

## CLINICAL TRIAL PROTOCOL

### DETERMINE STUDY

#### **A Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase 3 Trial to Evaluate Efficacy and Safety of Lenabasum in Dermatomyositis**

**Protocol Number:** JBT101-DM-002

**Version** 2.2

**Study Product:** Lenabasum

**Investigational New** 116313

**Drug number:**

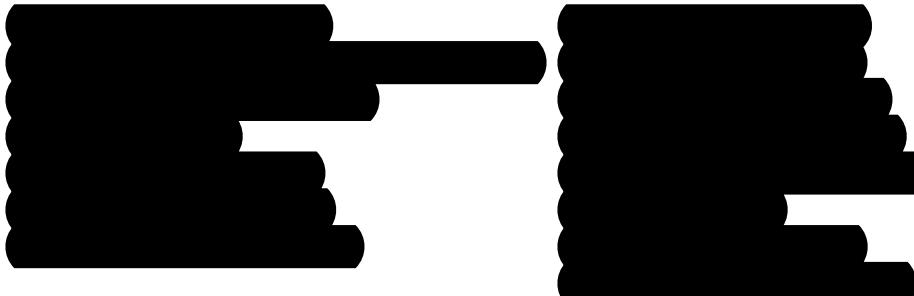
**EudraCT number:** 2018-003273-10

**Indication:** Dermatomyositis

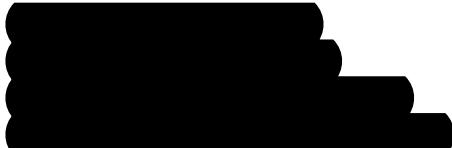
**Phase:** 3

**Date of Protocol:** 13 Jan 2021

**Name and Affiliation of  
Coordinating Principal  
Investigators:**



**Responsible Medical  
Officer:**



**Sponsor:** Corbus Pharmaceuticals, Inc.  
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#### **Statement of Compliance**

This trial will be carried out in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), Good Clinical Practice (GCP), Japanese Good Clinical Practice (J-GCP), the Ministerial Ordinance on Good Clinical Practice for Drugs in Japan (where applicable), and United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812), including the archiving of essential documents.

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## SPONSOR APPROVAL

**Protocol Title:** A Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase 3 Trial to Evaluate Efficacy and Safety of Lenabasum in Dermatomyositis

**Protocol Number:** JBT101-DM-002

**Version:** 2.2

**Date:** 13 January 2021

[REDACTED]

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[REDACTED]

[REDACTED]

## **INVESTIGATOR AGREEMENT PROTOCOL JBT101-DM-002**

I agree:

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

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*Investigator Signature*

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*Date*

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*Printed Name and Title of Investigator*

*Site #* \_\_\_\_\_

*Site Name* \_\_\_\_\_

## PROTOCOL SYNOPSIS

**Title:** A Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase 3 Trial to Evaluate Efficacy and Safety of Lenabasum in Dermatomyositis

### Objectives and Endpoints:

Primary Objective	Primary Efficacy Endpoint
To evaluate the efficacy of lenabasum compared to placebo in subjects with dermatomyositis (DM)	<p>Total Improvement Score (TIS) by the 2016 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) Myositis Response Criteria at Week 28</p> <p>The TIS is comprised of 6 core set measures and absolute value and change from baseline in each core set measure will be presented to support the composite TIS:</p> <ol style="list-style-type: none"><li>1. Physician global activity (MDGA)</li><li>2. Patient global activity (PtGA)</li><li>3. Manual Muscle Testing (MMT)</li><li>4. Health Assessment Questionnaire (HAQ)</li><li>5. Muscle enzymes</li><li>6. Extramuscular global activity (EMGA)</li></ol> <p>A MMT that assesses strength in 8 muscle groups (MMT-8) will be used in this study.</p>
Secondary Efficacy Endpoints	
	<p>The following endpoints will be compared in lenabasum 20 mg BID and placebo cohorts and lenabasum 5 mg BID and placebo cohorts at Week 28, unless otherwise specified. All outcomes involving continuous variables will be assessed as absolute values and, if relevant, change from Baseline. All categorical variables will be assessed as number and proportion of subjects in each category:</p> <ol style="list-style-type: none"><li>1. Subjects who achieve Definition of Improvement (DOI), defined as <math>\geq 3</math> of 6 core set measures improved by <math>\geq 20\%</math> (relative to Baseline) with no more than 2 core set measures worsening by <math>\geq 25\%</math> (MMT-8 may not decrease by <math>\geq 25\%</math> from baseline)</li><li>2. Subjects who improve by at least one category on the Investigator Global Assessment (IGA) scale of skin activity</li><li>3. Subjects who achieve TIS <math>\geq 40</math> (at least moderate improvement)</li></ol>

	<ol style="list-style-type: none"><li>4. TIS in subjects receiving any immunosuppressant medication for &gt; 1 year at Baseline</li><li>5. TIS at Visit 10 (Week 52)</li><li>6. Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI) activity score</li><li>7. TIS (lenabasum 5 mg compared to placebo cohorts only)</li></ol>
	<b>Tertiary Efficacy Endpoints</b>
	<p>These endpoints will be assessed at all visits at which they are measured, if not already included as the primary or secondary efficacy endpoints. Additional tertiary efficacy endpoints may be included in the Statistical Analysis Plan (SAP).</p>
	<p><b>Change from Baseline compared to placebo in physician or laboratory assessments:</b></p> <ol style="list-style-type: none"><li>1. Forced vital capacity (FVC) absolute change in mL and percent predicted</li><li>2. CDASI damage score</li><li>3. MDGA (Likert Scale)</li><li>4. Corticosteroid dose</li></ol> <p><b>Change from Baseline compared to placebo in patient reported outcomes:</b></p> <ol style="list-style-type: none"><li>1. Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Score</li><li>2. 5-D Itch Score</li><li>3. National Institutes of Health Patient-Reported Outcomes Measurement Information System (PROMIS)-29 Short Form domain scores</li><li>4. Patient Visual Analog Scale (VAS) scores of Pain</li><li>5. Skindex-29+3</li><li>6. European Quality of Life 5-domain (EQ-5D) questionnaire score</li><li>7. SF-36 domain scores</li></ol> <p><b>Proportion of subjects:</b></p> <ol style="list-style-type: none"><li>1. Achieving a CDASI activity score of <math>\leq 14</math></li><li>2. Achieving clear or almost clear skin on the IGA scale of skin activity</li><li>3. Achieving a TIS of <math>\geq 20</math>, <math>\geq 40</math>, and <math>\geq 60</math></li></ol>

	<ol style="list-style-type: none"><li>4. Achieving a reduction in dose of any immunosuppressive medication (including corticosteroid) for &gt; 28 days, among subjects receiving immunosuppressive medications at Baseline</li><li>5. Requiring an increase in dose of any immunosuppressive medication (including corticosteroids), or rescue immunosuppression for &gt; 28 days</li></ol> <p><b>Subset analyses of outcomes above by Baseline characteristics:</b></p> <ol style="list-style-type: none"><li>1. TIS by: MMT-8 score and other core set measures as continuous variables</li><li>2. TIS and core set measures and secondary outcomes by: age (continuous variable); geographic region (US, ex-US); any non-corticosteroid immunosuppressive treatment (yes, no); dose of oral prednisone or equivalent</li></ol> <p><b>Minimal Important Difference (MID):</b></p> <ol style="list-style-type: none"><li>1. Determine MID in TIS, HAQ-DI and CDASI in DM</li><li>2. Subset analysis to determine proportion of subjects that achieve MID in TIS, HAQ-DI and CDASI</li></ol>
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Secondary Objective	Safety Endpoints
To evaluate the safety and tolerability of lenabasum in subjects with DM	<ol style="list-style-type: none"><li>1. Adverse events (AEs)</li><li>2. Changes in vital signs, physical examinations, blood and urine laboratory safety tests, and ECGs associated with lenabasum treatment</li><li>3. Number of subjects who permanently discontinue study product due to AEs probably- or definitely-related to treatment</li></ol>
Tertiary Objectives	Tertiary Endpoints and Evaluations
[REDACTED]	[REDACTED]
Additional Objectives	Additional Endpoints
To evaluate the long-term efficacy and safety of lenabasum in completed subjects who continue to receive treatment in an optional open-label extension (OLE)	<p><b>In an open-label extension (OLE) phase (Part B):</b></p> <ol style="list-style-type: none"><li>1. Evaluate long-term signals of efficacy</li><li>2. Evaluate long-term safety</li></ol>

**Study Design:** This is a Phase 3, multicenter, interventional, double-blind, randomized, placebo-controlled study designed to assess the efficacy and safety of lenabasum in subjects with DM.

The study consists of 2 parts:

- Part A: Double-Blind, Placebo Controlled Phase
- Part B: Open Label Extension Phase (Optional)

The overall design for this study is summarized in [Figure 1](#) of the protocol.

### **Part A Double-Blind, Placebo Controlled Phase**

The initial plan is for approximately 150 dosed subjects to receive at least 1 dose of study product. The final number of subjects to be dosed will be decided after a blinded interim analysis. The timing and methods for the interim analyses will be outlined in the statistical analysis plan (SAP). It is expected that approximately 200 subjects will be screened to dose 150 subjects. Subjects will be randomized to receive lenabasum 20 mg, lenabasum 5 mg, or placebo twice-daily (BID) in a 2:1:2 ratio. It is hypothesized that subjects receiving lenabasum will have greater improvement in the TIS score (2016 ACR/EULAR Myositis Response Criteria) at Week 28 compared to subjects receiving placebo.

The total duration of participation for an individual subject is approximately 60 weeks and includes the following: a screening visit (up to 4 weeks before Visit 1), up to 52-week treatment period, and a Safety Follow-up Visit that will be conducted  $4 \pm 1$  weeks after the last visit. Subjects will be assessed for safety and efficacy parameters every 6 weeks (except for Visit 2, which will occur 4 weeks after Visit 1) for a total of up to 10 treatment visits. Study personnel will also contact subjects by telephone halfway between Visit 9 and Visit 10 (Week  $49 \pm 1$ ) to assess compliance, safety and overall status of DM, if applicable.

A subject's corticosteroid or other immunosuppressant treatments may be reduced if the investigator determines that clinical improvement in the subject's dermatomyositis has occurred and a reduction is warranted. It is recommended that a reduction in corticosteroid or immunosuppressant treatment should not occur before Visit 4 or after Visit 8. A preferred schedule for reduction is provided in [Section 5.5.1](#) of the protocol.

### **Main Eligibility Criteria:**

- Male or female subjects  $\geq 18$  years of age with a known diagnosis of DM and active disease.
- Must meet one of the following for DM diagnosis:
  1. Bohan and Peter's criteria for probable or definite DM ([Bohan and Peter, 1975a](#); [Bohan and Peter 1975b](#))
  2. ACR/EULAR criteria ([Lundberg et al, 2017](#))
- Must meet one of the following for disease activity / severity:
  - i. MDGA  $\geq 3$  cm (0 – 10 cm scale) and MMT-8 score  $\leq 142$  (out of 150 total possible)
  - ii. Sum of MDGA, PtGA and EMGA VAS scores is  $\geq 10$  cm (all scales individually on 0-10 cm scale)
  - iii. MDGA  $\geq 3$  cm and CDASI activity score of  $> 14$

Doses of non-corticosteroid immunosuppressant medications should be stable for  $\geq$  8 weeks at screening. Doses of oral corticosteroids should be stable for  $\geq$  4 weeks at Visit 1.

**Phase: 3**

**Study Sites:** Up to approximately 75 sites in North American, European, and Asian Pacific regions.

**Study Treatment:**

All treatments: lenabasum (20 mg or 5 mg) or placebo, will be administered orally BID for up to 52 weeks.

**Study Duration:** Estimated duration for Part A is anticipated to be approximately 36 months from first subject first visit to last subject last visit and will depend on the rate of enrollment across the various sites.

**Statistical Methodology:** It is planned that about 150 subjects will be dosed at a ratio of 2:1:2 to lenabasum 20 mg, lenabasum 5 mg, or placebo arms, respectively, with a total of 120 subjects expected to complete the study (assuming  $\sim$  20% drop out rate). A total of 120 subjects (48 subjects each in the 20 mg BID and placebo groups, and 24 subjects in the 5 mg BID dose group) achieves 95% power to detect a significant difference in the TIS score between the lenabasum 20 mg BID group and placebo. This assumes a two-sided test at alpha = 0.05 and a common standard deviation of 20.00 in both treatment arms for the primary efficacy outcome, and a difference in the TIS between lenabasum 20 mg BID and placebo of 15.0. The number of subjects to be randomized may be adjusted further during the study after a blinded interim analysis of the emerging data. The intent is to perform a blinded interim examination of the variance of the TIS to potentially increase the sample size to maintain power (with no statistical adjustment to the alpha level required). The projected maximum number of subjects to be randomized is about 230 subjects (for 183 completers), which corresponds to standard deviation of 30.00, and 85% power.

Randomization will be stratified based on screening MMT-8 score ( $< 135$  or  $\geq 135$ ), prednisone dose ( $\leq 10$  mg or  $> 10$  mg per day or equivalent), and region (US vs. ex-US). The primary efficacy variable is the TIS. The primary analysis is to compare the TIS at Week 28 between the lenabasum 20 mg BID treated group and the placebo group using a mixed model for repeated measures (MMRM). The model will have TIS score as a dependent variable, treatment, visit, treatment\*visit interaction as factors, Baseline MMT-8 score, prednisone use, and region as covariates, and subject as the repeated random effect using an unstructured covariance matrix. Two-sided p-values and 95% confidence intervals associated with the least-square (LS) mean difference between the lenabasum group and placebo will be presented for each visit. If the distribution of the TIS score does not meet the assumptions of normality, a nonparametric analysis may be performed (e.g., MMRM analysis on the ranked data).

Continuous secondary and tertiary outcome variables will be analyzed similarly to the primary MMRM model, using change from Baseline as the dependent variable, with the Baseline of each endpoint also included in the model. Other outcomes based on the proportion of subjects achieving defined criteria will be analyzed using a Fisher's exact or Cochran-Mantel-Haenzel test.

All primary and secondary efficacy analyses will be two-sided at the 0.05 significance level. The overall Type I error rate will be controlled for the primary and secondary efficacy outcomes with independent hierarchical assessments of efficacy at each comparison of lenabasum to placebo. The order of the tests for treatment effect will be as follows:

- Primary efficacy outcome (at Week 28): TIS, lenabasum 20 mg BID versus placebo. Change from baseline in each core set measure of the composite TIS will be presented to support the TIS: MDGA; PtGA; MMT-8; HAQ; muscle enzymes; EMGA
- Secondary efficacy outcomes (Change from Baseline or proportion of subjects at Week 28, unless otherwise specified). The list will be done in order below for comparisons between lenabasum 20 mg BID and placebo cohorts:
  - Subjects who achieve DOI
  - Subjects who improve by at least one category on the IGA scale of skin activity
  - Subjects who achieve TIS  $\geq 40$  (at least moderate improvement)
  - TIS in subjects receiving any immunosuppressant medication for  $> 1$  year at Baseline
  - TIS at Visit 10 (Week 52)
  - CDASI activity score

The list will continue in order below for comparisons between lenabasum 5 mg BID and placebo cohorts:

- TIS
- Subjects who achieve DOI
- Subjects who improve by at least one category on the IGA scale of skin activity
- Subjects who achieve TIS  $\geq 40$  (at least moderate improvement)
- TIS in subjects receiving any immunosuppressant medication for  $> 1$  year at Baseline
- TIS at Visit 10 (Week 52)
- CDASI activity score

Note that statistical significance within an endpoint must be achieved to continue in the assessment of the next endpoint.

No formal statistical testing will be performed to compare the safety in lenabasum versus placebo cohorts. The number and percentage of subjects with AEs will be summarized for each treatment by system organ class and preferred term. Similar summaries will be presented for AEs related to study product, AEs leading to permanent discontinuation of study product, SAEs, and AEs resulting in death. Any AE with a relationship category of possible, probable, or definite is considered related to study product. The AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). All reported AEs will be provided in separate data listings. Descriptive statistics will be used to summarize clinical laboratory parameters, vital signs and their corresponding change from Baseline for each treatment by scheduled timepoint.

### **Part B Open-Label Extension Phase (Optional)**

Upon completing Part A treatment (Visit 10), at the investigator's discretion, consenting subjects may directly rollover into open-label treatment (Part B).

All subjects in the open-label extension (OLE) will receive lenabasum 20 mg BID.

The same efficacy and safety parameters described as primary and secondary objective for Part A will be evaluated in Part B as described in the SAP.

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## ABBREVIATIONS

5-D itch	Five-dimension itch
AE	Adverse event
ARCI-M	Addiction research center inventory - marijuana
AUC	Area under the curve
AUC <sub>0-24</sub>	Area under the curve from hour 0 - 24
BID	Twice daily
BP	Blood pressure
CB1	Cannabinoid type 1 receptor
CB2	Cannabinoid type 2 receptor
CDASI	Cutaneous dermatomyositis disease area and severity index
CF	Cystic fibrosis
CK	Creatine phosphokinase
CRO	Contract research organization
CSR	Clinical study report
DM	Dermatomyositis
DMC	Data monitoring committee
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Forms
EDC	Electronic data capture
EQ-5D	European quality of life 5-domain questionnaire
FACIT	Functional assessment of chronic illness therapy
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone
FVC	Forced vital capacity
GCP	Good Clinical Practice
HAQ-DI	Health Assessment Questionnaire – Disability index
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
H <sub>0</sub>	Null hypothesis
H <sub>1</sub>	Alternative hypothesis
IB	Investigator's Brochure
IC	Informed consent
ICF	Informed consent form
ICH	International Conference on Harmonization
IFN	Interferon
IL-1 $\beta$	Interleukin 1 $\beta$
IRB	Institutional Review Board
IWRS	Interactive web-based randomization system
LH	Luteinizing hormone
LMP	Last menstrual period
LPLV	Last patient last visit
LS	Least-squares means

MedDRA	Medical Dictionary for Regulatory Activities
MID	Minimal important difference
mITT	Modified intent-to-treat
MMRM	Mixed model for repeated measures
MMT	Manual muscle testing
MMT-8	Manual muscle testing-8
mRNA	Messenger ribonucleic acid
PK	Pharmacokinetics
PP	Per-protocol
QT	Measure of the time between the start of the Q wave and the end of the T
QTc	QT corrected
SAE	Serious Adverse Event
SAF	Safety population
SAP	Statistical Analysis Plan
SD	Standard deviation
SID	Subject identification number
SOA	Schedule of Assessments
SSc	Systemic sclerosis
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
TIS	Total improvement score
UP	Unanticipated Problem
US	United States
VAS	Visual analog scale
WOCBP	Women of child-bearing potential

## 1. INTRODUCTION

Lenabasum (also known as JBT-101) is a novel, first-in-class “pro-resolving” small molecule cannabinoid type 2 receptor (CB2) agonist that is being developed for the treatment of inflammation and fibrosis in several diseases such as: dermatomyositis (DM), systemic sclerosis (SSc), systemic lupus erythematosus (SLE) and cystic fibrosis (CF).

### 1.1. Study Rationale

Results from the first-in-DM patient study (JBT101-DM-001) demonstrated improvement in the primary efficacy variable, Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI) activity score, as well as numerous secondary efficacy measures. Lenabasum was shown to have a favorable safety profile in this DM study, consistent with previous clinical studies with lenabasum in patients with CF and SSc. Given the small sample size of study JBT101-DM-001 and exclusion of patients with active muscle disease, this present study is designed to assess the safety and efficacy of lenabasum in a larger, broader population of DM patients.

### 1.2. Background

Dermatomyositis is a severe autoimmune disease with distinctive cutaneous and muscle symptoms that are frequently accompanied by other manifestations. Although robust epidemiologic data are not available, it is estimated that < 13,500 to ~70,000 individuals in the United States (US) may have DM (Jacobson et al, 1997; Reeder et al, 2010). The most common age of onset is between 50-60 years of age (Tansley et al, 2013); however, DM has been observed in younger populations. Juvenile DM occurs before the age of 16 and has an incidence rate of around 1 case per 1 million children (Quartier et al, 2013).

