

**A Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase 3 Study of  
Lenabasum in Diffuse Cutaneous Systemic Sclerosis: RESOLVE-1 Design and  
Rationale**

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Running head: Rationale for Phase 3 Study of Lenabasum in Systemic Sclerosis

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**ABSTRACT [250 word limit] I cut it from 272 to 249 words. DF**

**Objective:** The multi-systemic, heterogeneous nature of diffuse cutaneous systemic sclerosis (dcSSc) presents challenges in designing clinical studies that can demonstrate a treatment effect on overall disease burden. We describe the design of the first Phase 3 study in dcSSc patients where the American College of Rheumatology (ACR) Combined Response Index in diffuse cutaneous Systemic Sclerosis (CRISS) score was chosen prospectively as the primary outcome. The CRISS measures key clinical disease parameters and patient-reported outcomes (PROs).

**Methods:** RESOLVE-1 is a Phase 3, randomized, double-blind, placebo-controlled trial of dcSSc patients evaluating the efficacy and safety of lenabasum. Patients  $\geq 18$  years of age with dcSSc and disease duration  $\leq 6$  years were eligible. Patients could continue stable background therapy for dcSSc, including stable immunosuppressive therapies. They were randomized to lenabasum 5 or 20 mg twice daily or placebo. The primary efficacy outcome was the mean change from baseline to 52 weeks in the ACR CRISS score.

**Results:** The study enrolled 365 patients over 1.5 years at 77 sites in 13 countries in North America, Europe, Israel, and Asia-Pacific, with the last patient first visit on May 1, 2019.

**Conclusions:** RESOLVE-1 is the first Phase 3 interventional study to date in dcSSc to prospectively use the ACR CRISS as the primary efficacy outcome. Eligibility criteria allowed background therapy as might occur in clinical practice. This approach also facilitated timely patient enrollment. RESOLVE-1 provides a novel study design that may be used for future Phase 3 dcSSc studies to assess the holistic efficacy of therapy.

### **Significance and Innovations [2-4 bullets highlighting the key points]**

- An unmet need exists for pharmacological therapy of SSc that demonstrates overall clinical benefit (i.e. how the patient feels and functions).
- RESOLVE-1 is the first Phase 3 study in diffuse cutaneous SSc to prospectively use the ACR CRISS as the primary efficacy outcome assessment.
- The use of broad patient selection criteria was designed to reflect the real-world population of patients with systemic sclerosis, including allowance of background therapy with immunosuppressives.

**INTRODUCTION [maximum 3800 words] please include at least one reference from JSRD, ok? dan**

Systemic sclerosis (SSc) is a potentially life-threatening autoimmune disease characterized by thickened skin resulting from vasculopathy, inflammation, and fibrosis (Denton and Khanna, 2017; Royle et al, 2018; Katsumoto et al, 2011; Sierra-Sepúlveda et al, 2019). Patients with diffuse cutaneous systemic sclerosis (dcSSc) experience more widespread disease and can have multiple organ systems including gastrointestinal, pulmonary, musculoskeletal, cardiovascular, and renal disease (Sierra-Sepúlveda et al, 2019). Patients with SSc experience markedly impaired health status compared to the general population, as well as increased mortality (Morrisroe et al, 2019; Zhou et al, 2019). Patients with SSc often are treated with immunosuppressants. Currently there are no approved treatments that specifically target both inflammation and fibrosis, key drivers of SSc pathophysiology (Iwamoto and Distler, 2012; Khanna et al, 2019a). Recently, nintedanib was approved for slowing the rate of decline in pulmonary function in patients with SSc-associated interstitial lung disease (SSc-ILD), but improvement in other SSc disease domains was not demonstrated. Thus, a need exists for pharmacological treatments that comprehensively address the total disease burden in SSc.

Clinical investigations of pharmacological approaches to SSc have consisted mostly of placebo-controlled studies, usually of 6-12 months that often fail to include patient-focused outcomes (Iudici et al, 2020). An unmet need remains for new treatments that meaningfully improve overall disease, effecting patients survival, function, and/or quality

of life. Identifying such therapies is challenging because there is a paucity of patients available for study, the patient population is highly heterogeneous, displaying variable disease features, and there had been no validated outcome measures to assess the overall disease (Denton, 2019; Khanna et al, 2019). Recent publications called for study designs of at least 12 months duration with broad patient selection criteria and which incorporate both clinical and patient focused assessments.

