential effect on the contraceptive should be addressed
- Birth control vaginal ring

Acceptable methods of contraception (those that result in a failure rate of more than 1% per year) that are allowed in this study are:

- Combination of condom and spermicide