Skin findings associated with DM include rashes characterized by erythema as well as pruritus of the scalp, face, dorsum of the hands, and upper back (Klein et al, 2007; Goreshi et al, 2011). Other manifestations of DM can include: muscle weakness (Bohan et al, 1977; Koh et al, 1993; Volochayev et al, 2012; Na et al, 2009); pulmonary complications (Kalluri et al, 2010; Ascherman et al, 2002); cardiac findings (Bazzani et al, 2010), esophageal involvement (de Merieux et al, 1983; Marie, 2012), joint disease (Marie, 2012), and associated malignancies (Hill et al, 2001; Yamasaki et al, 2011). Quality of life is significantly impacted in DM patients (Goreshi et al, 2011). Mortality in patients with DM is high with survival estimated to be 70% at 5 years and 57% at 10 years (Schiopu et al, 2012).

The clinical presentation of DM is a result of underlying, unresolved chronic inflammation. Classic inflammatory mediators include activated immune cells and proinflammatory cytokines such as tumor necrosis factor  $\alpha$  (TNF $\alpha$ ), interleukin 1 beta (IL-1 $\beta$ ), and type 1 interferons (IFNs) (Wong et al, 2012; Kim et al, 2012; Nabatian et al, 2012). Consequently, the current standard of care for DM includes the use of corticosteroids. Long-term systemic use of corticosteroids has shown to be associated with a number of adverse events (AEs) such as: osteoporosis and fractures; adrenal suppression; hyperglycemia and diabetes; cardiovascular disease and dyslipidemia, dermatological and gastrointestinal events; psychiatric disturbances; and immunosuppression (Liu et al, 2013). Side-effects of corticosteroid have been reported to affect 32% (Baron and Small, 1985) to 41% (Tymms and Webb, 1985) of treated patients with DM. In

long-term studies, disability associated with corticosteroid side-effects, especially osteonecrosis and osteoporotic vertebral fractures has also been reported ([Choy and Isenberg, 2002](#)).

If a patient is unresponsive to steroid therapy, i.e., no improvement after 3 - 6 months of prednisone, or if the patient relapses while tapering, a second-line immunosuppressive agent should be added ([Findlay et al, 2015](#)). Common second line choices include azathioprine ([Bunch et al, 1980](#)), methotrexate ([Newman et al, 1995](#)), and intravenous immunoglobulin ([Dalakas et al, 1993](#)). Other agents used in the treatment of DM are rituximab ([Oddis et al, 2013](#)), mycophenolate mofetil ([Pisoni et al, 2007](#)), tacrolimus ([Wilkes et al, 2005](#)), cyclosporine ([Qushmaq et al, 2000](#)), and cyclophosphamide ([Bombardieri et al, 1989](#)). Use of second line agents for their steroid-sparing effect is based on empirical data, and their use as a sole treatment may provide little benefit ([Dalakas, 2011](#)). In addition to lack of proof of efficacy ([Liu et al, 2013](#)), these second line immunosuppressive therapy agents are well known to be associated with significant side effects. Due to the severe side effects, reduction of immunosuppressive medication is an important goal for DM treatment.

Lenabasum is being developed as a therapy for the treatment of inflammation and fibrosis through the targeting of the CB2 receptor. CB2 is mainly distributed throughout immune cells ([Castaneda et al, 2013; Munro et al, 1993](#)). CB2 is expressed at 10- to 100-fold higher levels than cannabinoid type 1 (CB1) receptor on activated immune cells ([Carayon et al 1998; Galiegue et al, 1995; Munro et al, 1993](#)). Cell surface expression of CB2 returns to baseline levels once the immune response is resolved ([Carayon et al 1998](#)). As an agonist of CB2, lenabasum triggers a class switch of lipid mediators to favor pro-resolving lipid mediators which facilitate the transition of an active innate immune response back to an inactive response ([Shinohara et al, 2012; Zurier et al, 2009](#)).

Lenabasum has demonstrated potent pro-resolution (anti-inflammatory, anti-fibrogenic) effects in multiple non-clinical and clinical models (see [Sections 4 and 5](#) of the Investigator's Brochure).

A detailed description of the chemistry, pharmacology, efficacy, and safety of lenabasum is provided in the [Investigator's Brochure](#).

### **1.3. Risk/Benefit Assessment**

Lenabasum is an investigational product not currently approved outside of clinical trial use; therefore, individual subjects may or may not experience a benefit from lenabasum for the disease condition under study. Subjects who receive placebo are unlikely to receive any benefit from participation in the study other than a potential placebo benefit and an opportunity to participate in the open-label extension (OLE) study. Individual subjects should carefully consider the risks versus benefits from participation in this clinical trial before signing the informed consent (IC).

In multiple nonclinical studies, cells isolated from patients with inflammatory / fibrotic diseases, animal models of disease, and mechanism of action studies conducted in healthy volunteers, lenabasum has demonstrated the potential to resolve innate immune responses as well as fibrotic processes. Efficacy signals have been observed in Phase 2 studies in SSc (JBT101-SSc-001), CF (JBT101-CF-001) and DM (JBT101-DM-001). Evidence of on-target biologic effects of lenabasum has been shown in the skin in DM and SSc subjects and in sputum from CF subjects, supporting potential clinical benefit. Efficacy signals have also been observed in subjects with

refractory traumatic neuropathic pain (CPL7075/02/01/001/1). Anticipated AEs in clinical trials with lenabasum include those related to the subject population being studied, concomitant medications that subjects may be taking (e.g., immunosuppressive medications) and lenabasum.

To date, the majority of AEs related to lenabasum have been mild in severity; serious adverse events (SAE) considered related to lenabasum have primarily been infective pulmonary exacerbations in subjects with CF. The most frequent AEs thought to be causally related to lenabasum (within 1-60 mg dose range) by the investigators include dry mouth and dizziness. The most frequent AEs observed in study subjects who received lenabasum in the 1-60 mg dose range, independent of relatedness to lenabasum, included fatigue, upper respiratory tract infection, infective pulmonary exacerbation (in subjects with CF), dry mouth, dizziness, cough, hemoptysis (in subjects with CF), and headache. Other AEs listed as class effects of CB1/CB2 agonists (e.g., , feeling drunk or abnormal or jittery, hot or hot and cold or cold, hangover, feeling relaxed or feeling of movements slower than normal) have been reported in < 5% of lenabasum-treated subjects.

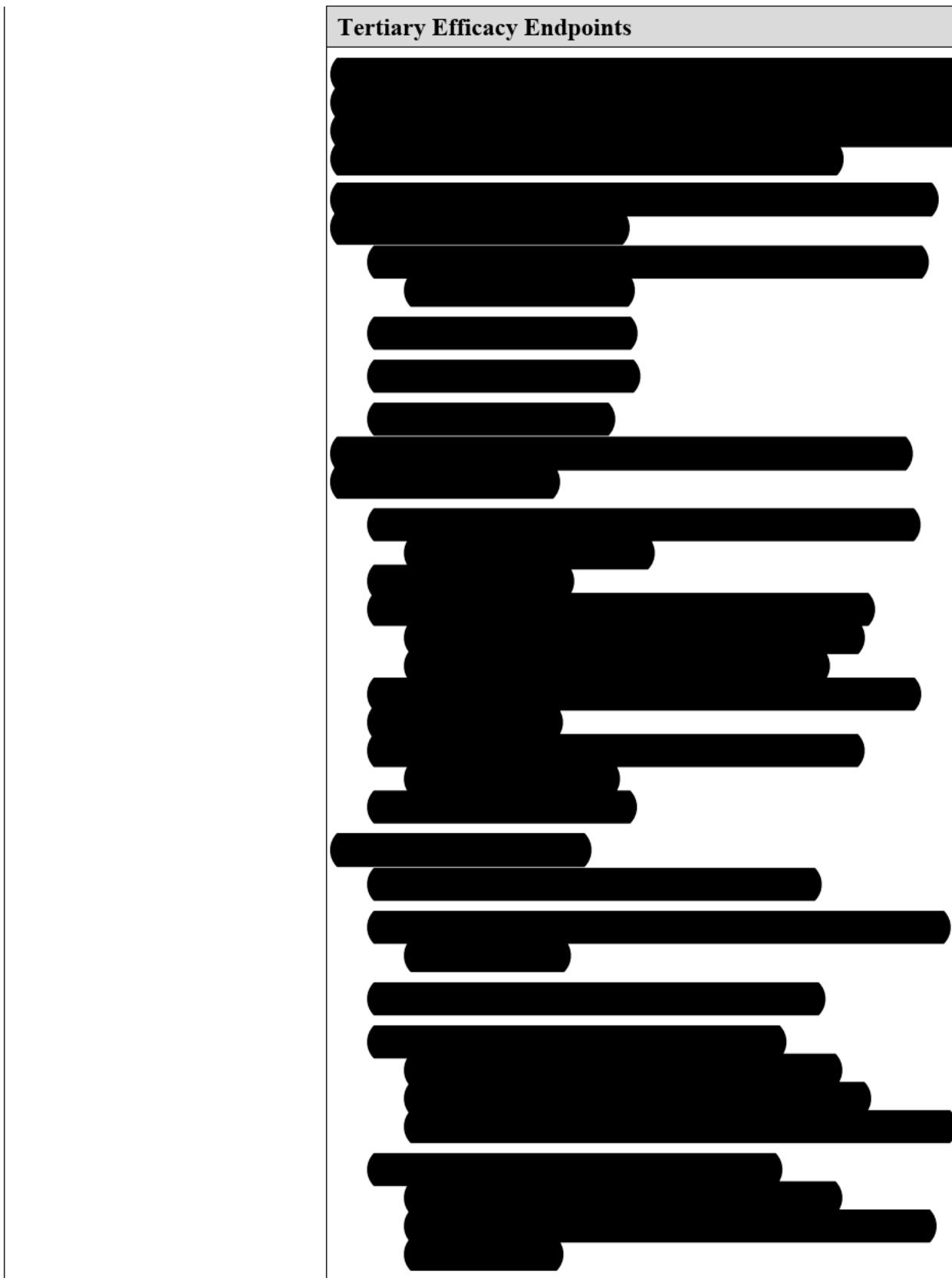
Lenabasum has shown to inhibit human ether a-go-go (hERG) current with an  $IC_{50}$  value of 7  $\mu\text{mol/L}$  (2800 ng/ml). This concentration is  $\geq 146\times$  higher than the maximum free therapeutic concentration of 20 mg lenabasum twice-daily (BID) in humans, indicating a low liability for causing torsade de pointes ([Redfern et al, 2003](#)). In initial safety and tolerability studies, prolongations of QTc were observed using single electrocardiogram (ECGs); however, no QTc exceeded 500 msec (maximum QTc observed was 487 msec) and all were considered not clinically significant. In the SSc (JBT101-SSc-001) and CF (JBT101-CF-001) studies, triplet standardized ECGs with QT/QTc interval measurements showed no prolongation of QTc intervals or other significant ECG findings compared with placebo. QT/QTc intervals will be measured in this study. Convulsions consistent with CB1 effect on the brain have been observed in some non-clinical studies; however, lenabasum did not lower seizure threshold in a study done in rats specifically to evaluate the effect of lenabasum on seizure potential. No convulsions/seizures have been observed in any clinical studies done to date. Ataxia was observed at high doses in rats and mice and at  $\geq 10 \text{ mg/kg/day}$  in dogs where plasma exposures were approximately  $7.6\times$  higher than the anticipated maximum area under the curve (AUC) exposure achieved with lenabasum 20 mg BID (40 mg total daily dose). Ataxia has not been observed in humans.

Lenabasum has been found to be well-tolerated in clinical studies conducted to date with only mild or moderate AEs related to lenabasum observed. Together, results from the preclinical safety, toxicology and pharmacokinetic (PK) studies, efficacy studies in animal models of disease, studies with human biomaterials, and safety and preliminary efficacy data in humans support a favorable benefit-risk profile of lenabasum. These results support further study of lenabasum as a treatment for rare and serious inflammatory and fibrotic diseases with significant unmet medical need.

Additional information about the known and expected benefits and risks and reasonably expected AEs of lenabasum may be found in the [Investigator's Brochure](#).

## 2. OBJECTIVES AND ENDPOINTS

Primary Objective	Primary Efficacy Endpoint
To evaluate the efficacy of lenabasum compared to placebo in subjects with dermatomyositis (DM)	<p>TIS by the 2016 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) Myositis Response Criteria at Week 28</p> <p>The TIS is comprised of 6 core set measures and absolute value and change from baseline in each core set measure will be presented to support the composite TIS:</p> <ol style="list-style-type: none"><li>1. Physician global activity (MDGA)</li><li>2. Patient global activity (PtGA)</li><li>3. Manual Muscle Testing (MMT)</li><li>4. Health Assessment Questionnaire (HAQ)</li><li>5. Muscle enzymes</li><li>6. Extramuscular global activity (EMGA)</li></ol> <p>A MMT that assesses strength in 8 muscle groups (MMT-8) will be used in this study.</p>
Secondary Efficacy Endpoints	
	<p>The following endpoints will be compared in lenabasum 20 mg BID and to placebo cohorts and lenabasum 5 mg BID compared to placebo cohorts at Week 28, unless otherwise specified.</p> <p>All outcomes involving continuous variables will be assessed as absolute values and, if relevant, change from Baseline. All categorical variables will be assessed as number and proportion of subjects in each category:</p> <ol style="list-style-type: none"><li>1. Subjects who achieve Definition of Improvement (DOI)</li><li>2. Subjects who improve by at least one category on the Investigator Global Assessment (IGA) scale of skin activity</li><li>3. Subjects who achieve TIS <math>\geq 40</math> (at least moderate improvement)</li><li>4. TIS in subjects receiving any immunosuppressant medication for <math>&gt; 1</math> year at Baseline</li><li>5. TIS at Visit 10 (Week 52)</li><li>6. Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI) activity score</li><li>7. TIS (lenabasum 5 mg compared to placebo cohorts only)</li></ol>



	<p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p>
Secondary Objective	Safety Endpoints
To evaluate the safety and tolerability of lenabasum in subjects with DM	<ol style="list-style-type: none"><li>1. Adverse events (AEs)</li><li>2. Changes in vital signs, physical examinations, blood and urine laboratory safety tests, and ECGs associated with lenabasum treatment</li><li>3. Number of subjects who permanently discontinue study product due to AEs probably- or definitely-related to treatment</li></ol>
Tertiary Objectives	Tertiary Endpoints and Evaluations
[REDACTED]	<p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p>
[REDACTED]	<p>[REDACTED]</p> <p>[REDACTED]</p>
[REDACTED]	<p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p>
[REDACTED]	<p>[REDACTED]</p>

Additional Objectives	Additional Endpoints
To evaluate the long-term efficacy and safety of lenabasum in completed subjects who continue to receive treatment in an optional open-label extension (OLE)	<b>In an open-label extension (OLE) phase (Part B):</b> <ol style="list-style-type: none"><li>1. Evaluate long-term signals of efficacy</li><li>2. Evaluate long-term safety</li></ol>

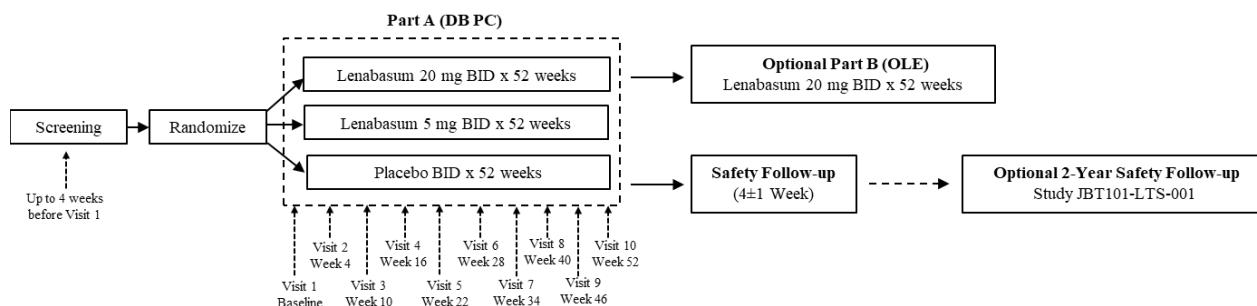
Endpoints will be finalized in the statistical analysis plan (SAP) prior to unblinding.

### 3. STUDY DESIGN

#### 3.1. Overall Design

This is a Phase 3, multicenter, interventional, study designed to assess the efficacy and safety of lenabasum in subjects with DM. The study consists of two parts: Part A is a double-blind, placebo-controlled phase. Part B is an optional OLE phase with a single treatment arm. The overall design for this study is presented in Figure 1.

**Figure 1: Study Design for JBT101-DM-002**



Abbreviations: BID = twice daily, DB = double blind, OLE = open label extension, PC = placebo controlled

##### 3.1.1. Part A: Double-Blind, Placebo-Controlled Phase

The initial plan is for approximately 150 dosed subjects to receive at least 1 dose of study product. The final number of subjects to be dosed will be decided after a blinded interim analysis. The timing and methods for the interim analysis will be outlined in the SAP. It is expected that approximately 200 subjects will be screened to dose 150 subjects.

Subjects will be randomized to receive lenabasum 20 mg, lenabasum 5 mg, or placebo BID in a 2:1:2 ratio. It is hypothesized that subjects receiving lenabasum will experience greater improvement in the TIS score at Week 28 compared to subjects receiving placebo.

The total subject duration is approximately up to 60 weeks and includes the following: a screening visit (up to 4 weeks prior to Visit 1), up to a 52-week treatment period, and a Safety Follow-up Visit that will be conducted 4±1 weeks after the last visit. Subjects will be assessed for safety and efficacy parameters every 6 weeks except for Visit 2, which will occur 4 weeks after Visit 1, for a total of up to 10 treatment visits. Study personnel will contact subjects by telephone about halfway between Visit 9 and Visit 10 (Week 49 ± 1) to assess compliance, safety and overall status of DM, if applicable.

A subject's corticosteroid or other immunosuppressant treatments may be reduced if the investigator determines that clinical improvement in the subject's DM has occurred and a reduction is warranted. It is recommended that a reduction in corticosteroid or immunosuppressant treatment should not occur prior to Visit 4 or after Visit 8. A preferred schedule for reduction is provided in [Section 5.5.1](#) of the protocol.

### **3.1.2. Part B: Optional Open-label Extension**

Upon completing Part A (Visit 10), at the investigator's discretion, consenting subjects may directly rollover into the optional OLE Phase (Part B). All subjects in the OLE will receive lenabasum 20 mg BID (see [Table 4](#)).

Subjects will continue their standard of care treatment as in Part A. Subject's corticosteroid or other immunosuppressant treatments may be reduced during this study if the investigator determines that clinical improvement in the subject's dermatomyositis has occurred and a reduction is warranted. A preferred schedule for reduction of corticosteroid is provided in [Section 5.5.1](#).

The OLE may be extended beyond 1 year. Sites will be notified by an administrative memo as to any extension and will inform their EC/IRB. The design of an extended OLE will follow the same design and procedures as described in Table 4. At the investigator's discretion, consenting subjects will rollover at the conclusion of Visit B8. The extension visits will be captured in the electronic data capture (EDC) as C1-C8 respectively.

Subjects who discontinue the study at any stage and for any reason will be encouraged to complete the procedures described in the Early Termination (ET) Visit as well as complete the Safety Follow-up Visit  $4 \pm 1$  weeks later.

The same efficacy and safety parameters described as primary and secondary objective for Part A will be evaluated in Part B as described in the SAP.

The results of Part B are expected to be analyzed after Part A results have been completed and will be reported as either an addendum to the clinical study report (CSR) or as a separate CSR.

### **3.1.3. Study JBT101-LTS-001: 2-year Observational Safety Follow-up**

Subjects who participated in Part A but are ineligible for the OLE (e.g., completed Part A and declined participation in the OLE, or subjects who discontinued from Part A for whatever reason), will be offered the opportunity to participate in a separate 2-year non-interventional safety surveillance study (Study JBT101-LTS-001).

## **3.2. Scientific Rationale for Study Design**

### **3.2.1. Part A: Double-blind, Placebo-controlled Phase**

In Part A, a double-blind, randomized, placebo-controlled design will be used. Part A will include up to 52-weeks of treatment to facilitate an unbiased assessment of the efficacy, safety and tolerability of lenabasum in the treatment of DM (see [Table 3](#)). Twenty-eight weeks treatment is expected to be sufficient to demonstrate long-term safety and efficacy of lenabasum compared to placebo, to support long-term use of lenabasum and 52-weeks treatment and OLE are expected to provide further evidence of long-term-safety and efficacy.

Subjects will be allowed to continue their current treatment, which will reduce the risk of disease flare precipitated by discontinuation of medication to meet entry criteria.