In a 16-week Phase 2 study in patients with dcSSc, lenabasum, an oral, selective, cannabinoid receptor type 2 (CB2) agonist, was safe and well-tolerated and was associated with improvements in the American College of Rheumatology (ACR) Combined Response Index in diffuse cutaneous Systemic Sclerosis (CRISS) score (Spiera et al, 2020). RESOLVE-1 is a Phase 3 study designed to evaluate the efficacy, safety, and tolerability of lenabasum vs. placebo in patients with dcSSc. We describe the rationale supporting the design, patient selection, outcome measures, and statistical analysis plan of RESOLVE-1.

## **METHODS AND ANALYSIS**

The primary objective of RESOLVE-1 was to evaluate the efficacy of lenabasum compared to placebo in the treatment of SSc by assessing the American College of Rheumatology (ACR) Provisional Combined Response Index in diffuse cutaneous Systemic Sclerosis (CRISS; Khanna et al, 2016a) score at Week 52. The study is registered at ClinicalTrials.gov: NCT03398837.

## **Study Design**

This 52-week, randomized, double-blind, placebo-controlled study enrolled patients who satisfied 2013 American College of Rheumatology (ACR) criteria for SSc (van den Hoogen et al, 2013) (**Figure 1**). The study consisted of a Screening phase of up to 4 weeks and a treatment phase of 52 weeks. The study included 11 study visits (Visits 1 – 11), which occurred at Day 1 and at the completion of Weeks 4, 8, 14, 20, 26, 32, 38, 44, 48, and 52. Patients were enrolled at clinical sites located in North America, Europe (including UK and Israel), and the Asia-Pacific region (**Figure 2**).

## **Ethics and Safety Monitoring**

This study was conducted in accordance with the principles of the Declaration of Helsinki and International Conference on Harmonization and complied with Good Clinical Practices. The study protocol and any amendments and informed consent forms were reviewed and approved by an Institutional Review Board/Ethics Committee for each study site. Patients provided written informed consent prior to participation in any study procedures. An independent, unblinded Data Monitoring Committee (DMC) evaluated safety data to provide recommendations on safe continuation of the study.

## **Patient Selection**

To be eligible, patients had to be  $\geq 18$  years of age, had to fulfill 2013 ACR classification criteria for SSc (van den Hoogen, 2013) and had to have dcSSc (skin thickening on upper arms proximal to the elbows, upper legs proximal to the knees, or trunk). In

addition, patients were required to have SSc disease duration  $\leq 6$  years from the time of the first non-Raynaud's symptom; if the disease duration was  $>3$  years and  $\leq 6$  years, then the modified Rodnan skin score (mRSS; Khanna et al, 2017a) had to be  $\geq 15$  of 51 (max score) Enrollment of patients with a disease duration  $>3$  years and  $\leq 6$  years and mRSS  $\geq 15$  was limited to no more than one-third of the total study enrollment. At screening, a Patient Global Assessment score  $\geq 3$  or physician global assessment (MDGA) score  $\geq 3$  was required. Patient were required to be on stable treatment for SSc  $\geq 28$  days before the first dose of study drug (Visit 1); be willing to remain on their baseline immunosuppressive treatment for SSc throughout the study; be willing to not use any cannabinoids including recreational marijuana, medical marijuana or other prescription cannabinoids throughout the study.

Patient were excluded if they were medically unstable or had SSc with end-stage organ involvement; concomitant inflammatory myositis, rheumatoid arthritis or systemic lupus erythematosus by ACR criteria; or a positive test for anti-centromere antibody, although patients with a positive test and definite dcSSc could be enrolled, when agreed by both investigator and medical monitor. Full inclusion and exclusion criteria are provided in **Table 1**. The eligibility of each patient had to be reviewed and approved by a medical monitor designated by the Sponsor.