The primary endpoint chosen for this study is the TIS ([Aggarwal et al., 2017](#)) at 28 weeks. Because of heterogeneity in the organ-involvement in DM, organ-specific efficacy outcome does not reflect the extent of disease in DM. The TIS score is based on 6 core measures: patient and

physician global activity on a 10-cm VAS, muscle strength measured by MMT, physical function measured by the HAQ, extramuscular global activity (EMGA) measured by the physician on a 10-cm VAS, and the most abnormal serum muscle enzyme. Absolute value and change from Baseline in each core set measure will be provided to support the TIS assessment. The patients with DM targeted for inclusion in this study are those who reflect the totality of DM manifestations, making TIS a reasonable primary endpoint. Definition of Improvement (DOI), Investigator Global Assessment (IGA) scale of skin activity, TIS  $\geq 40$  (at least moderate improvement), TIS in subjects receiving any immunosuppressant medication for  $> 1$  year, TIS at Week 52, and Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI) activity score are selected as secondary efficacy outcomes that provide additional measures of improvement on various aspects of DM disease. Change in corticosteroid dose and other immunosuppressives will be captured as a tertiary efficacy outcome, because long term side effects from systemic corticosteroids and other immunosuppressant medications pose a major safety risk to patients.

### **3.2.2. Part B: Open-Label Extension**

In Part B, all subjects will receive open-label lenabasum 20 mg BID. Similar efficacy and safety assessments will be performed at regularly scheduled visits (see [Table 4](#)) based on the scientific rationale for Part A.

### **3.3. Justification of Dose**

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

## 4. STUDY POPULATION

### 4.1. Inclusion Criteria

Subjects must meet ALL of the following criteria to be eligible for the study:

1. Able to understand and voluntarily sign the informed consent
2. Male or female  $\geq 18$  years of age at the time of signing the informed consent
3. Fulfill one of the following criteria for DM:
  - a. Bohan and Peter's criteria for probable or definite DM ([Bohan and Peter, 1975a](#); [Bohan and Peter 1975b](#))
  - b. ACR/EULAR criteria ([Lundberg et al, 2017](#))
4. Subject has active DM as determined by the investigator
5. Disease activity/severity fulfils one of the following three criteria:
  - i. MDGA  $\geq 3$  cm (0-10 cm scale) and MMT-8 score  $\leq 142$  (out of 150 total possible)
  - ii. Sum of MDGA, PtGA and EMGA VAS scores is  $\geq 10$  cm (all scales individually on 0-10 cm scale)
  - iii. MDGA  $\geq 3$  cm and CDASI activity score of  $>14$
6. Stable doses of immunosuppressive medications for DM as defined by:
  - a. Unchanged dose of oral corticosteroids  $\leq 20$  mg per day prednisone or equivalent for  $\geq 4$  weeks before Visit 1
  - b. Unchanged dose of immunosuppressive medications other than oral corticosteroids for  $\geq 8$  weeks before Screening
7. Willing to not start or stop any immunosuppressive medications for DM from Screening through end of study, unless a change is part of the protocol or considered in the subject's best medical interest by the site investigator or another physician who has primary responsibility for treating the subject's DM.
8. Willing to not use any cannabinoids, including recreational marijuana, medical marijuana and other prescription cannabinoids from Screening through end of study.
9. Able to adhere to the study visit schedule and other protocol requirements and follow study restrictions.
10. Women of childbearing potential (WOCBP) must not be pregnant or breastfeeding and they or their male sexual partner must be using at least one acceptable method of contraception (see [Appendix 1](#)) for at least 4 weeks before Visit 1 and be willing to continue its use for at least 4 weeks after discontinuation of study product.
11. Male subjects must be willing to follow acceptable contraceptive requirements (see [Appendix 1](#)) and should not get anyone pregnant while they are taking the study product or within 4 weeks after taking the last dose of the study product, during which time period they or their female sexual partner must be willing to use at least one recommended method of contraception.

## 4.2. Exclusion Criteria

Subjects are excluded from the study if any of the following criteria apply:

1. Unstable DM or DM with end-stage organ involvement at Screening or Visit 1, including:
  - a. On an organ transplantation list or has received an organ transplant, except corneal transplant
  - b. Interstitial lung disease requiring constant oxygen therapy. This excludes oxygen used to aid sleep or exercise
  - c. Pulmonary hypertension requiring constant oxygen therapy. This excludes oxygen used to aid sleep or exercise
  - d. Subjects requiring supplemental tube feeding or parenteral nutrition
2. Certain medications at Visit 1, including:
  - a. Treatment with intravenous or intramuscular corticosteroids within 4 weeks before Visit 1 (Note: treatment with intra-articular corticosteroids within 4 weeks before Visit 1 is allowed)
  - b. Treatment with oral or intravenous antibiotics or antiviral treatments for new bacterial or viral infections within 4 weeks of Visit 1. This does not include prophylactic antibiotics or antiviral treatments
  - c. Any investigational agent within 30 days 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:
  - a. Acute or chronic hepatitis B or C infection (see [Section 8.2.6](#))
  - b. Human immunodeficiency virus infection (see Section 8.2.6)
  - c. History of active tuberculosis or positive tuberculosis test without a completed course of appropriate treatment. Having already completed at least 1 month of appropriate treatment is eligible.
  - d. Evidence of cancer (except for treated basal or squamous cell carcinoma of the skin or cervical carcinoma in situ) within 3 years of Visit 1
4. Any of the following values for laboratory tests at Screening:
  - a. A positive pregnancy test in women of child-bearing potential (WOCBP) - also at Visit 1
  - b. Hemoglobin < 9 g/dL in males and < 8 g/dL in females
  - c. Neutrophils <  $1.0 \times 10^9/L$
  - d. Platelets <  $75 \times 10^9/L$
  - e. Creatinine clearance < 50 mL/ min/1.73 m<sup>2</sup> on screening blood test, per the Modification of Diet in Renal Disease Study or in 24-hour urine creatine clearance measurement
5. Any known hypersensitivity to lenabasum or any of its excipients.

6. Any medical, psychiatric or substance abuse condition, concurrent medical therapies, or abnormal laboratory values that in the opinion of the site investigator may put the subject at greater safety risk, influence response to study product, or interfere with study assessments.
7. Subjects who have been accommodated in an institution as a result of official or judicial decision.

When there is doubt as to subject eligibility, the investigator or qualified designee should discuss a subject's eligibility with the Medical Monitor.

#### **4.3. Screen Failures**

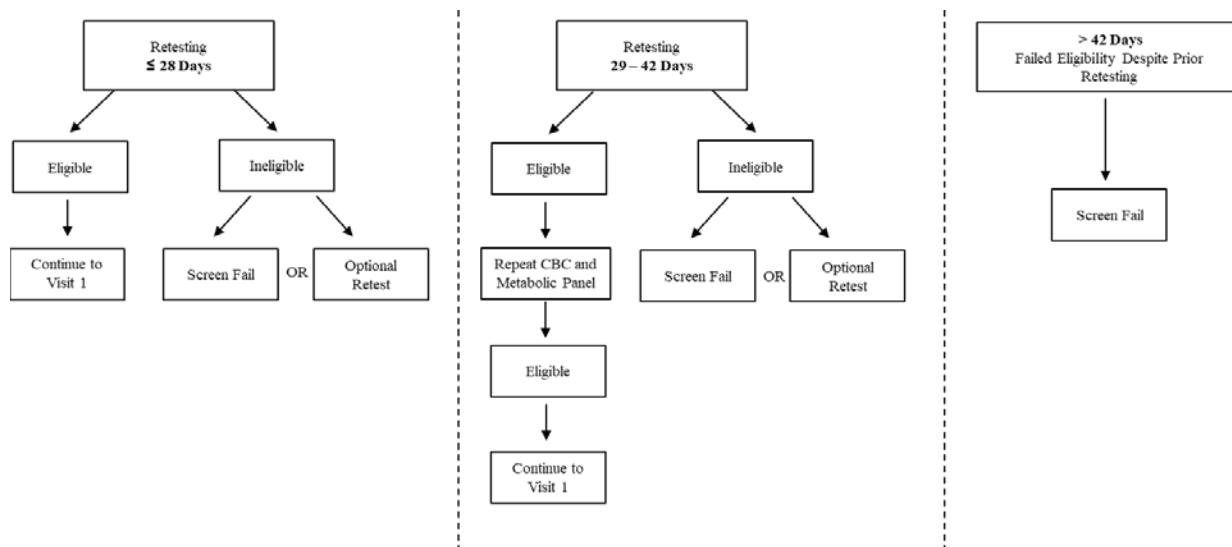
Screen failures are defined as subjects who consent to participate in the clinical trial but are not subsequently randomized to the study intervention or entered in the study following Screening Visit. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event(s) (SAE).

Individuals who fail to meet eligibility criteria at Screening may have repeat screening evaluations done without being considered screen failed as long as eligibility criteria are met within 42 days. If the interval between the Screening Visit and Visit 1 is longer than 28 days but  $\leq$  42 days because of repeat screening evaluations, then repeat metabolic panel and hematology laboratory testing must be done within 28 days of Visit 1 and results reviewed by the investigator before dosing at Visit 1. Ideally, any repeat laboratory screening tests will be done at the central laboratory. If returning to the clinic for repeat screening laboratory tests would cause major inconvenience for the subject, for example because of long distance travel, repeat laboratory tests can be done at a local laboratory only if results are made available to the investigator for review before dosing.

If the patient did not meet eligibility criteria, despite retesting, within 42 days, the patient will be considered a screen fail.

Individuals who are screen failures may be rescreened once again at the discretion of the investigator. The subject is eligible for enrollment if the results of repeated screening assessments meet eligibility criteria.

**Figure 2: Rescreening of Subjects**



Screen failed patients may be rescreened once again at the discretion of the Investigator.

#### **4.4. Subjects Randomized Erroneously**

Subjects who do not meet all of the inclusion criteria or meet any exclusion criteria should not be randomized. If a subject is randomized in error and the error is recognized before dosing, the subject should not be dosed with study product. If the error is recognized after dosing, discontinuation of dosing as outlined in [Section 6](#) should be followed.

#### **4.5. Strategies for Recruitment and Retention**

The target enrollment (i.e., randomized and dosed) for this study is approximately 150 subjects. Most subjects will be recruited from clinics run by the investigators or at which the investigators participate. It is preferred that enrolled subjects have been followed in the investigator's clinic prior to study start. Advertisement for subjects outside the investigator's site is not preferred, although it is allowed.

Target screening of approximately 200 subjects (to achieve about 150 subjects randomized and dosed) is expected to take place over approximately 24 months and may be extended depending on enrollment rate. Number of subjects screened may be adjusted depending upon the screen failure rate, to ensure approximately 150 dosed subjects (mITT population). The number of subjects dosed may be adjusted depending on blinded interim analysis as noted in [Section 9.4.9](#).

To encourage retention in the study, every effort will be made to be respectful of the subject's time. The total time required from the subject for study visits will vary with the efficiency of each site and is expected to be about 4-5 hours for Visit 1, 0.5-1 hour for visits when efficacy assessments are not done, and 1-2 hours for visits when efficacy assessments are done.

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

To reduce missing data, subjects who discontinue study product for reasons of safety or tolerability will be asked to remain in the study and return for evaluations on Visit 4, Visit 6, Visit 8 (if they have not already had Visit 4, 6, and 8) and Visit 10 unless the subject withdraws consent or is lost to follow-up. These off-treatment safety and efficacy data will be included in data analyses.

#### **4.6. Women, Minorities, and Children (Special Populations)**

Women and minorities are allowed in the study. Prevalence rates of DM are higher in women than in men (approximately 2:1 ratio reported), and more female than male subjects are expected in the study.

## 5. STUDY INTERVENTION

### 5.1. Study Intervention(s) Administration

Lenabasum is (6aR,10aR)-1-hydroxy-6,6-dimethyl-3-(2-methyl-2-octanyl)-6a,7,10,10a-tetrahydro-6H-benzo[c]chromene-9-carboxylic acid (previously known as anabasum, ajulemic acid, CT-3, IP751 and CPL7075 and also known as JBT-101).

Placebo is microcrystalline cellulose and magnesium stearate (no active ingredient).

The study products to be administered in this trial are summarized in Table 1.

**Table 1 Study Products, Dose, and Mode of Administration**

Study Arm	Active	Active	Placebo
<b>Intervention</b>	Lenabasum	Lenabasum	Placebo (microcrystalline cellulose and magnesium stearate, no active ingredient)
<b>Dose Formulation</b>	Capsule	Capsule	Capsule
<b>Unit Dose Strength</b>	20 mg (Parts A & B)	5 mg (Parts A only)	NA (Parts A only)
<b>Dosage Level</b>	1 capsule, BID	1 capsule, BID	1 capsule, BID
<b>Route of Administration</b>	Oral	Oral	Oral

In Part A, blinded study product (lenabasum 20 mg, lenabasum 5mg, or placebo) will be dispensed at Visit 1 according to the randomization schedule and the subject will take the first dose of study product at the site. Thereafter, blinded study product will be dispensed as outlined in [Table 3](#). In Part B, study product (lenabasum 20 mg) will be dispensed as outlined in [Table 4](#). Subjects will self-administer study product by the oral route BID with at least 8 hours between the two doses.

**The study product must be taken per the following regimen:**

- Capsules should be swallowed whole
- Ideally, morning and evening doses will be about 12 hours apart. Morning and evening doses must be at least 8 hours apart
- Doses can be taken without regard to fed state

- Subjects who take more than the prescribed dose of study product should be instructed to contact site staff immediately and to seek emergency medical care, if needed

**Instructions for Missed Dosing:**

- If a dose is missed, it should be taken as soon as possible on the same day
- If a dose is missed and it is time for the next dose, take the next dose as regularly scheduled and do not take a make-up dose
- If dosing is missed for the entire day, it should not be made up and take the regularly scheduled dose for the following day

**Instructions for Dosing before Study Visits (Part A PK Visits ONLY – Visits 2, 4, 6 and 10):**

- The site staff should instruct the subject to hold the dose of study product on the morning of the visit or take the dose earlier on that morning if necessary to ensure that the blood sample will be drawn within an 8- to 16-hour window. Instructions on whether the subject should take or hold dosing on the morning of Visits 2, 4, 6, and 10 requires the site staff to know when the subject typically takes the study product and the likely time of blood drawing at the visit.
- The time of last dose of study product should be recorded at each visit. If a subject held the morning dose of study product, the subject may take that dose of study product as convenient after blood for plasma concentration and metabolites of lenabasum is drawn.
- Every effort should be made to remind the subject of this requirement 1-3 days prior to the scheduled visit.

## **5.2. Preparation/Handling/Storage/Accountability**

### **5.2.1. Acquisition and Accountability**

The study product will be dispensed from the site pharmacy or the investigator's storage cabinet in a blinded fashion upon request from the investigator or designee. In Part A, the study product will be dispensed to the subject in accordance with the study product bottle/kit assignments raised by the interactive web-based randomized system (IWRS) and will be based on treatment assignment for that individual. In Part B, all subjects will receive the same treatment of lenabasum 20 mg.

No more than a 6-week (+2) supply of study product plus packaged overage in the bottle(s) may be provided to the subject at time of dispensing in Part A and 8-week (+2) in Part B. Detailed instructions will be in a manual provided to the site by Corbus. A repository of study product will be held at distribution depots. Study product will be distributed to the site pharmacy or investigator by express mail with tracking.

Depending upon the arrangements at the individual site, either the investigator or designee or the designated site pharmacist is responsible for maintaining accountability for the receipt, dispensing, and return of all study medication. Procedures for tracking shipment, receipt,

distribution, and collection of unused study product will be in a manual provided by Corbus to each site.

### **5.2.2. Formulation, Appearance, Packaging, and Labeling**

The formulation of lenabasum used for clinical supply is powder-in-capsules (PIC). Details of lenabasum and placebo study products are provided below:

- **Lenabasum:** The preparation of lenabasum clinical drug product is presented as size no. 2 white opaque hard gelatin capsules containing neat Drug Substance at either 20 mg or 5 mg of lenabasum with a purity  $\geq$  98.5%. There are no other excipients contained in lenabasum capsules.
- **Placebo:** The preparation of placebo is presented as identical size no. 2 white opaque hard gelatin capsules of lenabasum and contains 20 mg of a powder blend composed of microcrystalline cellulose and magnesium stearate. Both excipients are commonly used together in the pharmaceutical industry as regular excipients.

Lenabasum and placebo capsules will be packaged in the same type bottle with the same number of capsules in each bottle. All study product will have an expiry date that exceeds the last date when the study product will be administered to that subject. The bottles will be indistinguishable from each other in appearance.

Lenabasum and placebo will be dispensed to study subjects in the original packaging with a label clearly indicating that the contents are for investigational purposes only. The label will be created according to each country's specific requirements. Additional labels must not cover the caution label or the name of the manufacturer.

### **5.2.3. Product Storage and Stability**

Both lenabasum and placebo are packaged in 35 capsules per bottle in 60 cc high density polyethylene bottles, with the oxygen scavenger, a child resistant cap and induction seal.

Bottles of study product are to be stored at the site within the temperature range specified in the IP Manual (15 – 25°C) away from temperature and humidity extremes, and under conditions appropriate for small quantities of Controlled drugs Act Schedule 1 substances, where applicable. The receipt, security, and storage of study product will comply with the country and local legal and/or regulatory requirements for each participating investigator site. Storage of study product including undispensed and returned (used and unused) study product will remain under these storage conditions until returned to Corbus or designee for destruction.

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

Any lost or damaged study product should be documented in the source documents and reported to Corbus and regulatory authorities, as required.

Subjects will be instructed to store study product at home within the temperature range specified in the IP Manual (15 to 25°C), away from temperature and humidity extremes, with the labeling and child-proof cap intact, in areas that are not accessible to children. All study product that is not ingested by study subjects must be returned to the site and disposed of according to instructions provided by Corbus in the Investigational Product Manual.

#### **5.2.4. Preparation**

Site personnel are not required to prepare study product.

### **5.3. Measures to Minimize Bias: Randomization and Blinding**

Subjects will be randomized and dosed at a ratio of 2:1:2 to lenabasum 20 mg, lenabasum 5 mg, or placebo arms using an IWRS once a subject meets eligibility criteria and before first dose of study product.

Randomization will be stratified based on the following:

- Screening MMT-8 score (< 135 or ≥ 135)
- Prednisone dose (≤ 10 mg or > 10 mg per day or equivalent)
- Region (US vs. ex-US)

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

A central randomization scheme will be used. Randomization does not require the subject's presence at the site. The randomization steps are the following:

- Before accessing the IWRS the investigator or designee should confirm the subject meets all eligibility criteria
- The investigator or designee confirms the site and subject ID and that subject meets eligibility criteria within the IWRS
- The IWRS randomizes the subject to a treatment (lenabasum or placebo) and assigns the study product bottle(s) to be provided to the subject

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.

Part A of this study is double-blinded and will remain blinded until all data entry and processing are complete and the database has been locked. Except for necessary unblinding (see [Section 5.3.1](#)), all Corbus medical and clinical operations staff associated with this study, both internal Corbus staff and contract staff, including the Medical Monitor, project management, and site monitors, will remain blinded to treatment randomization until the database is closed (except for certain personnel detailed below). 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, study coordinators, and pharmacists will be blinded to intervention groups, except in the case of necessary unblinding (see Section 5.3.1). The final unblinding of all study subjects will occur only after the database has been locked. If treatment allocation for a subject otherwise becomes known to the clinical site staff, the principal investigator must be notified immediately of the unblinding (but not of the treatment allocation), and the principal investigator will notify Corbus of the unblinding but not of the treatment allocation.

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

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

### **5.3.1. Unblinding Procedures During the Study**

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

- Any AE where knowledge of the treatment assignment is necessary to treat the subject
- A child accidentally takes the study product
- Pregnancy of a subject in the study

If the investigator decides that a safety concern warrants unblinding, the investigators will have 24-hour access to an IWRS through which the code can be broken. Procedures for unblinding through the IWRS will be described in a manual supplied to the site. The investigator should make every effort to contact the sponsor before unblinding a subject's treatment assignment unless this could delay emergency treatment of the subject. In all circumstances other than a medical emergency, unblinding will be done only after discussion with the Medical Monitor.

Emergency treatment unblinding must be reported to the Medical Monitor immediately, and Corbus will be notified through the IWRS regarding the unblinding. When it is necessary to break the blind, the investigator must notify the EC/IRB as applicable.

If a subject is unblinded, the subject will discontinue treatment with study product and will have either a routine scheduled visit if due or an unscheduled visit as soon as possible to evaluate the safety concern that prompted the unblinding and there will be no further efficacy assessments.

If unblinding is deemed necessary, the investigator should not disclose the treatment assignment to other study personnel until after database lock and disclosure of treatment assignment to all subjects.

### **5.3.2. Unblinding Procedures at the End of Part A**

After Part A completion, when all data have been collected, all queries have been resolved, the DMC has had a final review of the safety data, and the database has been locked, the lead statistician will be authorized by Corbus to generate a request to the IWRs to unblind the treatment code for all subjects for purposes of data analyses.

After the database has been locked and the blind has been broken for the study, the investigators will be notified by Corbus of individual subject treatment allocation. The investigators may then inform subjects of their blinded treatment allocation, if the subjects choose to know, and EC/IRB requirements for disclosure, if any, have been met.

### **5.4. Study Intervention Compliance**

The number of capsules of study product returned to the site will be counted and recorded as a measure of subject compliance with treatment.

### **5.5. Concomitant Therapy**

Doses of non-corticosteroid immunosuppressant medications should be stable for  $\geq$  8 weeks at screening. Doses of oral corticosteroids should be stable for  $\geq$  4 weeks at Visit 1. Examples of allowed background immunosuppressive agents include and are not limited to prednisone or other glucocorticoid medications, mycophenolate, methotrexate, azathioprine, cyclosporine, cyclophosphamide, intravenous gamma globulin, and monoclonal antibody treatments. If there is any question about use of concomitant immunosuppressant medications, the investigator should discuss eligibility with the Medical Monitor.

Concomitant therapies taken for chronic treatment of pre-existing conditions may be continued during the study. It is preferred that these medications be stabilized before entry and continued wherever practical without variation of dose or regimen during the study.

During the study, concomitant medications and new medications should be administered at the discretion of the investigator or treating physician to provide the subject with the best possible medical care. It is recommended that changes in ongoing treatments or introduction of new therapies are kept to a minimum to avoid confounding efficacy and safety evaluations.

#### **5.5.1. Guidelines for Reduction in Concurrent Immunosuppressant Medications including Corticosteroids**

For both Part A and Part B, doses of concurrent immunosuppressive medications including oral corticosteroids may be reduced during the study at the discretion of the investigator. Appropriate reasons for reduction would be AEs or intolerance related to the immunosuppressant medication or clinical improvement in DM during the study. These general principles should be observed for dose reduction in immunosuppressant medications:

- A reduction in immunosuppressant medications can be done at any time during the study for AEs or tolerability concerns related to that immunosuppressant medication.

Subjects who require a reduction in concurrent immunosuppressive medications for safety or tolerability reasons will have their doses adjusted at the investigator's discretion.

- *Part A only:* A subject's immunosuppressant medications (including oral corticosteroids) may be reduced between Visits 4-8 if the investigator determines that clinical improvement in the subject's DM has occurred and a reduction is warranted.
- *Part A only:* No reduction in immunosuppressive medications (including oral corticosteroids) should be done between Visits 9 and 10, except for reasons of safety and tolerability. This provides approximately 12 weeks of stability on medications before assessment of the primary efficacy outcome.
- Dose reduction in oral corticosteroids should occur before dose reduction in non-corticosteroid medications. It is recommended that doses of non-corticosteroid immunosuppressive medications are reduced only if average daily oral corticosteroid dose is  $\leq$  5 mg prednisone or equivalent.
- Dose reduction in chronic oral corticosteroids generally should be gradual with progressive decrements at intervals of no less than 4 weeks. The recommended schedule for reduction in chronic corticosteroids dose provided in Table 2.

**Table 2 Recommended Schedule for Reduction in Chronic Oral Corticosteroid Dose When Determined by the Investigator to be Appropriate at Visits 4-8**

Daily oral prednisone dose or equivalent at time of visit	Reduction in daily oral prednisone dose or equivalent
> 15 mg	5 mg
> 5 mg to $\leq$ 15 mg	2.5 mg
$\leq$ 5 mg	Investigator decision for 2.5 mg or discontinue corticosteroids completely

A non-exhaustive conversion table of frequently used corticosteroids and dosage is found in [Appendix 7](#).

The recommended schedule for reduction in doses of chronic non-corticosteroid immunosuppressive medication for subjects who meet the general guidelines for reduction in immunosuppressive medications at Visits 4-8 is provided:

- Selected immunosuppressive medication dosage can be reduced  $\leq$  50% on the first visit that subject meets criteria.
- At subsequent visits, selected immunosuppressive medication may be discontinued or have further dose reduction based on the judgement of the investigator.

### **5.5.2. Guidelines for New or Increased Dose of Immunosuppressive Medications or Rescue Treatment**

Eligibility criteria permit subjects enrolling in this study to receive treatment with stable doses of concomitant immunosuppressive medications except oral prednisone > 20 mg per day or equivalent at Visit 1. For Part A, the intent is that the subject remains on stable doses of any Baseline concomitant immunosuppressive medications through Visit 4 at Week 16 and then reduce dose according to the pre-specified schedule in [Section 5.5.1](#) only if the subject meets reduction criteria.

If the subject has worsened between Screening and Visit 1 and requires new or increased doses of immunosuppressive medications at the time of Visit 1, that subject should be discontinued from the study before randomization and if already randomized, should be discontinued before dosing.

After Visit 1, and throughout the study, including Part B, if applicable, doses of current concomitant immunosuppressive medication(s) may be increased or new immunosuppressive medication(s) may be started under the following circumstances:

- The subject requires a temporary increase in chronic corticosteroid dose for safety reasons to prevent adrenal insufficiency, for example, in the setting of acute concurrent illness or surgery.
- The subject has a concurrent illness that requires new corticosteroid medication or an increase in corticosteroid dose, such as acute severe allergic reaction.
- The subject has medically significant worsening in their DM, and the site investigator or other physician primarily responsible for treating the subject's DM considers it in the subject's best medical interest to treat the increase in DM signs or symptoms with new or increased doses of immunosuppressive medications. The reason(s) for this decision must be documented and any medically significant worsening of the disease should be reported as an AE.
- If a subject has worsening of DM following reduction in immunosuppressive medication ([Section 5.5.1](#)), a higher dose of that immunosuppressive medication may be given again.

As soon as practical and ideally before any increase in immunosuppressive medications, the site investigator should have a discussion with the Medical Monitor about the reasons for increase. Keeping the subject in the study is generally preferred over withdrawing the subject from the study, even when that subject requires rescue medication.

### **5.5.3. Prohibited Medications During the Study**

- Any investigational agent within 30 days or 5 therapeutic half-lives of that agent, whichever is longer, before Visit 1 and throughout the study.
- Any cannabinoid, including recreational marijuana, medicinal marijuana or other prescription cannabinoids are prohibited from Screening throughout the study.

## **6. DISCONTINUATION OF STUDY TREATMENT, SUBJECT WITHDRAWAL, AND EARLY TERMINATION**

### **6.1. Discontinuation of Study Treatment and Subject Withdrawal**

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

A subject will not receive any further study product if any of the following events occur:

- Subject lost to follow-up
- Withdrawal of consent for study participation
- Subject decision to discontinue treatment
- Pregnancy
- Any serious or life-threatening AE probably or definitely-related to lenabasum
- Any AE, which in the opinion of investigator, can jeopardize the safety of an individual subject
- Subjects recognized as being treated despite being wrongly randomized (i.e., not meeting all eligibility criteria)
- Other event(s) which in the opinion of the site investigator or Medical Monitor contraindicates further dosing such as, but not limited to, repeated failure to meet protocol requirements, significant concurrent illnesses or disease complications

Subjects withdrawn for the above reasons, except lost to follow-up or withdrawn consent, will be asked to return to Visit 4, Visit 6, Visit 8 (if they have not already had Visit 4, 6, and 8), and Visit 10; Weeks 16, 28, 40 and 52, respectively. These subjects will not be required to but may undergo optional blood sampling, skin photography, or skin biopsies at the remaining visits if they had opted in previously.

Subjects 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 who are withdrawn due to pregnancy, or partners of subjects who become pregnant, will require additional follow-up as outlined in Pregnancies, [Section 8.2.7.8](#).

Subjects who withdraw consent will be asked to complete the early termination (ET) visit; however, completion of the visit will not be mandated.

A subject will be considered lost to follow-up if he/she does not respond to the following:

- Three attempts at contacting the subjects (including phone calls, emails, or texts and a certified letter) from a member of the research staff over a period of up to a month;
- A certified letter updating him/her on the study status.

Documentation of the contact attempts and the certified letter should be filed with the subject's source documents.

The reason for subject discontinuation or withdrawal from the study will be recorded in the eCRF. If the subject is discontinued from treatment due to an AE, the reason for discontinuation should be listed as due to an AE. The number of subjects screened may be adjusted to achieve the target number of subjects who receive at least 1 dose of study product.

Study product will be stopped without tapering because abrupt discontinuation of lenabasum is not known to cause any harmful effects. All remaining study product will be returned to the study staff.

## 6.2. Early Termination of Study

This study (either or both Part A and/or Part B) may be suspended or prematurely terminated at the discretion of the Sponsor if there is sufficient reasonable cause. For example, any new information about the execution of the trial, that, in the opinion of the Sponsor, 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.

If any of the following events occur during enrollment, then study entry and randomization of new subjects into the study or rollover to Part B will be suspended until review of the event in question occurs by the DMC:

- Death in any subject considered to be related to lenabasum
- Two life-threatening clinical events judged to be probably- or definitely-related to lenabasum. NOTE: The term 'life-threatening' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe
- Determination of unexpected, significant, or unacceptable risk to subjects that contradict dosing of additional subjects, in the opinion of the Corbus Chief Medical Officer

Administration of study product may continue during the time of review in subjects who are already receiving study product in either Part A and/or Part B, based on the judgment of the Corbus Chief Medical Officer.

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

Written notification, documenting the reason for study suspension or termination, will be provided by the Sponsor to the site investigators and relevant regulatory agencies. If the study is suspended or prematurely terminated, the site investigators will promptly inform their site IRB/EC and will provide the reason(s) for the suspension or termination. Review and approval by the reviewing IRB/IEC at each site may be required for resumption of the study in the event the study is interrupted.

## **7. SCHEDULE OF ASSESSMENTS AND STUDY VISITS**

### **7.1. Assessments**

**Table 3 Schedule of Assessments – Part A**

Study Activity	Visit	Screening	Treatment Period										ET	Follow-up <sup>x</sup> 4±1
			V1	V2	V3	V4	V5	V6	V7	V8	V9	V10		
	Week	Up to -4	Day 1	4±1	10±1	16±1	22±1	28±1	34±1	40±1	46±1	52±1		
<b>ELIGIBILITY ASSESSMENTS</b>														
Informed Consent		X											X <sup>w</sup>	
Eligibility criteria	X		X											
Medical history	X													
Physician assessment of DM activity	X													
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs and weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height	X													
Full physical examination	X	X											X	X
Brief physical examination			X	X	X	X	X	X	X	X	X			X
HIV, HBV and HCV testing	X													
FSH and LH	X													
Contraceptive assessment and record LMP for WOCBP	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum β HCG for WOCBP	X													
Urine β HCG for WOCBP			X	X	X	X	X	X	X	X	X	X	X	X
<b>SAFETY ASSESSMENTS</b>														
AE monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12 lead ECG	X	X	X					X				X		X
Safety phone call to subject												X		
<b>RANDOMIZATION</b>														
Randomization (IWRS)			X											
<b>STUDY PRODUCT ADMINISTRATION</b>														
Administer study product in clinic			X											
Dispense study product			X	X	X	X	X	X	X	X	X			
Collect and count capsules of returned study product				X	X	X	X	X	X	X	X	X		X
<b>PATIENT-REPORTED EFFICACY ASSESSMENTS</b>														
PtGA	X	X	X		X		X		X		X		X	X
HAQ-DI	X	X	X		X		X		X		X		X	X
SF-36	X	X	X		X		X		X		X		X	X
PROMIS-29 Short Form	X	X	X		X		X		X		X		X	X
Patient VAS score for pain	X	X	X		X		X		X		X		X	X
FACIT-Fatigue Score	X	X	X		X		X		X		X		X	X

Study Activity	Visit	Screening	Treatment Period										ET	Follow-up <sup>a</sup> 4±1
			V1	V2	V3	V4	V5	V6	V7	V8	V9	V10		
	Week	Up to -4	Day 1	4±1	10±1	16±1	22±1	28±1	34±1	40±1	46±1	52±1		
5-D Itch Questionnaire		X	X	X		X		X		X		X	X	
Skindex-29+3		X	X	X		X		X		X		X	X	
EQ-5D questionnaire		X	X	X		X		X		X		X	X	
<b>PHYSICIAN ASSESSMENTS OF EFFICACY</b>														
MMT-8		X	X	X		X		X		X		X	X	
CDASI score		X	X	X		X		X		X		X	X	
IGA scale of skin activity		X	X	X		X		X		X		X	X	
EMGA (10 cm VAS)		X	X	X		X		X		X		X	X	
MDGA (10-cm VAS and Likert Scale)		X	X	X		X		X		X		X	X	
<b>LABORATORY ASSESSMENTS</b>														
CBC with differential and platelets		X	X	X	X	X	X	X	X	X	X	X	X	
Metabolic panel (includes ALT, AST and LDH)		X	X	X	X	X	X	X	X	X	X	X	X	
CK and aldolase		X	X	X		X		X		X		X	X	
Blood biomarkers			X					X				X	X	
Blood for flow cytometry (at selected sites)			X					X				X	X	
Paxgene tube collection			X									X	X	
Autoantibody measurements			X									X	X	
Urine dipstick			X	X				X				X	X	
<b>PHARMACOKINETIC ASSESSMENTS</b>														
Lenabasum plasma concentration and metabolite profiling			X	X		X		X				X	X	
<b>ADDITIONAL ASSESSMENTS</b>														
Spirometry		X	X			X		X				X	X	
Skin biopsies (optional at selected sites)			X			X						X	X	
Skin photography (optional at selected sites)			X									X	X	
Patient Improvement Questionnaire for Subjects						X		X				X	X	
Patient Improvement Questionnaire for Physicians						X		X				X	X	

<sup>a</sup> Must fulfill Bohan and Peter's criteria for probable or definite DM or ACR/EULAR criteria for DM

<sup>b</sup> Medical history includes the following: subject demographic information, history and disease manifestations of DM including ILD, concurrent illnesses and past, smoking history (packyears) classified into one of the following categories: current smoker; ever smoked (>= 1 cigarette/day for > 1 year); never smoked, and any other relevant medical history.

<sup>c</sup> Doses of immunosuppressive medications (including corticosteroids) should be assessed at every study visit along with all other concomitant medications.

<sup>d</sup> Systolic and diastolic BP will be measured with the subject supine for at least 5 minutes. The same arm should be used for the measurement throughout the study as much as possible. Pulse and respiration will also be measured with the subject supine for at least 5 minutes. Body temperature will be measured on the skin or in the mouth.

<sup>e</sup> Weight will be measured with coats, jacket, and footwear removed.

<sup>f</sup> Standing height will be measured with footwear removed.

<sup>g</sup> Full physical examination includes the following assessments: alertness and orientation, general appearance, skin, head, eyes, ears, nose, and throat, lungs, heart, abdomen, musculoskeletal examination, and lymph nodes. Breast and genitourinary examinations are not required.

<sup>h</sup> Brief physical examination includes the following assessments: skin, lung, heart, abdomen, and any other area as indicated by changes in medical history.

<sup>i</sup> Applicable for women  $\leq$  55 years of age with no menses for  $\geq$  1 year.

<sup>j</sup> Refer to [Appendix 1](#) for the criteria for determining reproductive potential and acceptable methods of contraception.

<sup>k</sup> AE monitoring should begin at subject consent.

<sup>l</sup> 12-lead ECG with QT/QTc intervals should be recorded with the subject in a rested supine position  $\geq$  10 minutes before the test.

<sup>m</sup> Study personnel will be required to contact subjects  $3 \pm 1$  week after Visit 9.

<sup>n</sup> To occur at or before Visit 1.

<sup>o</sup> The first dose of study product on Visit 1 will be taken in clinic from the dispensed study product. Vital signs include blood pressure, pulse rate, respiratory rate, and temperature and will be measured pre-dose and  $3.0 \pm 0.5$  hours after administration of first dose of study product at Visit 1 in the clinic. ECGs will be recorded pre-dose and  $3.0 \pm 0.5$  hours after administration of first dose of study product in the clinic.

<sup>p</sup> Study product will be dispensed for administration in WOCBP only if urine pregnancy test is negative.

<sup>q</sup> Ideally, all patient-reported efficacy assessments should be completed before all other study procedures, in the order listed.

<sup>r</sup> It is preferred that physician assessments of efficacy are performed in the order listed.

<sup>s</sup> Metabolic panel includes 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 (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH); AST, ALT and LDH are three of the five muscle enzymes comprising the TIS (see [Section 8.1.2](#)).

<sup>t</sup> Urine dipstick for blood, protein, glucose

<sup>u</sup> Pharmacokinetic blood samples will be collected at Visit 1 pre-dose and  $3.0 \pm 0.5$  hours after administration of first dose of study product in the clinic. Time of administration of the first study dose and time of PK sample collection (blood draw for PK) should be recorded. At Visits 2, 4, 6, and 10, PK blood samples will be collected once during the visit and time of most recent dose of study product and blood collection should be recorded. Time of the blood draw should be 8-16 hours after the last dose of the study product, which typically would have been taken at subject's home the evening before the visit.

<sup>v</sup> Five optional, 4 mm skin biopsies will be collected: two at Visit 1, two at Visit 4 and one at Visit 10. At Site 1001, subjects will have the option to consent to two 6 mm and three 4 mm biopsies (e.g., one 4 mm and one 6 mm at Visit 1; one 4 mm and one 6 mm at Visit 4, and one 4 mm at Visit 10). Skin biopsies will only be conducted at selected sites.

<sup>w</sup> Subjects who rollover into Part B should sign an ICF by Visit 10 and preferably earlier than Visit 10, if possible.

<sup>x</sup> The Safety Follow-up Visit is to occur  $4 \pm 1$  weeks after the last visit (V10/ET) and is to be completed by subjects who do not rollover into Part B.

**Table 4: Schedule of Assessments – Part B**

Study Activity	Visit	Treatment Period								ET <sup>o</sup>	Follow-up <sup>p</sup> 4±1
		VB1	VB2	VB3	VB4	VB5	VB6	VB7	VB8		
	Week	Day 1	4±1	12±1	20±1	28±1	36±1	44±1	52±1		
<b>ELIGIBILITY ASSESSMENTS</b>											
Informed Consent		X <sup>a</sup>									
Concomitant medications <sup>b</sup>			X	X	X	X	X	X	X	X	X
Vital signs <sup>c</sup> and weight <sup>d</sup>			X	X	X	X	X	X	X	X	X
Full physical examination <sup>e</sup>									X	X	
Brief physical examination <sup>f</sup>			X	X	X	X	X	X			X
Contraceptive assessment <sup>g</sup> and record LMP for WOCBP <sup>h</sup>			X	X	X	X	X	X	X	X	X
Urine β HCG for WOCBP			X	X	X	X	X	X	X	X	X
<b>SAFETY ASSESSMENTS</b>											
AE monitoring			X	X	X	X	X	X	X	X	X
12 lead ECG <sup>i</sup>						X			X	X	
<b>STUDY PRODUCT ADMINISTRATION</b>											
Dispense study product <sup>j</sup>		X	X	X	X	X	X	X			
Collect and count capsules of returned study product			X	X	X	X	X	X	X	X	
<b>PATIENT-REPORTED EFFICACY ASSESSMENTS<sup>k</sup></b>											
PtGA			X	X	X	X	X	X	X	X	
HAQ-DI			X	X	X	X	X	X	X	X	
SF-36			X	X	X	X	X	X	X	X	
PROMIS-29 Short Form			X	X	X	X	X	X	X	X	
Patient VAS score for pain			X	X	X	X	X	X	X	X	
FACIT-Fatigue Score			X	X	X	X	X	X	X	X	
5-D Itch Questionnaire			X	X	X	X	X	X	X	X	
Skindex-29+3			X	X	X	X	X	X	X	X	
EQ-5D questionnaire			X	X	X	X	X	X	X	X	
<b>PHYSICIAN ASSESSMENTS OF EFFICACY<sup>l</sup></b>											
MMT-8			X	X	X	X	X	X	X	X	
CDASI score			X	X	X	X	X	X	X	X	
IGA scale of skin activity			X	X	X	X	X	X	X	X	
EMGA (10 cm VAS)			X	X	X	X	X	X	X	X	
MDGA (10-cm VAS and Likert Scale)			X	X	X	X	X	X	X	X	

Study Activity	Visit	Treatment Period								ET <sup>o</sup>	Follow-up <sup>p</sup> 4±1
		VB1	VB2	VB3	VB4	VB5	VB6	VB7	VB8		
	Week	Day 1	4±1	12±1	20±1	28±1	36±1	44±1	52±1		
<b>LABORATORY ASSESSMENTS</b>											
CBC with differential and platelets			X		X		X		X	X	X
Metabolic panel (includes ALT, AST and LDH) <sup>m</sup>			X		X		X		X	X	X
CK and aldolase			X		X		X		X	X	
Blood biomarkers						X			X	X	
Autoantibody measurements									X	X	
Urine dipstick <sup>n</sup>			X		X		X		X	X	
<b>ADDITIONAL ASSESSMENTS</b>											
Spirometry				X		X		X		X	X

<sup>a</sup> Subjects who rollover into Part B should sign an ICF by or before Visit 10 in Part A. If OLE is extended beyond 1 year, ICF for the extended OLE should be signed by or before Visit B8

<sup>b</sup> Doses of immunosuppressive medications (including corticosteroids) should be assessed and may be reduced as specified in [Section 5.5.1](#) at every study visit along with all other concomitant medications.