## **Treatment**

Patients were randomized in a 1:1:1 ratio to twice daily treatment with lenabasum 5 mg, lenabasum 20 mg or matching placebo, and randomization was stratified by location (a)

United States; b) Canada, Europe, Australia; or c) Asia) and by SSc disease duration ( $\leq 24$  or  $>24$  months). An interactive web-based response system (IWRS) was used to assign a unique identification number to each patient at screening, and patients were randomized at Visit 1 (baseline) from a central location.

Lenabasum and placebo capsules had identical physical appearance. All patients, the clinical site study staff and Corbus remained blinded to treatment assignment during the entire study.

Eligibility criteria permitted patients to receive treatment with stable doses of concomitant immunosuppressive medications except oral prednisone  $>10$  mg per day or equivalent or cyclophosphamide. After baseline, doses of concomitant immunosuppressive medication(s) could be increased, or new non-investigational immunosuppressive medication(s) could be started by study investigators 1) if the patient had a documented increase in signs or symptoms of SSc; or 2) if it was considered in the best interest of the patient to treat the increase in signs or symptoms with a change in dose of concomitant immunosuppressive medications or the addition of new non-investigational immunosuppressive medications.

### **Efficacy Assessments**

The primary efficacy variable was the ACR CRISS score at Week 52 (**Table 2**). The ACR CRISS score is a continuous variable between 0.0 and 1.0. A higher score indicates greater likelihood of improvement during the study. No improvement was

defined as ACR CRISS score = 0, and subjects were automatically assigned that score if they developed any one or more of the following during the trial: 1) new scleroderma renal crisis; 2) decline from baseline in FVC % predicted by 15%, confirmed after 1 month with FVC <80% and confirmed diagnosis of ILD on HRCT (new or established); 3) new left ventricular failure (systolic ejection fraction <45%); or 4) new pulmonary artery hypertension on right heart catheterization requiring treatment. These outcomes assess the feel, function, and survival guidance by the FDA. For remaining patients, 5 outcome measures were assessed at Week 5 for the mRSS, FVC% predicted, PTGA(100 mm horizontal VAS), MDGA(100 mg horizontal VAS), and HAQ-DI(-0-3). The CRISS scored as a probability score from 0.00-1.00 .

A secondary efficacy outcome was the mRSS. The mRSS was performed by a healthcare professional experienced in assessment of SSc patients with the mRSS. The site investigator and a second independent assessor performed the mRSS at each study visit for each patient and had received formal training that satisfied certification standards of the Scleroderma Clinical Trials Consortium (Khanna et al, 2017c).

Other secondary efficacy outcomes were the Health Assessment Questionnaire-Disability Index (HAQ-DI; Cole, 2006); FVC % predicted (Hankinson et al, 2010); Functional Assessment of Chronic Illness Therapy (FACIT; Butt, 2013); Physician Global Assessment (MDGA) of Overall Health; European Quality of Live Five-domain questionnaire (EQ-5D-3L; Gualtierotti, 2016); Patient-Reported Outcomes Measurement Information System-29 item (PROMIS-29) questionnaire (Khanna et al, 2011; Hinchcliff,

2011); Medical Outcomes Study Short Form-36 (SF-36; Hinchcliff et al, 2015); Scleroderma Skin Patient Reported Outcome (SSPRO; Man et al, 2017); The University of California at Los Angeles Scleroderma Clinical Trials (UCLA SCTC) Consortium Gastrointestinal Tract symptoms questionnaire (GIT 2.0) (Khanna, 2009); 5-Dimension Itch Scale (5-D Itch Scale; Elman, 2010); and Digital Ulcer Visual Analog Scale (Steen, 1997).

These efficacy assessments as described are reflected in the study protocol for the US and Europe. For the study protocol in Japan, mRSS will be the primary efficacy endpoint with ACR CRISS score as the first secondary efficacy endpoint.