<sup>c</sup> Systolic and diastolic BP will be measured with the subject supine for at least 5 minutes. The same arm should be used for the measurement throughout the study as much as possible. Pulse and respiration will also be measured with the subject supine for at least 5 minutes. Body temperature will be measured on the skin or in the mouth.

<sup>d</sup> Weight will be measured with coats, jacket, and footwear removed.

<sup>e</sup> Full physical examination includes the following assessments alertness and orientation, general appearance, skin, head, eyes, ears, nose, and throat, lungs, heart, abdomen, musculoskeletal examination, and lymph nodes. Breast and genitourinary examinations are not required.

<sup>f</sup> Brief physical examination includes the following assessments: skin, lung, heart, abdomen, and any other area as indicated by changes in medical history.

<sup>g</sup> Applicable for women ≤ 55 years of age with no menses for ≥ 1 year.

<sup>h</sup> Refer to [Appendix 1](#) for the criteria for determining reproductive potential and acceptable methods of contraception.

<sup>i</sup> 12-lead ECG with QT/QTc intervals should be recorded with the subject in a rested supine position ≥ 10 minutes before the test.

<sup>j</sup> Study product will be dispensed for administration in women of childbearing potential only if urine pregnancy test is negative.

<sup>k</sup> Ideally, all patient-reported efficacy assessments should be completed before all other study procedures, in the order listed.

<sup>l</sup> It is preferred that physician assessments of efficacy are performed in the order listed.

<sup>m</sup> Metabolic panel includes 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 (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH); AST, ALT and LDH are three of the five muscle enzymes comprising the TIS (see [Section 8.1.2](#)).

<sup>n</sup> Urine dipstick for blood, protein, glucose

<sup>o</sup> Subjects who discontinue the study at any stage, and for any reason, will be encouraged to complete the procedures described in the Early Termination (ET) Visit

<sup>p</sup> The Safety Follow-up Visit is to occur 4±1 weeks after the last visit (VB8 unless OLE is extended beyond 1 year); discontinued subjects will be encouraged to complete this visit 4±1 weeks after the ET Visit.

## 7.2. Study Visits

A detailed description of all study procedures is provided in [Section 8.2](#). Ideally, all patient-reported efficacy assessments should be completed before all other study procedures, in the order listed. It is preferred that physician assessments of efficacy are performed in the order listed.

### 7.2.1. Part A

#### 7.2.1.1. Screening (up to 4 weeks before Visit 1)

- Informed consent
- Patient-reported efficacy assessments, with instruction/ training in instrument by study staff
  - PtGA
  - HAQ-DI
  - SF-36
  - PROMIS-29 Short Form
  - Patient VAS score for pain
  - FACIT-Fatigue Score
  - 5-D Itch Questionnaire
  - Skindex-29+3
  - EQ-5D questionnaire
- Medical history (including a detailed history of DM)
- Record concomitant medication(s)
- AE monitoring
- Contraceptive assessment and record of last menstrual period (LMP) for WOCBP
- Height, which will be used throughout trial as Baseline
- Vital signs (including blood pressure [BP], pulse rate, respiratory rate, and temperature) and weight
- 12 lead ECG
- Spirometry for FVC
- Full physical examination
- Physician assessments of efficacy
  - MMT-8
  - CDASI score

- IGA scale of skin activity
- EMGA (10-cm VAS)
- MDGA (10-cm VAS and Likert Scale)
- Physician assessment of DM activity (see [Appendix 5](#))
- Laboratory tests:
  - HIV, HBV and HCV testing
  - FSH and LH (if applicable)
  - Serum  $\beta$  HCG for WOCBP
  - Complete blood count (CBC) with differential and platelets
  - Metabolic panel (includes ALT, AST, and LDH)
  - Creatine phosphokinase (CK) and aldolase
- Verify eligibility criteria (including verification of DM)

#### 7.2.1.2. Randomization

Randomization within IWRS will occur before or at Visit 1. The subject does not need to be present in clinic for randomization to occur. See [Section 5.3](#) for additional details.

#### 7.2.1.3. Visit 1 (Day 1)

##### Pre-dose:

- Verify eligibility criteria (including verification of DM)
- Patient-reported efficacy assessments
  - PtGA
  - HAQ-DI
  - SF-36
  - PROMIS-29 Short Form
  - Patient VAS score for pain
  - FACIT-Fatigue Score
  - 5-D Itch Questionnaire
  - Skindex-29+3
  - EQ-5D questionnaire
- Record concomitant medication(s)
- AE monitoring
- Contraceptive assessment and record of LMP for WOCBP

- Vital signs (including BP, pulse rate, respiratory rate, and temperature) and weight
- 12 lead ECG
- Spirometry for FVC
- Full physical examination
- Physician assessments of efficacy
  - MMT-8
  - CDASI score
  - IGA scale of skin activity
  - EMGA (10-cm VAS)
  - MDGA (10-cm VAS and Likert Scale)
- Laboratory tests
  - CBC with differential cell count and platelets
  - Metabolic panel (includes ALT, AST and LDH)
  - CK and aldolase
  - Blood biomarkers
  - Blood for flow cytometry (optional at selected sites)
  - Paxgene tube collection
  - Autoantibody measurements
  - Urine  $\beta$ hCG in WOCBP
  - Urine dipstick
- Skin biopsies (optional at selected sites)
- Skin photography (optional at selected sites)
- Lenabasum plasma concentration and metabolite profiling
- Dispense study product

**Dosing:**

- The first dose of study product will be administered in the clinic using dispensed study product.

**Post-dose (3  $\pm$  0.5 hrs)**

- Vital signs (including BP, pulse rate, respiratory rate, and temperature)
- 12 lead ECG
- Lenabasum plasma concentration and metabolite profiling

#### 7.2.1.4. Visit 2 (Week 4 ± 1)

- Every effort should be made to remind the subject of dosing requirements for PK sampling ([Section 5.1](#)) 1-3 days prior to the scheduled visit
- Patient-reported efficacy assessments
  - PtGA
  - HAQ-DI
  - SF-36
  - PROMIS-29 Short Form
  - Patient VAS score for pain
  - FACIT-Fatigue Score
  - 5-D Itch Questionnaire
  - Skindex-29+3
  - EQ-5D questionnaire
- Collect and count capsules of returned study product
- Record concomitant medication(s)
- AE monitoring
- Contraceptive assessment and record of LMP for WOCBP
- Vital signs (including BP, pulse rate, respiratory rate, and temperature) and weight
- 12 lead ECG
- Brief physical examination
- Physician assessments of efficacy
  - MMT-8
  - CDASI score
  - IGA scale of skin activity
  - EMGA (10-cm VAS)
  - MDGA (10-cm VAS and Likert Scale)
- Laboratory tests
  - CBC with differential cell count and platelets
  - Metabolic panel (includes ALT, AST and LDH)
  - CK and aldolase
  - Urine  $\beta$ hCG in WOCBP

- Urine dipstick
- Lenabasum plasma concentration and metabolite profiling
- Dispense study product

**7.2.1.5. Visit 3, Visit 5, Visit 7, Visit 9<sup>1</sup> (Weeks 10, 22, 34, and 46)**

- Collect and count capsules of returned study product
- Record concomitant medication(s)
- AE monitoring
- Contraceptive assessment and record of LMP for WOCBP
- Vital signs (including BP, pulse rate, respiratory rate, and temperature) and weight
- Brief physical examination
- Laboratory tests
  - CBC with differential cell count and platelets
  - Metabolic panel (includes ALT, AST and LDH)
  - Urine βhCG in WOCBP
- Dispense study product

**7.2.1.6. Visit 4 (Week 16 ± 1)**

- Every effort should be made to remind the subject of dosing requirements for PK sampling ([Section 5.1](#)) 1-3 days prior to the scheduled visit
- Patient-reported efficacy assessments
  - PtGA
  - HAQ-DI
  - SF-36
  - PROMIS-29 Short Form
  - Patient VAS score for pain
  - FACIT-Fatigue Score
  - 5-D Itch Questionnaire
  - Skindex-29+3
  - EQ-5D questionnaire
- Patient Improvement Questionnaire for Subjects (see [Appendix 4](#))

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<sup>1</sup> Study personnel will be required to contact subjects 3±1 weeks after Visit 9 to assess compliance and safety.

- Collect and count capsules of returned study product
- Record concomitant medication(s)
- AE monitoring
- Contraceptive assessment and record of LMP for WOCBP
- Vital signs (including BP, pulse rate, respiratory rate, and temperature) and weight
- Spirometry
- Brief physical examination
- Physician assessments of efficacy
  - MMT-8
  - CDASI score
  - IGA scale of skin activity
  - EMGA (10-cm VAS)
  - MDGA (10-cm VAS and Likert Scale)
- Patient Improvement Questionnaire for Physicians (see [Appendix 3](#))
- Laboratory tests
  - CBC with differential cell count and platelets
  - Metabolic panel (includes ALT, AST, and LDH)
  - CK and aldolase
  - Urine  $\beta$ hCG in WOCBP
- Skin biopsies (optional at selected sites)
- Lenabasum plasma concentration and metabolite profiling
- Dispense study product

#### 7.2.1.7. Visit 6 (Week 28 $\pm$ 1)

- Every effort should be made to remind the subject of dosing requirements for PK sampling ([Section 5.1](#)) 1-3 days prior to the scheduled visit
- Patient-reported efficacy assessments
  - PtGA
  - HAQ-DI
  - SF-36
  - PROMIS-29 Short Form
  - Patient VAS score for pain

- FACIT-Fatigue Score
- 5-D Itch Questionnaire
- Skindex-29+3
- EQ-5D questionnaire
- Patient Improvement Questionnaire for Subjects (see [Appendix 4](#))
- Collect and count capsules of returned study product
- Record concomitant medication(s)
- AE monitoring
- Contraceptive assessment and record of LMP for WOCBP
- Vital signs (including BP, pulse rate, respiratory rate, and temperature) and weight
- 12 lead ECG
- Spirometry
- Brief physical examination
- Physician assessments of efficacy
  - MMT-8
  - CDASI score
  - IGA scale of skin activity
  - EMGA (10-cm VAS)
  - MDGA (10-cm VAS and Likert Scale)
- Patient Improvement Questionnaire for Physicians (see [Appendix 3](#))
- Laboratory tests
  - CBC with differential cell count and platelets
  - Metabolic panel (includes ALT, AST, and LDH)
  - CK and aldolase
  - Blood biomarkers
  - Blood for flow cytometry (optional at selected sites)
  - Urine dipstick
  - Urine  $\beta$ hCG in WOCBP
- Lenabasum plasma concentration and metabolite profiling
- Dispense study product

### 7.2.1.8. Visit 8 (Week 40 ± 1)

- Patient-reported efficacy assessments
  - PtGA
    - HAQ-DI
    - SF-36
  - PROMIS-29 Short Form
    - Patient VAS score for pain
    - FACIT-Fatigue Score
  - 5-D Itch Questionnaire
    - Skindex-29+3
    - EQ-5D questionnaire
- Collect and count capsules of returned study product
- Record concomitant medication(s)
- AE monitoring
- Contraceptive assessment and record of LMP for WOCBP
- Vital signs (including BP, pulse rate, respiratory rate, and temperature) and weight
- Brief physical examination
- Physician assessments of efficacy
  - MMT-8
  - CDASI score
    - IGA scale of skin activity
    - EMGA (10-cm VAS)
    - MDGA (10-cm VAS and Likert Scale)
- Laboratory tests
  - CBC with differential cell count and platelets
  - Metabolic panel (includes ALT, AST, and LDH)
  - CK and aldolase
  - Urine  $\beta$ hCG in WOCBP
- Dispense study product

#### 7.2.1.9. Visit 10<sup>2</sup> (Week 52 ± 1) or Early Termination (ET)

- Every effort should be made to remind the subject of dosing requirements for PK sampling ([Section 5.1](#)) 1-3 days prior to the scheduled visit
- Patient-reported efficacy assessments
  - PtGA
  - HAQ-DI
  - SF-36
  - PROMIS-29 Short Form
  - Patient VAS score for pain
  - FACIT-Fatigue Score
  - 5-D Itch Questionnaire
  - Skindex-29+3
  - EQ-5D questionnaire
- Patient Improvement Questionnaire for Subjects (see [Appendix 4](#))
- Collect and count capsules of returned study product
- Record concomitant medication(s)
- AE monitoring
- Contraceptive assessment and record of LMP for WOCBP
- Vital signs (including BP, pulse rate, respiratory rate, and temperature) and weight
- 12 lead ECG
- Spirometry
- Full physical examination
- Physician assessments of efficacy
  - MMT-8
  - CDASI score
  - IGA scale of skin activity
  - EMGA (10-cm VAS)
  - MDGA (10-cm VAS and Likert Scale)
- Patient Improvement Questionnaire for Physicians (see [Appendix 3](#))
- Laboratory tests

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<sup>2</sup> For subjects who rollover into the OLE, data collected at Part A, Visit 10, will also be used for Part B, Visit B1.

- CBC with differential cell count and platelets
- Metabolic panel (includes ALT, AST, and LDH)
- CK and aldolase
- Blood biomarkers
- Blood for flow cytometry (optional at selected sites)
- Paxgene tube collection
- Autoantibody measurements
- Urine  $\beta$ hCG in WOCBP
- Urine dipstick
- Skin biopsies (optional at selected sites)
- Skin photography (optional at selected sites)
- Lenabasum plasma concentration and metabolite profiling
- Informed Consent for Part B<sup>3</sup>

## 7.2.2. Part B

### 7.2.2.1. Visit B1 (Day B1)

- For subjects who rollover into the OLE, data collected at Part A, Visit 10 (see [Section 7.2.1.9](#)), will also be used for Part B, Visit B1.
- Informed Consent for Part B<sup>3</sup>
- Dispense study product

### 7.2.2.2. Visit B2, Visit B4, and Visit B6 (Weeks 4, 20, and 36)

- Patient-reported efficacy assessments
  - PtGA
  - HAQ-DI
  - SF-36
  - PROMIS-29 Short Form
  - Patient VAS score for pain
  - FACIT-Fatigue Score
  - 5-D Itch Questionnaire
  - Skindex-29+3

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<sup>3</sup> Subjects who rollover into Part B should sign an ICF by Visit 10 in Part A and preferably earlier than Visit 10, if possible.

- EQ-5D questionnaire
- Collect and count capsules of returned study product
- Record concomitant medication(s)
- AE monitoring
- Contraceptive assessment and record of LMP for WOCBP
- Vital signs (including BP, pulse rate, respiratory rate, and temperature) and weight
- Spirometry
- Brief physical examination
- Physician assessments of efficacy
  - MMT-8
  - CDASI score
  - IGA scale of skin activity
  - EMGA (10-cm VAS)
  - MDGA (10-cm VAS and Likert Scale)
- Laboratory tests
  - CBC with differential cell count and platelets
  - Metabolic panel (includes ALT, AST, and LDH)
  - CK and aldolase
  - Urine  $\beta$ hCG in WOCBP
  - Urine dipstick
- Dispense study product

#### **7.2.2.3. Visit B3, Visit B5, and Visit B7 (Weeks 12, 28, and 44)**

- Patient-reported efficacy assessments
  - PtGA
  - HAQ-DI
  - SF-36
  - PROMIS-29 Short Form
  - Patient VAS score for pain
  - FACIT-Fatigue Score
  - 5-D Itch Questionnaire
  - Skindex-29+3

- EQ-5D questionnaire
- Collect and count capsules of returned study product
- Record concomitant medication(s)
- AE monitoring
- Contraceptive assessment and record of LMP for WOCBP
- Vital signs (including BP, pulse rate, respiratory rate, and temperature) and weight
- Brief physical examination
- Physician assessments of efficacy
  - MMT-8
  - CDASI score
  - IGA scale of skin activity
  - EMGA (10-cm VAS)
  - MDGA (10-cm VAS and Likert Scale)
- Dispense study product

#### **Additional Procedures for Visit B5 ONLY**

- 12 lead ECG
- Blood Biomarkers

#### **7.2.2.4. Visit B8 (Week 52) or Early Termination (ET)**

- Patient-reported efficacy assessments
  - PtGA
  - HAQ-DI
  - SF-36
  - PROMIS-29 Short Form
  - Patient VAS score for pain
  - FACIT-Fatigue Score
  - 5-D Itch Questionnaire
  - Skindex-29+3
  - EQ-5D questionnaire
- Collect and count capsules of returned study product
- Record concomitant medication(s)
- AE monitoring

- Contraceptive assessment and record of LMP for WOCBP
- Vital signs (including BP, pulse rate, respiratory rate, and temperature) and weight
- 12 lead ECG
- Spirometry
- Full physical examination
- Physician assessments of efficacy
  - MMT-8
  - CDASI score
  - IGA scale of skin activity
  - EMGA (10-cm VAS)
  - MDGA (10-cm VAS and Likert Scale)
- Laboratory tests
  - CBC with differential cell count and platelets
  - Metabolic panel (includes ALT, AST, and LDH)
  - CK and aldolase
  - Urine  $\beta$ hCG in WOCBP
  - Urine dipstick
  - Blood biomarkers
  - Autoantibody measurements

### **7.2.3. Safety Follow-up (4 $\pm$ 1 Weeks after last visit)**

**Part A:** The Safety Follow-up Visit is to occur 4 $\pm$ 1 weeks after the last visit (Visit 10/ET) and is to be completed by subjects who do not rollover into Part B.

**Part B:** The Safety Follow-up Visit is to occur 4  $\pm$  1 weeks after the last visit (Visit B8 or Visit C8 if OLE is extended). Subjects who discontinue at any stage and for any reason will be encouraged to complete the Safety Follow-up Visit 4  $\pm$  1 weeks after the ET Visit.

#### **Procedures for Safety Follow-up include:**

- Record concomitant medication(s)
- AE monitoring
- Contraceptive assessment and record of LMP for WOCBP
- Vital signs (including BP, pulse rate, respiratory rate, and temperature) and weight
- Brief physical examination
- Laboratory tests

- CBC with differential cell count and platelets
- Metabolic panel (includes ALT, AST and LDH)
- Urine  $\beta$ hCG in WOCBP

#### **7.2.4. 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:

- AE monitoring
- Record concomitant medications
- Vital signs
- Medical history as relevant to the reason for the unscheduled visit
- Physical examination as relevant to the reason for the unscheduled visit
- Laboratory tests as relevant to the reason for the unscheduled visit

#### **7.2.5. End of Study**

End of Study is defined as the date of Last Patient Last Visit where the final study subject is examined or receives an intervention for the purpose of data collection pertaining to primary and secondary outcome measures and adverse events, regardless of whether the study concluded according to the pre-specified protocol or was terminated. [Section 6.2](#) details the events that would lead to study suspension or premature termination by Corbus.

## 8. STUDY ASSESSMENTS AND PROCEDURES

Planned time points for all study procedures are provided in the schedule of assessments (SOA) in [Section 7.1](#).

### 8.1. Efficacy Assessments

#### 8.1.1. Training in Efficacy Assessments

Physicians or a designated health care professional will be trained in the performance of all physician assessments of efficacy. It is expected that the same individual will perform the physician assessments of efficacy at all visits, except in uncommon circumstances. There is a 2-week window for each study visit starting with Visit 2 to facilitate scheduling to allow for consistency in the assessor of efficacy outcomes. In general, it is preferred that a given visit be slightly delayed to allow for the same individual to assess efficacy outcomes throughout the study, rather than have a different assessor. This is particularly important for visits when TIS is being evaluated (see [Table 3](#) and [Table 4](#)).

Subjects will be trained in the questionnaires used to assess patient-reported efficacy outcomes. This training will be done at Screening, so subjects can become familiar with the instruments prior to establishing Baseline values at Visit 1. Starting with Visit 1, it is expected that patient-reported efficacy assessments should be completed independent of input from study staff.

Study staff will be trained in the performance of spirometry using centrally supplied equipment. It is preferred that the same individual perform spirometry at each visit for a given subject, as practicable.

All efficacy assessments for the TIS will be calculated centrally.

#### 8.1.2. Total Improvement Score (TIS)

Efficacy will be assessed using the 2016 ACR/EULAR Myositis Response Criteria Total Improvement Score, comparing the change from Baseline between lenabasum and placebo groups.

Myositis response criteria were developed for both juvenile and adult populations and are based on a 0 – 100 scale. Six core measures are used to calculate the TIS ([Aggarwal et al., 2017](#)). Higher scores indicate better improvement in myositis.

The six measures that comprise the TIS are summarized below:

- **Physician Global Activity (MDGA):** An assessment of overall global disease activity by the physician will be done using a 10-cm VAS. The Physician Assessments should ideally be done by the same investigator. The physician should refer to subject's MDGA score from the previous visit to ensure consistency in rating.
- **Patient Global Activity (PtGA):** An assessment of overall global disease activity by the patient will be done using a 10-cm VAS.
- **Manual Muscle Testing-8 (MMT-8):** For MMT assessment, a MMT that assesses strength in 8 muscle groups (MMT-8) will be used. Strength in 8 muscle groups will be assessed on a 0 – 10 point scale (see [Table 5](#)) and recorded. Strength in the following 7

muscle groups will be assessed bilaterally: deltoid, biceps, wrist extensors, gluteus maximus, gluteus medius, quadriceps, ankle dorsiflexors. In addition, strength in the neck flexors will be assessed.

**Table 5: Description of Rating of Muscle Strength in Individual Muscle Groups for MMT-8 Scoring**

Rating (lower score is weaker, higher score is stronger)	Description
0	No contraction of muscle is felt
1	Moves through partial range of motion in the horizontal plane
2	Moves through completion of range of motion in the horizontal plane
3	Moves through completion of range of motion against resistance in the horizontal plane or holds against pressure or moves through partial range of motion in an antigravity position
4	Gradual release from test position in an antigravity position
5	Holds test position (no added pressure) in an antigravity position
6	Holds test position against slight pressure in an antigravity position
7	Holds test position against slight to moderate pressure in an antigravity position
8	Holds test position against moderate pressure in an antigravity position
9	Holds test position against moderate to strong pressure in an antigravity position
10	Holds test position against strong pressure in an antigravity position

- **Health Assessment Questionnaire-Disability Index (HAQ-DI):** The HAQ-DI provides a patient-reported assessment of functional disability ([Aggarwal et al, 2017](#)) and includes 8 sections: dressing, arising, eating, walking, hygiene, reach, grip, and activities. There are 2 to 3 questions for each section; the recall period is 1 week. Scoring within each section is from 0 (without any difficulty) to 3 (unable to do). Scores are adjusted for use of aides, devices, or help from others. For the HAQ-DI, the score of each individual section is the highest score in that section. A higher total score indicates more functional disability.

- **Extramuscular Global Activity (EMGA):** The EMGA encompasses an overall evaluation for the disease activity in all the extramuscular organ systems and excludes muscle disease activity. EMGA will be assessed by drawing a vertical mark on a 0-10cm VAS scale. Anchored at each end of the 10-cm VAS are the descriptors “absent” and “maximum.”
- **Muscle Enzymes:** The serum activities of the following muscle-associated enzymes will be assessed: the transaminases (ALT, AST), LDH, CK, and aldolase. The AST, ALT and LDH values will be done as part of the metabolic panel and CK and aldolase will be measured as additional muscle enzymes. The most abnormal (by percentage) muscle enzyme at Baseline will be used in calculations of TIS. All muscle enzymes will be done at a central laboratory.

Please see [Appendix 6](#) for algorithm to calculate TIS ([Aggarwal et al, 2017](#)).

Because TIS is a composite score, absolute values and change from Baseline in each core set measure will be presented to support the primary efficacy endpoint.

### **8.1.3. Definition of Improvement (DOI)**

The definition of improvement (DOI) (Oddis et al, 2013) is  $\geq 20\%$  improvement in 3 of any 6 core set measures (same as used to determine the TIS), with no more than 2 core set measures worsening by  $\geq 25\%$ . For DOI to be achieved, the MMT-8 cannot worsen by  $\geq 25\%$ . For improvement in muscle enzymes to contribute to DOI, the muscle enzyme value must be greater than the upper limit of normal at Baseline. For worsening in muscle enzymes to contribute to the DOI, the muscle enzyme value must be greater than the upper limit of normal at the time of worsening.

### **8.1.4. Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI) Score**

CDASI is a validated outcome measure that systematically quantifies cutaneous DM disease activity and damage ([Klein et al, 2007](#); [Yassaei et al, 2010](#)). In the CDASI, DM skin disease activity is evaluated based on the physician's/qualified health personnel 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. Damage is evaluated based on poikiloderma and calcinosis at fifteen anatomic locations as well as Gottron's sign.

### **8.1.5. Investigator Global Assessment (IGA) scale of skin activity**

The IGA is a 5-point scale to evaluate overall skin disease by the investigator. Skin will be assessed as clear, almost clear, mild, moderate, or severe based on the overall description of each category as provided in [Appendix 2](#).

### **8.1.6. Short-Form-36 (SF-36)**

The Short Form 36-question health survey (SF-36) is a widely used tool that assesses the global medical quality of life, functional health, and well-being of general and specific populations. The SF-36 is comprised of 36 questions that cover the following 8 health concepts: physical functioning, bodily pain, role limitations due to physical health problems, role limitations due to

personal or emotional problems, emotional well-being, social functioning, energy/fatigue, and general health perceptions.

### **8.1.7. Corticosteroid Dose**

Corticosteroids are commonly prescribed for the treatment of signs and symptoms of DM. Corticosteroid dose will be recorded as a concomitant medication, with start and stop dates. Change from Baseline in corticosteroid dose will be compared between the lenabasum 20 mg BID and placebo groups and the lenabasum 5 mg BID and placebo groups (see [Section 9.4.3](#)).

### **8.1.8. Forced Vital Capacity**

Spirometry to measure FVC (actual and % predicted values) will be done using equipment supplied by the Sponsor. Study staff will be trained in the proper use of the spirometry equipment. As possible, the same operator should record spirometry for a given subject. FVC values will be measured and calculated in compliance with American Thoracic Society standards for spirometry ([Miller et al, 2005](#)). Hankinson's reference values ([Hankinson et al, 2010](#)) will be used to determine FVC percent prediction with additional correction for Asian subjects.

### **8.1.9. Physician Global Activity (MDGA) – Likert Scale**

A second assessment of overall global disease activity by the physician will be done with a 5-point Likert scale that uses the following scoring: 0 = None; 1 = Mild; 2 = Moderate; 3 = Severe; 4 = Extremely severe.

### **8.1.10. Patient Improvement Questionnaire for Physicians**

A brief questionnaire (see [Appendix 3](#)) will be administered that will determine overall improvement with treatment in the investigator's judgment.

### **8.1.11. Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue score**

The FACIT-F score is a 13-item patient-reported questionnaire that assesses tiredness, weakness, and difficulty conducting everyday activities due to fatigue in the last 7 days ([Butt et al, 2013](#)). Items are scored on a 5-point scale (0 = not at all, 4 = very much). All items except item 7 and 8 are reverse-scored before item scores are summed to obtain a total score (range 0-52). A higher score indicates less fatigue. The FACIT fatigue tool has been previously validated in a study by [Chandran et al, 2007](#).

### **8.1.12. 5-Dimension (5-D) Itch Score**

The 5-D Itch scale is a validated patient-reported assessment of itch in skin diseases ([Elman et al, 2010](#)). It is a brief, multidimensional questionnaire with five dimensions of itch - degree, duration, direction, disability and distribution. The period of recall is 2 weeks. Single-item domain scores range from 1-5. The scores of each domain are summed to obtain a total 5-D Itch score. Total 5-D Itch scores can range between 5 (no itch) and 25 (most severe itch). A higher score indicates worse itch.

### **8.1.13. National Institutes of Health Patient-Reported Outcomes Measurement Information System (PROMIS)-29 Short Form**

The PROMIS-29 Short Form (Version 2.0) will be used to assess patient-reported state of health. The National Institutes of Health established PROMIS ([www.nihpromis.org](http://www.nihpromis.org)) to create a standardized and uniformly scored set of patient-reported-outcomes instruments. The PROMIS network developed item (question) banks and Short Forms in more than 20 health domains as well as a set of global health items and 29-, 43-, and 57-item profile measures. To create a brief, practical-yet-inclusive short profile, a consensus-building process was used to identify 7 of these 20 domains to produce the PROMIS-29. The seven domains specifically relate to physical, mental and social health and cover the most relevant areas of self-reported health for the greatest majority of people with chronic illness: pain interference, fatigue, depression, anxiety, sleep disturbance, physical function and social role. The PROMIS-29 includes four items each from these seven core PROMIS domains as well as one 11-point rating scale for pain intensity. Norm-based scores have been calculated for each domain, such that a score of 50 represents the mean of the general population (standard deviation = 10). High scores represent more of the domain being measured. Thus, on symptom-oriented domains of PROMIS-29 (anxiety, depression, fatigue, pain interference, and sleep disturbance), higher scores represent worse symptomatology. On the function-oriented domains (physical functioning and social role) higher scores represent better functioning.

### **8.1.14. Patient Visual Analog Scale (VAS) scores of Pain**

All subjects will record their overall pain by drawing a vertical mark on a 0-10cm VAS scale. The 10-cm VAS is anchored at each end with descriptors of “no pain” (0) and “pain as bad as it could be” (10) anchored at each end.

### **8.1.15. Skindex-29+3**

The Skindex-29 ([Chren 1997](#)) is a validated, 29-item skin-specific quality of life questionnaire used to calculate three subscales: symptoms, emotions and functioning. The Skindex-29+3 includes the addition of a fourth subscale, consisting of three questions, to assess photosensitivity and alopecia ([Klein 2011](#)). Each question and subscale range from 0-100 points, with higher scores indicating worse quality of life.

### **8.1.16. European Quality of Life 5-domain (EQ-5D) questionnaire score**

The EQ-5D is a standardized measure of health status intended to provide a simple and generic measure of health and is comprised of 5 dimensions - anxiety/depression, mobility, self-care, usual activities, and pain/discomfort.

### **8.1.17. Patient Improvement Questionnaire for Subjects**

A brief questionnaire (see [Appendix 4](#)) will be administered to determine overall improvement with treatment from study start (Yes or No), as per the subject’s perception. Subjects who answer “Yes” will be asked to rate whether the degree of improvement was slight, moderate, or marked. The MID for TIS, HAQ-DI score, and CDASI activity score in DM will be calculated separately as the mean score of each of these outcomes in all subjects who answered that they had slight improvement at that given timepoint (16 Weeks, 26 Weeks, and 52 Weeks).

### **8.1.18. Blood Biomarkers of Inflammation**

Blood to assess biomarkers of inflammation will be collected at Baseline and post-treatment in all subjects. The messenger ribonucleic acid (mRNA) levels of key cytokines and chemokines in DM will be analyzed. The exact biomarkers to be analyzed will be decided after completion of the study, but may include Type 1 IFN, IL-1 $\beta$ , IFN $\beta$ , IL-6, IFN $\gamma$ , and TNF $\alpha$ , and results may be reported separately from the main CSR.

### **8.1.19. Paxgene**

Blood will be collected for transcriptomic analysis, at Baseline and post-treatment in all subjects. Results of such analysis may be reported separately from the main CSR.

### **8.1.20. Blood for Flow Cytometry**

Blood will be collected for flow cytometry at selected sites. It is expected that all subjects at these subsites will provide a blood sample for flow cytometry at the visits specified in the SOA.

### **8.1.21. Autoantibodies**

Blood will be collected to assess autoantibodies commonly seen in DM patients, at Baseline and post-treatment in all subjects. Results of such analysis may be reported separately from the main CSR.

### **8.1.22. Skin Biopsies**

Skin biopsies (at Baseline, Visit 4, and at and at the end of treatment [Visit 10 or Early Termination]) will be collected in consenting subjects at selected sites. Five 4mm skin biopsies will be collected (other than site 1001) 2 each at Visit 1 and Visit 4 respectively for histology and transcriptome and 1 at Visit 10 for transcriptome. The biopsies will preferentially be taken from an area of involved skin that is active or worsening, rather than improving, in the opinion of the site investigator. No biopsies will be taken from the face, neck, hands or feet. Biopsies should be taken from the same location at each biopsy visit, provided that this area is active or worsening at that timepoint. If a subject has no active skin involvement in an area that can be biopsied at Visit 1, then no biopsies should be taken at Visit 1 or any subsequent visit (because there will be no Baseline biopsy for comparison). If biopsies are obtained at Visit 1, then subsequent biopsies should be obtained within 1-2 cm of the first biopsy sites, without regard to disease activity at that site at that time.

Histology will be evaluated by a blinded pathologist post-treatment and compared to Baseline. Flow cytometry may be conducted to analyze cell subsets in the skin and transcriptome analysis may be performed to assess RNA levels. Skin biopsy results may be reported separately from the main CSR.

### **8.1.23. Skin Photographs**

Skin photographs will be collected in consenting subjects at selected study sites. An instruction manual, detailing standardized procedures for taking skin photographs will be provided. Photographs will be taken of pre-specified body areas and any area with the most severe skin activity if that area is not included in the pre-specified body areas. Photographs of these areas

will be taken at Baseline (Visit 1) and at end of treatment (Visit 10 or ET), regardless of activity. The photos should have all identifiers removed to protect the identity and privacy of subjects and subjects should be referred to by SID only. Skin photography results may be reported separately from the main CSR.

#### **8.1.24. Pharmacokinetic Assessments**

Lenabasum and metabolite plasma concentration will be measured at Visits 1, 2, 4, 6, and 10. At Visit 1, blood will be drawn pre-dose and then  $3 \pm 0.5$  hours post-dose at the approximate time of the anticipated  $t_{max}$ . At Visits 2, 4, 6, and 10, blood will be drawn pre-dose to assess trough concentration levels. To obtain trough concentrations of lenabasum on Visit 2, 4, 6, and 10, the blood sample for lenabasum plasma concentration should be obtained between 8 and 16 hours after the last dose of study product.

### **8.2. Safety Assessments**

#### **8.2.1. Medical History and Use of Contraception**

Medical history will include subject demographics, history of DM and current treatment for DM. The medical history also will include concurrent illnesses, other current medications, past relevant medical history, smoking history (classified as one of the following: current smoker, ever smoker (defined as  $\geq 1$  cigarette per day for  $> 1$  year), or never smoker), child-bearing potential, last menstrual period (LMP) for women, and review of systems. Date of LMP and method of contraception will be assessed at screening and all visits in WOCBP.

Acceptable contraceptive methods (as stated in [Appendix 1](#)), may not be available or approved in all countries; thus, the Sponsor does not restrict respective countries from excluding unavailable contraceptive methods in the ICF.

#### **8.2.2. Concomitant Medications**

A list of current prescription and over-the-counter medications and supplements will be obtained. Concomitant medications and supplements will be recorded on the concomitant medication eCRF at screening and all visits. The medication or supplement, dose, frequency, route, start date, stop date and indication will be captured.

#### **8.2.3. Physical Examinations**

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

A brief physical examination will include at a minimum assessments of skin, lung, heart, abdomen, and any other area as indicated by changes in medical history.

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

#### **8.2.4. Vital Signs, Height and Weight**

Vital signs measurements include blood pressure, pulse rate, respiratory rate, and temperature and are assessed at Screening and all study visits. Systolic and diastolic BP will be measured with the subject supine for at least 5 minutes. The same arm should be used for the measurement throughout the study as much as possible. Pulse and respiration will also be measured with the subject supine for at least 5 minutes. Body temperature will be measured on the skin or in the mouth.

Height will be measured in standing position with footwear removed and weight will be measured with coats, jackets, and footwear removed.

#### **8.2.5. Electrocardiograms**

Twelve-lead ECGs are to be recorded with the subject in a rested supine position for  $\geq 10$  minutes before the test, using ECG machines supplied by the Sponsor. The ECGs will be read centrally. The medical significance of any new ECG abnormality will be assessed by the investigator.

#### **8.2.6. Clinical Safety Laboratory Assessments**

Blood and urine laboratory safety tests will be performed at each visit with the frequency of measures varying between laboratory parameter (sampling visits detailed below). The results of all tests will be reviewed by the investigator or designee, who will make judgments on the medical significance of any new or worsening abnormal value. New medically significant abnormal laboratory results that are related to safety of study product should be repeated as soon as possible to confirm the abnormality. The Schedules of Assessments are provided in [Table 3 \(Part A\)](#) and [Table 4 \(Part B\)](#).

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

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

- Complete blood count with differential
- Human immunodeficiency virus
  - At Screening, a HIV 1/2 antibody test will be performed. If the results are not negative, a HIV 1/2 antibody confirmatory test will be performed.
- Follicle stimulating hormone and leutinizing hormone
- Hepatitis B and C
  - At Screening, a test for Hepatitis B surface antigen will be performed. If the results are positive, a Hepatitis B core antibody confirmatory test will be performed.

- At Screening, a test for Hepatitis C antibody will be performed. If the results are reactive, a Hepatitis C RNA confirmatory test will be performed.
- Serum  $\beta$  human chorionic gonadotropin, for WOCBP
- 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, ALT, AST, LDH, CK, Aldolase.

If retesting is required as part of Screening, any repeat laboratory screening tests will be done at the central laboratory. If returning to the clinic for repeat screening laboratory tests would cause major inconvenience for the subject, for example because of long distance travel, repeat laboratory tests can be done at a local laboratory only if results are made available to the investigator for review before dosing.

The following urine tests will be performed locally using supplies provided by the Central laboratory:

- Urine  $\beta$  human chorionic gonadotropin, for WOCBP
- Urine dipstick for blood, protein, and glucose.

Since this clinical trial is conducted globally, the same lab test kits are used in all countries in order to test under the same conditions at each site. For this reason, several kits that are not yet approved by regulatory/governmental agencies (such as MHLW in Japan) will be used (e.g., punch for skin biopsy and blood collection tube). However, these kits have almost the same structure and use as kits currently used in Japan and other countries.

## **8.2.7. Adverse Events and Serious Adverse Events**

### **8.2.7.1. Definition of Adverse Events (AE)**

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related (Code of Federal Regulations Title 21, Volume 5, Section 312). Another definition of an AE is any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment (Article 2(m) of Directive 2001/20/EC).

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. Intercurrent illnesses or injuries will be regarded as AEs. Any event of abuse, misuse or addiction should be reported as an AE. Drug abuse is defined as the intentional, non-therapeutic use of a drug product or substance, even once, to achieve a desired psychological or physiological effect. Drug misuse is defined as the use of a substance for a purpose not consistent with legal or medical guidelines (World Health Organization, 2006). Addiction (according to American Psychiatric Association) is a complex condition, a brain disease that is manifested by compulsive substance use despite harmful consequence (World Health Organization, 2006).

When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately. This definition also includes accidental injuries, reasons for any change in medication (drug and/or dose) other than planned titration, reasons for admission to a hospital or reasons for surgical procedures.

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

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

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

The investigator will assess all abnormal laboratory results for their clinical significance. If any abnormal laboratory result is considered clinically significant, the investigator must provide details about the action taken with respect to the study product and about the subject's outcome.

AEs will be captured from time of signing of IC to the end of the subject's participation in the study.

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

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

#### **8.2.7.2. Definition of Serious Adverse Events (SAE)**

Serious AEs are a subset of AEs. A serious adverse event (SAE) is defined as any untoward medical occurrence that has any of the following outcomes:

- Results in death
- Is life-threatening

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

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

Medical judgment should be exercised in deciding whether expedited reporting is appropriate in situations where none of the outcomes listed above occurred. Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above should also usually be considered serious. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse. A new diagnosis of cancer during treatment should be considered as medically important.

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

#### **8.2.7.3. Adverse Events That Cause Discontinuation**

Adverse events leading to discontinuation of treatment will be recorded and narratives will be generated for AEs that caused discontinuation.

#### **8.2.7.4. Disease Worsening**

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

#### **8.2.7.5. Procedures for Assessing and Recording Adverse Events and Serious Adverse Events**

Throughout the duration of the study, the investigator or designees will closely monitor each subject. All AEs which occur during the study will be recorded, whether observed by the investigator or by the subject and whether thought to be related or unrelated to study product. The description of the AEs as recorded on the eCRF will include a description of event, start date, stop date, intensity, if it was serious, relationship to study product, what actions were taken with respect to the study product, if treatment was required and the subject's outcome.

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

#### **8.2.7.6. Time Period and Frequency for Event Assessment and Follow-Up**

Safety events will be assessed from the time of signing of IC through the last visit which can include a withdrawal visit. At each study visit, the investigator will inquire about the occurrence of AEs since the last visit. All AEs considered related to study product must be followed until resolution or until they become stable.

#### **8.2.7.7. Classification of an Adverse Event**

##### **Severity of Event**

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

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

##### **Relationship to Study Intervention**

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

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

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

#### **8.2.7.8. Reporting Procedures**

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

### **Controlled Substance Reporting**

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

### **Unanticipated Problem Reporting to Competent Authorities and Ethics Committees**

Unanticipated problems are events that may occur during a clinical trial which do not fall within the definition of suspected unexpected serious adverse reaction (SUSAR) and thus are not subject to the reporting requirements for SUSARs, even though they may be relevant in terms of subject safety. Examples include:

- An SAE which could be associated with the trial procedures and which could modify the conduct of the trial;
- A major safety finding from a newly completed animal study (such as carcinogenicity).

In relevant countries, incidents or events that meet the criteria for unanticipated problems, may need to be reported to the EC or competent authority. This information is to be reported to the Sponsor using the AE eCRF within 24 hours of learning of the event.

### **SAE Reporting**

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

Any AE that meets the specified SAE criteria ([Section 8.2.7.2](#)) will be recorded on an SAE eCRF, by the investigator or qualified designee. The investigator must complete the SAE eCRF immediately, which will prompt an electronic notification to the Sponsor or designated representative. Follow-up information on the SAE will be provided in a timely manner to the Medical Monitor and recorded on eCRF form(s). If eCRF is unavailable, paper forms must be completed and submitted to the Sponsor or designated representative expediently to maintain the reporting timelines.

The mandatory reporting of safety events to regulatory authorities will be followed as required by applicable regulatory authority, and as per the applicable reporting timelines. Reporting to Corbus, regulatory agencies, ECs, and investigators will be in accordance with all applicable local laws and regulations.

### **Reporting Events to Subjects**

Any change in benefit-risk assessment relating to lenabasum administration will be reported to study subjects in compliance with applicable local laws and regulations.

### **Reporting of Pregnancy**

Pregnancy itself is not an AE. The effect of lenabasum in pregnancy is unknown. Women subjects of childbearing potential will be instructed to inform the investigator if they become pregnant during the study or within 4 weeks after taking the final dose of study product. If the pregnancy occurs during the treatment period, the investigator should immediately discontinue the study product and instruct the subject to return any unused portion of study product to the study staff. Pregnancies occurring while the subject is on lenabasum or within 4 weeks after the subject's last dose of lenabasum should be reported by the site to the Sponsor within 24 hours of

the site being made aware. The investigator will counsel the subject about the risks of the pregnancy and the possible effects on the fetus.

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

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

If the outcome of the pregnancy meets the criteria for immediate classification as an 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 to the EC 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.

## 9. STATISTICAL CONSIDERATIONS

### 9.1. Statistical Hypotheses

#### 9.1.1. Primary Efficacy Endpoint

Week 28 TIS:

$H_0$ : The difference in the TIS between the active group and placebo (lenabasum group – placebo) at Week 28 = 0.

$H_1$ : The difference in the TIS between the active group and placebo (lenabasum group – placebo) at Week 28  $\neq 0$ , with superiority of active to placebo claimed if the difference between the active group and the placebo group  $> 0$  (i.e., indicates greater improvement in the active group).

### 9.2. Sample Size Determination

This study is expected to Screen 200 subjects with 150 subjects anticipated to be dosed at a ratio of 2:1:2; 60 subjects in the lenabasum 20 mg BID cohort, 30 subjects in the 5 mg BID cohort, and 60 subjects in the placebo cohort. Given 150 dosed subjects, it is expected that 120 subjects will complete at least Week 28 assuming a ~20% drop out rate. This is based on a TIS treatment group difference of 15.0, standard deviation (SD) 20.00, Alpha 0.05 two-sided, Power 95%.

The final number of subjects to be dosed will be decided based on a blinded interim analysis to assess variability in the TIS score as described in the SAP and [Section 9.4.7](#).

### 9.3. Populations for Analyses

There are 4 analysis populations defined in this study:

**The modified intent to treat (mITT) 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 before unblinding the study). Analysis on the PP population will be used as secondary efficacy analyses, analyzing subjects under the treatment actually received.

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

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

## **9.4. Statistical Analyses**

### **9.4.1. General Approach**

All data will be provided in data listings sorted by treatment group, subject number, and visit. Summary data will be presented in tabular format by treatment group. Categorical data will be summarized by the number and percentage of subjects in each category. Continuous data will be summarized by descriptive statistics including the sample size (n), mean, standard deviation, median, minimum and maximum. All percentages will be rounded to one decimal place. Differences between treatment groups will be calculated as lenabasum placebo and change from Baseline will be calculated as visit Baseline. The Baseline measure will be defined as the last non-missing measure before initiation of study product.

Data will be presented by randomized treatment group for efficacy data and by actual treatment group for safety data.

P-values and 2-sided 95% confidence intervals will be presented for all efficacy endpoints.

#### **9.4.1.1. Handling of Missing Data**

The analysis of the primary endpoint will be performed on the mITT population, using a mixed-effect model for repeated measures (MMRM), on observed data, using last observation carried forward (LOCF) for  $\leq 2$  missing core set items. If more than 2 core items are missing, the TIS score will not be calculated for that visit. Sensitivity analyses for the primary endpoint will include imputing missing data using last observation carried forward, the completer population, and the per-protocol population.

#### **9.4.1.2. Adjustments for Multiplicity**

The overall type I error rate will be controlled for primary and secondary outcomes with a hierarchical ordering of assessments. The order of the tests for treatment effect will be as follows:

- Primary efficacy outcome: Mean TIS, lenabasum 20 mg BID versus placebo, at Week 28.
- Secondary efficacy outcomes (Change from Baseline at Week 28):

The following endpoints will be compared in lenabasum 20 mg BID compared to placebo cohorts and lenabasum 5 mg BID compared to placebo cohorts at Week 28. All outcomes involving continuous variables will be assessed as absolute values and, if relevant, change from Baseline. All categorical variables will be assessed as number and proportion of subjects in each category. The list will be done in order below for comparisons between lenabasum 20 mg BID and placebo cohorts:

- Subjects who achieve DOI
- Subjects who improve by at least one category on the IGA scale of skin activity
- Subjects who achieve TIS  $\geq 40$  (at least moderate improvement)
- TIS in subjects receiving any immunosuppressant medication for  $> 1$  year at Baseline
- TIS at Week 52
- CDASI activity score

The list will continue in order below for comparisons between lenabasum 5 mg BID and placebo cohorts:

- TIS
- Subjects who achieve DOI Subjects who improve by at least one category on the IGA scale of skin activity
- Subjects who achieve TIS  $\geq 40$  (at least moderate improvement)
- TIS in subjects receiving any immunosuppressant medication for  $> 1$  year at Baseline
- TIS at Week 52
- CDASI activity score

Note that, in Part A, statistical significance for each endpoint must first be achieved in order to continue in the assessment of the next endpoint, following the testing sequence above.

#### **9.4.2. Analysis of the Primary Efficacy Endpoint(s)**

The primary efficacy variable is the TIS. The primary analysis is to compare the TIS at Week 28 between the lenabasum 20 mg BID treated group and placebo using a mixed model for repeated measures (MMRM). The model will have TIS score as a dependent variable, treatment, visit, treatment\*visit interaction, baseline MMT-8 score, baseline prednisone use, and region as fixed factors, and subject as a repeated random effect. The model may incorporate other baseline factors as covariates, which will be further defined in the statistical analysis plan. Two-sided p-values and 95% confidence intervals associated with the least-square (LS) mean difference between the lenabasum group and placebo will be presented for each visit. If the distribution of the TIS score does not meet the assumptions of normality, a nonparametric analysis may be performed (e.g., MMRM analysis on the ranked data).

Two-sided p-values and 95% confidence intervals associated with the least-square (LS) mean difference between the lenabasum group and placebo will be presented for each visit.

Because TIS is a composite score, absolute values and change from Baseline in each core set measure will be presented to support the primary efficacy endpoint.

#### **9.4.3. Analysis of the Secondary Efficacy Endpoint(s)**

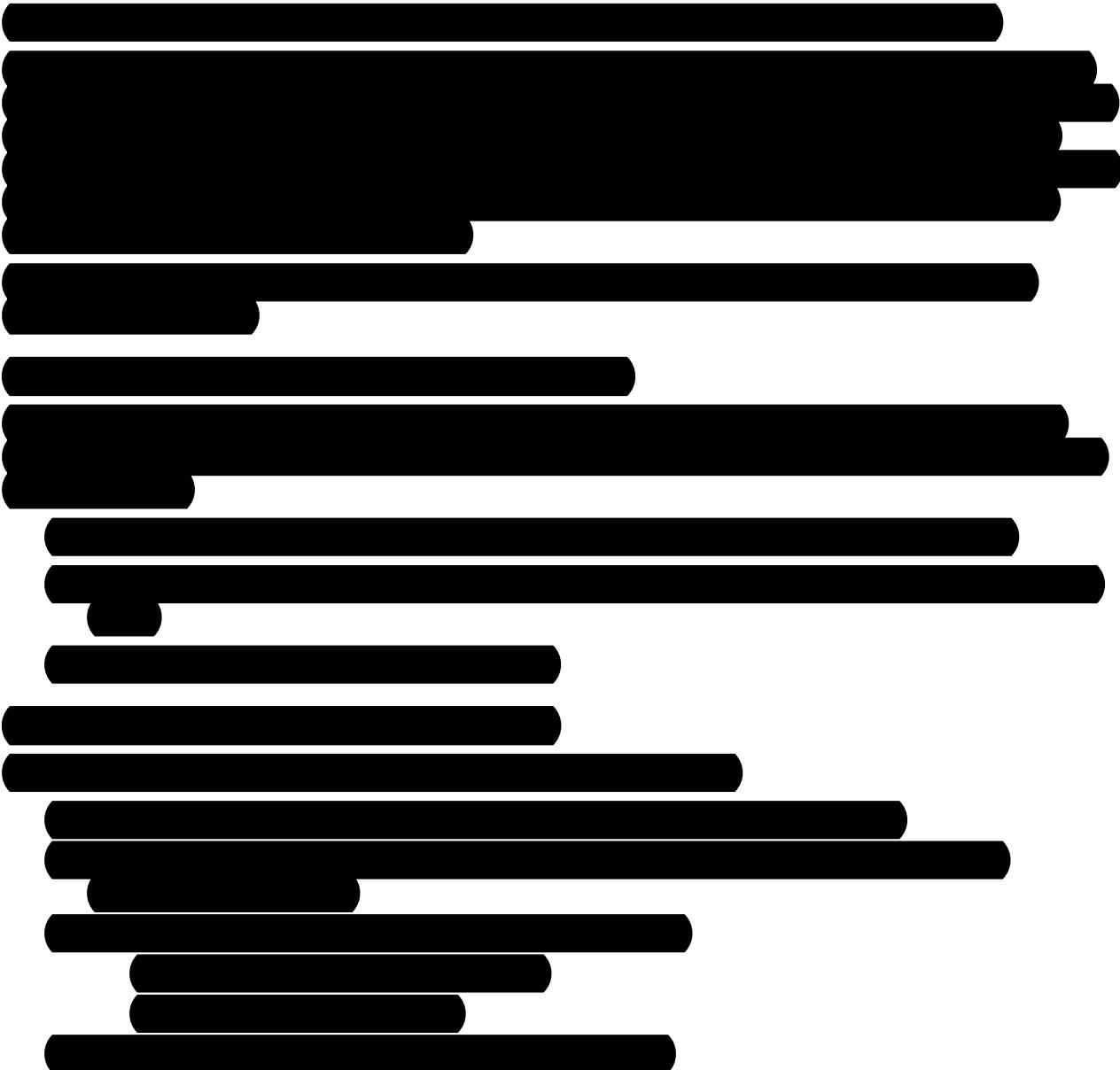
Continuous secondary and tertiary outcome variables will be analyzed similarly to the primary MMRM model, using change from Baseline as the dependent variable, with the Baseline of each endpoint also included in the model. Other outcomes based on the proportion of subjects achieving defined criteria will be analyzed using a Fisher's exact or Cochran-Mantel-Haenzel test.

Secondary efficacy endpoints in this study include:

1. Subjects who achieve DOI
2. Subjects who improve by at least one category on the IGA scale of skin activity
3. Subjects who achieve TIS  $\geq 40$  (at least moderate improvement)
4. TIS in subjects receiving any immunosuppressant medication for  $> 1$  year at Baseline
5. TIS at Visit 10 (Week 52)
6. CDASI activity score

7. TIS (lenabasum 5 mg compared to placebo cohort only)

**9.4.4. Analyses of the Tertiary Efficacy Endpoints**



**9.4.7. Safety Analyses**

No formal statistical testing will be performed to compare the safety in lenabasum versus placebo cohorts.

The number and percentage of subjects with AEs will be summarized for each treatment by system organ class and preferred term. Similar summaries will be presented for AEs related to study product, AEs leading to permanent discontinuation of study product, SAEs, and AEs resulting in death. Any AE with a relationship category of possible, probable, or definite is considered related to study product. The AEs will be coded using the Medical Dictionary for

Regulatory Activities (MedDRA) using the latest version available. All reported AEs will be provided in separate data listings.

Descriptive statistics will be used to summarize clinical laboratory parameters, vital signs and their corresponding mean change from Baseline for each treatment by scheduled timepoint. For all lab parameters shift tables will also be generated.

The number and percentages of subjects with normal, abnormal and clinically significant, and abnormal and not clinically significant ECG findings during treatment will be summarized for each treatment by scheduled timepoint. QTcF change from Baseline for each treatment would be calculated. Tables with number of subjects with QTcF > 500 msec, 30 msec change from Baseline, 60 msec change from Baseline will be presented.

#### **9.4.8. Baseline Descriptive Statistics**

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

Medical history will be summarized by treatment group using discrete summaries by coded terms (MedDRA - system organ class and preferred term). Other Baseline characteristics will be summarized by treatment group using discrete or continuous summary statistics as appropriate.

#### **9.4.9. Planned Interim Analyses**

The number of subjects to be dosed may be adjusted further during the study after a blinded interim analysis of the emerging data. The timing and methods for the interim analysis will be outlined in the SAP. The intent is to perform a blinded interim examination of the variance of the TIS, to potentially increase the sample size to maintain power (with no statistical adjustment to the alpha level required). The projected maximum number of subjects to be randomized is 230 subjects (for 183 completers), which corresponds to standard deviation of 30, and 85% power.

#### **9.4.10. Tabulation of Individual Subject Data**

Individual subject data (demographic, safety, and efficacy) will be provided in listings for Screening, active treatment period, and Follow-up.

#### **9.4.11. Part B**

The same efficacy and safety parameters described as primary and secondary objective for Part A will be evaluated in Part B as described in the SAP.

## **10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS**

### **10.1. Regulatory, Ethical, and Study Oversight Considerations**

#### **10.1.1. Ethical Conduct of the Study**

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

#### **10.1.2. Ethics Committee/ Institutional Review Board**

This protocol will be submitted to the reviewing central or local Institutional Review Board (IRB) or Independent Ethics Committee (IEC), hereafter referred to as the Ethics Committee (EC), for review and approval before the study is initiated at any site. The EC must be constituted according to the local laws/customs of each participating country. Any protocol amendments will be submitted to the reviewing central or local EC for review and approval. The EC will review the informed consent form (ICF), its updates if any, and any written materials given to the subjects. Any other documents that the EC may need to fulfill its responsibilities, including subject recruitment procedures and any compensation available to subjects, will be submitted to the EC by the local monitor/investigator. The EC's written unconditional approval of the study protocol and the ICF will be in the possession of the investigator and Corbus before the study is initiated. The EC's unconditional approval statement will be transmitted by the investigator or designee to Corbus before shipment of study product supplies to the site. This approval must refer to the study by exact protocol title and number and should identify the documents by date and version reviewed, the date of review, and any updates after initial approval.

Corbus will write any amendment to the protocol that is needed. Protocol and/or IC modifications or changes may not be initiated without prior written EC approval except when necessary to eliminate immediate hazards to the subjects or when the change(s) involves only logistical or administrative aspects of the study. Such modifications will be submitted to the EC, and written verification that the modification was submitted should be obtained.

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

- Revisions of documents originally submitted for review.
- SAEs including SUSARs occurring during the study. Corbus will also be notified.

- New information that may adversely affect the safety of the subjects or the conduct of the study. Corbus will also be notified.
- Pregnancies occurring in female subjects or female partners of male subjects. Corbus will also be notified.
- Annual update and/or request for re-approval.
- Suspension or premature termination of the study. Review and approval by the EC is required for resumption of the study at a site, in the event the study is interrupted.
- Study completion.

The investigator must keep copies of all AE information, including correspondence with Corbus and the approving EC, on file. The investigator will retain all EC records related to this investigation for at least 3 years, or as long as required by local regulations, after completion of the research.

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

### **10.1.3. Informed Consent Process**

#### **10.1.3.1. Consent and Other Informational Documents Provided to Subjects**

ICFs describing in detail the study intervention, study procedures, and risks are given to the subject and written documentation of IC is required before starting intervention/administering study intervention.

#### **10.1.3.2. Consent Procedures and Documentation**

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

The principles of IC in the current edition of the Declaration of Helsinki must be implemented before any protocol-specified procedures or interventions are carried out and will also comply with local regulations. IC will be obtained by the investigator or designee in accordance with 21 CFR 50.25 or Directive 2001/20EC, depending upon site location in the US or EU, respectively. Information will be given in both oral and written form, and subjects must be given ample opportunity to inquire about details of the study.

ICFs must be written at a level that can be understood by the prospective subject. The explanation of the investigation will be in language that is understandable to the individual. If non-English speakers are enrolled, a translated consent document will be available, and an appropriate person will conduct the consent process. Subjects who so choose will be given the

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

If a subject is  $\geq 18$  and  $< 20$  years of age and additional parental / guardian consent is required by local / national regulators to participate in this clinical trial, then the unique requirements for that country will be followed for those subjects.

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

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

The ICF will explain the option of allowing leftover blood samples to be used in future research related to lenabasum, inflammation or DM. This option requires individual consent. If the subject declines to participate in this option, that choice will have no effect on his/her eligibility and will not interfere with the benefits to which he/she is otherwise entitled.

The extent of the confidentiality of subject records will be defined. Subjects will be informed that the study will comply with applicable data protection legislation. Health Insurance Portability and Accountability Act authorization (US only) will be obtained before conducting any protocol-related procedures, including screening evaluations. Subjects must be informed that, by signing the written ICF, they are granting direct access to their original medical records for verification of clinical trial procedures and/or data to the site monitor(s), medical monitor, auditor(s), EC representatives, and other regulatory authorities. Subjects' medical information obtained in this study is confidential and may be disclosed to third parties only as permitted by the ICF or separate authorization for use and disclosure of personal information signed by the subject, unless permitted or required by law.

#### **10.1.4. Confidentiality and Privacy**

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

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

- What protected health information will be collected from subjects in this study.
- Who will have access to that information and why.
- Who will use or disclose that information.

- The rights of a research subject to revoke their authorization for use of their protected health information.

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

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

#### **10.1.5. Future Use of Stored Specimens and Data**

Potential future use of stored specimens and other identifiable data include:

- Storage for and use of left-over blood and skin samples in future research related to lenabasum or DM (optional)

Left-over blood samples will be stored and may be used in future testing related to lenabasum or DM, as indicated by the results of this study and done by Corbus and its collaborators, including site investigators.

The subject has the option to refuse any or all of these options without jeopardy to their participation in the clinical trial or clinical care. The blood and skin samples will be maintained for up to five years from the completion of LPLV in Part A. To protect confidentiality for any future studies with the stored specimens, specimens will be barcoded and de-identified.

Pharmacogenomic (DNA) analysis will not be performed on any samples.

### 10.1.6. Key Roles and Study Governance

Role	Contact Information
Principal Investigator	[REDACTED]
Principal Investigator	[REDACTED]
Sponsor's Medical Officer	[REDACTED]
Sponsor's Project Manager	[REDACTED]

### 10.1.7. Safety Oversight

#### 10.1.7.1. Medical Monitoring

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

#### **10.1.7.2. Data Monitoring Committee (DMC)**

Oversight of subject safety in this trial will be provided by an independent unblinded DMC, which will advise Corbus and the investigators. The voting members of the DMC will include at least 3 external experts in DM who will be supported by an un-blinded biostatistician, who will be a non-voting member. A non-voting member may be added to provide clarifications and historical perspective, at least during Open Sessions of the DMC meeting. Additional experts in areas related to DM, safety, or regulatory requirements or practices can be added as needed.

The independent DMC will review the accumulated safety and operational data about every 6 months through the last subject/last visit or more frequently, if necessary. The DMC will review interim/cumulative data for evidence of study-related AEs and factors external to the study such as scientific or therapeutic developments that may impact subject safety. The DMC will also review progress of the study and efficacy outcomes. The DMC may make recommendations to Corbus about any of the items it reviews. In addition, if any of the following events occur during the enrollment, then the DMC will review all cumulative safety information and the event(s) of interest:

- Death in any subject related to lenabasum.
- Two life-threatening clinical events that are probably or definitely-related to lenabasum.
- Determination of unexpected, significant, or unacceptable risk to subjects in the opinion of the Corbus Chief Medical Officer.

The DMC should conclude each review with written recommendations to Corbus 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 whether study entry/randomization and dosing should be discontinued, whether the protocol should be modified, whether the study should be discontinued permanently, and reasons for these recommendations.

#### **10.1.7.3. Medical Care and Day-to-Day Safety of Subjects at the Site**

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

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

#### **10.1.8. Quality Assurance and Quality Control**

Quality control procedures will be implemented including the eCRF specifications, the data validation plan, data management plan, and other plans, procedures and Standard Operating

Procedures. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution

Following written Standard Operating Procedures, the monitors and other study team personnel will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonization Good Clinical Practice (ICH GCP), and applicable regulatory requirements [e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)].

The investigational site will provide access to all trial related sites, source data/documents, and reports for monitoring and auditing by the Sponsor and inspection by local and regulatory authorities.

#### **10.1.8.1. Clinical Monitoring**

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

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

Data quality will be monitored by Corbus or a designated CRO on a regular basis throughout the study period. The electronic record will be monitored/audited for the purposes of the study data management by site monitors and other study team personnel. A site monitor representing Corbus will visit study facilities at periodic intervals, in addition to maintaining necessary contact through telephone, e-mail, and letter. The monitor will assess: subject enrollment and informed consent procedures; investigational product storage, dispensing, administration and accountability; compliance with protocol procedures; completeness and accuracy of data entered onto the EDC; and the occurrence of AEs. All aspects of the study will be carefully monitored for compliance with the protocol, the study monitoring plan, applicable government regulations, GCP, and the site's standard operating procedures.

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

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

#### **10.1.8.2. Audit and Inspection of Sites**

Participation by the investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable institutional compliance and quality assurance offices. During the conduct of the study, Corbus may conduct audits of any data and facility participating in the study. The investigators and institutions involved in the study will permit

such study-related audits and provide direct access to all paper study records not contained within the electronic medical record or eCRFs and to the facilities. The investigator must maintain a comprehensive and centralized filing system of all study-related documentation that is not part of the electronic medical record or eCRFs and that is suitable for inspection by Corbus or its designated site monitors, Quality Assurance monitors, EC representatives, and representatives of government regulatory bodies. The investigators agree to participate in audits conducted at a convenient time in a reasonable manner.

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

### **10.1.9. Data Handling and Record Keeping**

#### **10.1.9.1. Data Handling, De-Identification and Source Records**

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

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

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

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

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

#### **10.1.9.2. Original Records**

Clinical trial data will be recorded on source documentation and entered by the investigator or a qualified designee into a validated 21 CFR Part 11 compliant internet-based EDC system. Changes to the clinical trial data can only be performed by the investigator or qualified designee through the change management methodology that is subject to a full audit trail.

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

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

#### **10.1.9.3. Confidentiality of Subject Data**

To maintain subject confidentiality, subjects will not be identified by name, subjects will be assigned a site number and subject number for any documentation submitted to Corbus. Additional subject confidentiality issues, if applicable, are covered in accordance with each participating country, and institution's laws, regulations and policies.

#### **10.1.9.4. Data Collection and Management Responsibilities**

Data collection and accurate documentation are the responsibility of the investigator and site staff under the supervision of the investigator. All source documents and laboratory reports must be reviewed by the study team and data entry staff, who will ensure that they are accurate and complete. A site monitor for Corbus will ensure the data are collected and maintained correctly and in compliance with [Section 10.1.8.1](#).

Electronic data capture on eCRFs will be used, using internet access with password protection and data quality checks. It is expected that the eCRFs should be submitted coincident with the subject visit or within 5 business days.

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

- The clinical database will be held and managed by an EDC vendor. The EDC will be used for online edit checks, batch edit checks and query management
- A Data Validation Plan will be created which will include the specifications for:
  - Online checks performed by the EDC system during data entry
  - Batch edit checks

- Manual checks performed by the site monitor, Medical Monitor data management, and/or other study team personnel
- Other data cleaning activities such as data reconciliation and coding listing reviews will be performed.

Queries are handled within the EDC application where the monitors and data managers can generate a query. Under direction of the investigator, the site team addresses the query. If the query is due to a data entry error, the site staff can immediately make the corrections in the applicable eCRF pages. If the query needs clarification, the site staff contacts the investigator for resolution. The site coordinator then enters the correct value or submits an answer to the query without modifying the data. The monitor or data managers then review the corrected eCRF pages and/or answer. If the data are changed correctly or the answer is acceptable, the monitor or data manager closes the query. If the answer is not acceptable, the monitor or data manager submits an additional query for clarification. All changes to the database require a “Reason for Change” and are subject to an audit trail. The audit trails identify the changed data, reason(s) for change, who changed the data, and the time and date of the change.

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

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

#### **10.1.9.4.1. Trial Master File**

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

#### **10.1.9.5. Study Records 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 2 years after discontinuing clinical development or after the last marketing approval): copies of the study specific documents and other sources of information such as original medical documents, data and records (such as hospital records, clinical and office charts, laboratory notes, memoranda, documents regarding subject treatment and study product accountability, and original signed ICFs). All EC records related to this study will be retained by the site for as long as required by the local EC.

In the event the investigator retires, relocates or for any other reason withdraws from the responsibility for maintaining records for the time required, custody of the records may be transferred to any other qualified person who will accept responsibility for the records. Notice of such a transfer must be given in writing to Corbus. The investigator must contact Corbus before disposal of any records related to this study.

#### **10.1.10. Protocol Deviations**

The investigator should not implement any deviation from or changes of the protocol without agreement by Corbus and prior review and documented approval from the reviewing EC, except

where necessary to eliminate an immediate hazard to trial subjects or when the change involves only logistical or administrative aspects of the trial (e.g., change in monitor[s], change of telephone number[s]).

The investigators and site staff are responsible to follow the written protocol as provided by Corbus and approved by their EC.

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

An emergency protocol deviation occurs in an emergency when an excursion from the protocol is required to protect the life or physical well-being of a subject. The medical monitor and the reviewing EC must be notified as soon as possible, but not later than 5 days after the emergency occurred. The medical monitor will be notified through the EDC system. Relevant regulatory agencies will be notified according to their timelines for reporting.

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

- Failure to comply with GCP guidelines
- Failure to meet eligibility criteria at randomization
- Use of a prohibited concomitant medication
- Failure to obtain all TIS core set measurements at Visit 1 or Visit 10
- Failure to report AE/SAE in a timely manner

Major protocol deviations must be reported to Corbus electronically in the manner specified within 5 days of the first time the investigator or site staff becomes aware of the deviation and must be reported to the EC within that EC's guidelines. Corbus will determine if an emergency or major protocol violation should result in early discontinuation of study treatment for a subject.

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

A minor or administrative protocol deviation is an excursion from the protocol that does not affect the scientific soundness of the research plan or the rights, safety, or welfare of human subjects. Examples of minor or administrative deviations could include: follow-up visits that occurred outside the protocol required time frame because of the subject's schedule or blood samples obtained at times close to but not precisely at the time points specified in the protocol. If a protocol deviation occurs which meets this definition, the deviation should be reported to the reviewing EC (if reporting is required) at the time stipulated such as when the continuing review application is submitted. These minor or administrative deviations will be reported by the investigator or designee in the specified manner within 28 days after their occurrence.

### **10.1.11. Schedule and Contents of Report**

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

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

### **10.1.12. Publication and Data Sharing Policy**

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

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

This clinical study will be listed on websites (e.g., [www.clinicaltrials.gov](http://www.clinicaltrials.gov)) as required by relevant regulatory authorities. Synopses of the clinical results will be provided on those same sites per timeframes established by those regulatory authorities.

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

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

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

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

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

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## 12. APPENDICES

<a href="#">Appendix 1</a>	Reproductive Potential and Highly Effective Methods of Contraception
<a href="#">Appendix 2</a>	Investigator Global Assessment of Skin Activity
<a href="#">Appendix 3</a>	Patient Improvement Questionnaire for Physicians
<a href="#">Appendix 4</a>	Patient Improvement Questionnaire for Subjects
<a href="#">Appendix 5</a>	Physician assessment of DM activity
<a href="#">Appendix 6</a>	Algorithm to Calculate Total Improvement Score (TIS)
<a href="#">Appendix 7</a>	Corticosteroid Conversion Table

## APPENDIX 1. REPRODUCTIVE POTENTIAL AND ACCEPTABLE METHODS OF CONTRACEPTION<sup>4</sup>

Women are considered to have “no childbearing potential” if they meet any of the following criteria:

- Hysterectomy
- Bilateral oophorectomy
- Bilateral tubal ligation
- Post-menopausal; menopause is defined as no menses for 12 months without an alternative medical cause, not using hormone contraception or hormonal replacement therapy. In women  $\leq$  55 years of age with no menses for  $\geq$  12 months, FSH and LH levels should be measured to confirm postmenopausal state.

Acceptable methods of contraception must be used by subjects who are women of child-bearing potential or their male sexual partners. Acceptable methods of contraception must be used by subjects who are male or their female sexual partners of child-bearing potential.

Acceptable and 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 effective methods of contraception when used consistently and correctly include:

- Combined (estrogen and progesterone containing) hormonal contraception associated with inhibition of ovulation
  - Oral
  - Intravaginal
  - Transdermal
- Progesterone-only hormonal contraception associated with inhibition of ovulation
  - Oral
  - Injectable
  - Implantable
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomized partner
- Sexual abstinence. Abstinence is only acceptable when this is the preferred and usual lifestyle of the individual. Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus) and lactational amenorrhea method are not acceptable means of contraception.

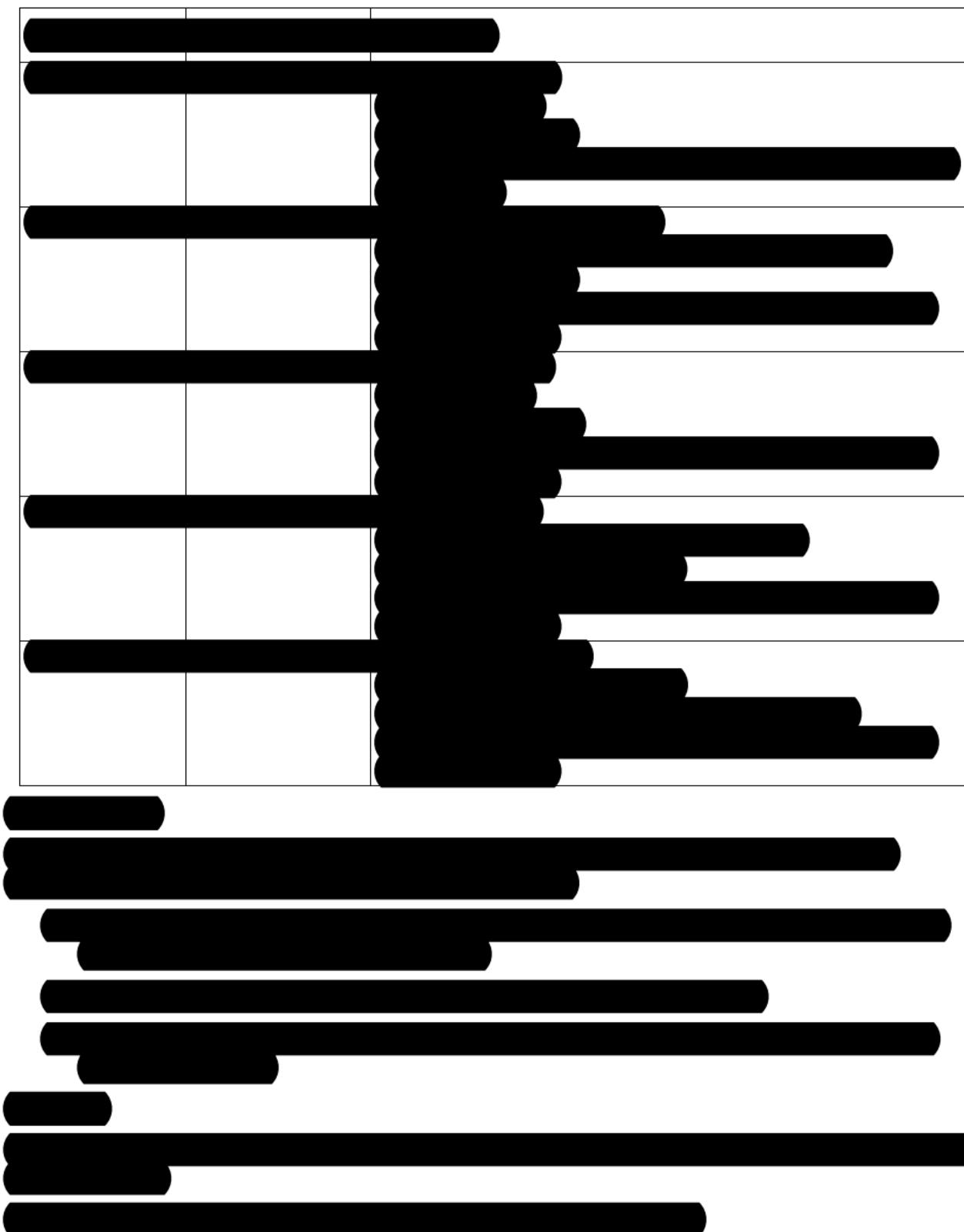
Another acceptable method of contraception that is allowed in the study is:

Combination of condom and spermicide

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<sup>4</sup> Acceptable contraceptive methods may not be available or approved in all countries; thus, the Sponsor does not restrict respective countries from excluding unavailable contraceptive methods in the ICF.

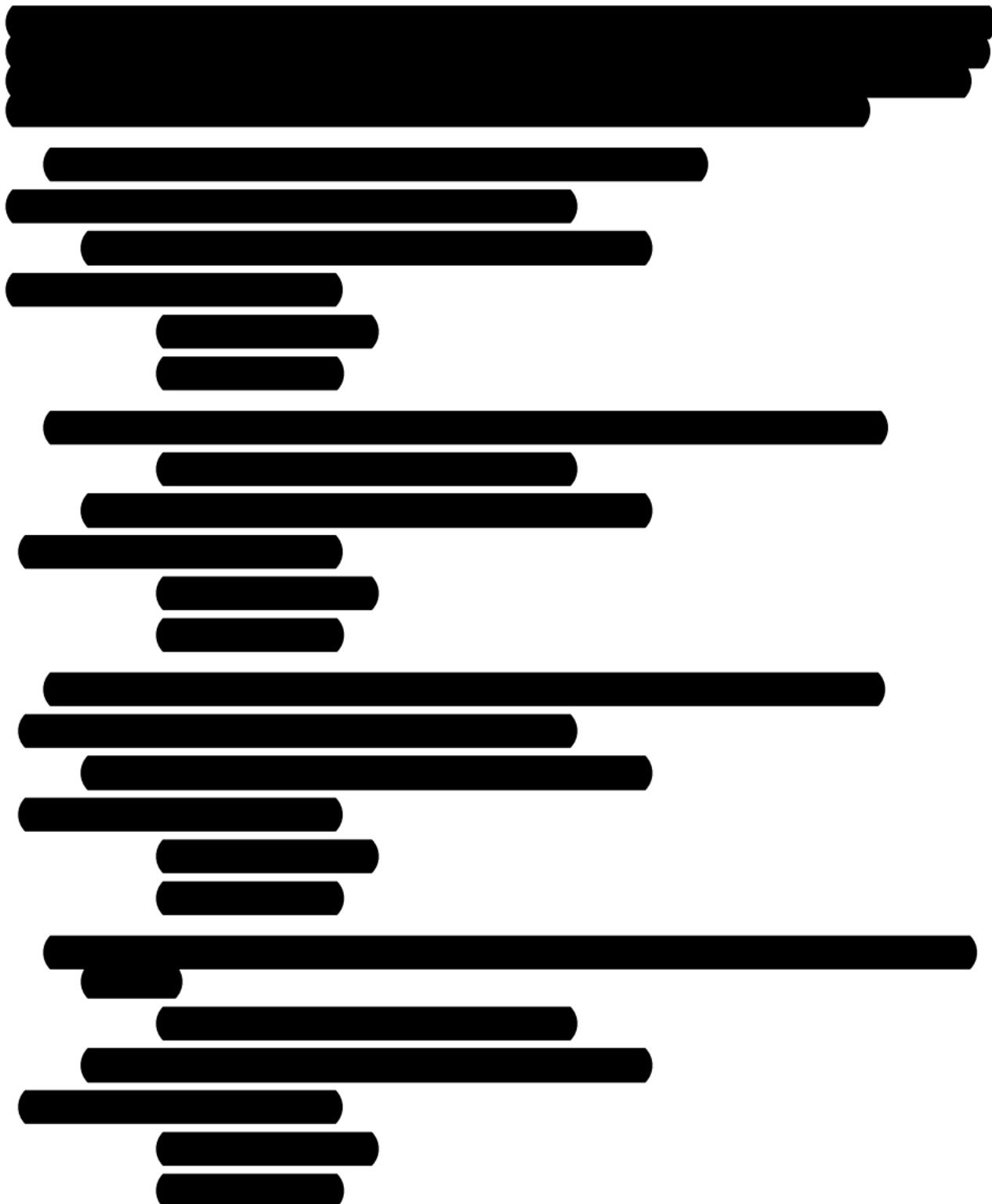
## APPENDIX 2. INVESTIGATOR GLOBAL ASSESSMENT OF SKIN ACTIVITY



## **APPENDIX 3. PATIENT IMPROVEMENT QUESTIONNAIRE FOR PHYSICIANS**

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## APPENDIX 4. PATIENT IMPROVEMENT QUESTIONNAIRE FOR SUBJECTS



## APPENDIX 5. PHYSICIAN ASSESSMENT OF DM ACTIVITY

## **APPENDIX 6. ALGORITHM TO CALCULATE TOTAL IMPROVEMENT SCORE (TIS)**

## APPENDIX 7. CORTICOSTEROID CONVERSION TABLE

	Closest Equivalents to Prednisone Doses:				
	<b>20 mg</b>	<b>15 mg</b>	<b>10 mg</b>	<b>5 mg</b>	<b>2.5 mg</b>
Prednisone					
Prednisolone	20 mg	15 mg	10 mg	5 mg	2.5 mg
Dexamethasone	3.2 mg	2.4 mg	1.5 mg	0.8 mg	0.5 mg
Triamcinolone	16 mg	12 mg	8 mg	4 mg	2 mg
Methylprednisolone	16 mg	12 mg	8 mg	4 mg	2 mg