### **Safety Assessments**

Treatment-emergent adverse events (TEAEs), physical examination, vital signs, 12-lead electrocardiogram (ECG), clinical laboratory results, and concomitant medications were assessed. Plasma concentrations and metabolites of lenabasum were measured and punch biopsies of involved skin were obtained at Visits 1 and 11. Prior to study completion and before entry into the open-label extension study, approximately 90 study patients in the U.S. will be consented to participate in a withdrawal sub-study to assess potential withdrawal effects of lenabasum. Patients will complete withdrawal-related patient-reported outcome questionnaires on depression, including suicidality. They will be instructed that if they feel this way at any time or discover they feel this way as they fill out the questionnaires, they need to seek immediate medical attention. As part of the withdrawal study, additional safety assessments included safety outcomes from the

Beck Depression Inventory (BDI; Beck et al, 1961); Cannabis Withdrawal Scale (CWS; Allsop et al, 2011); and Addiction Research Center Inventory – Marijuana (ARCI-M; Huestis et al, 2007) questionnaire (**Table 2**).

### **Statistical Analysis**

Sample size calculations were based on results from a Phase 2 study (Spiera et al, 2020). RESOLVE-1 was expected to enroll approximately 118 patients in each of the three treatment arms, for a total of approximately 354 randomized patients. To detect a statistically significant difference in the primary efficacy endpoint, ACR CRISS at Week 52, 107 evaluable patients per treatment arm (321 patients total) were required to complete Week 14. This provided >99% power assuming a 2-sided test at alpha = 0.05 and a common standard deviation (SD) of 0.41 in both treatment arms for the primary efficacy outcome, and a difference in the ACR CRISS score between lenabasum and placebo of 0.33. If the resulting treatment effect size was smaller (e.g., 0.20), and/or the resulting SD was larger (e.g., 50.0), the study would maintain  $\geq 83\%$  powered to detect a significant treatment difference for lenabasum versus placebo for the primary outcome. With 107 evaluable patients per treatment arm, the power to detect a significant treatment difference in the first secondary efficacy measure (HAQ-DI) was 95% with a corresponding treatment difference of 0.25, SD of 0.51.

For primary and secondary efficacy outcomes, the overall type I error rate was controlled with independent hierarchical assessments of efficacy at each dose of lenabasum. The order of tests for treatment effect was change from baseline for mRSS,

HAQ-DI, and FVC % predicted for lenabasum 20 mg twice daily vs. placebo, and ACR CRISS, mRSS, HAQ-DI, and FVC % predicted for lenabasum 5 mg twice daily vs. placebo. Statistical significance with each endpoint was required to continue with assessment of the next endpoint.

The primary and key secondary endpoints are listed in **Table 3**. Analysis of the primary and secondary efficacy endpoints was with a mixed-effect model repeated measures (MMRM) model that included region, disease duration, baseline immunosuppressive use, visit, treatment, and treatment-by-visit as fixed effects and baseline mRSS as a covariate. Data were presented as mean, SD, and 95% confidence intervals (CI). An unstructured covariance structure shared across treatment groups was used to model within-patient errors, and the Kenward-Rogers correction to degrees of freedom was applied. The assumption of normality for data was tested using the Shapiro-Wilk W test.

Sensitivity analyses on the CRISS score included Van Elteren's test with stratification factors for region, disease duration, and baseline immunosuppressive use; imputation of missing data using multiple imputation methods following Markov Chain Monte Carlo techniques; analysis using completers only; analysis after imputing missing ACR CRISS using last observation carried forward, where data after study product discontinuation were considered missing; and analysis using tipping point analyses to better understand the impact of data missing not at random data.

The modified intent-to-treat (mITT) population was used for efficacy analyses and included all randomized patients who received at least 1 dose of study drug and had at least one post-baseline efficacy evaluation. The safety population comprised all patients who received at least 1 dose of study drug.

## **DISCUSSION**

Historically, measurement of skin thickness with mRSS has been a primary endpoint in many SSc clinical studies, particularly in early dcSSc. mRSS has been used as a clinical surrogate marker for disease severity and predictor for disease progression and mortality (Pauling, 2020). Prior studies suggested a possible benefit of immunosuppressive strategies including methotrexate (Pope 2001, Van den Hoogen 1996) and cyclophosphamide (Tashkin 2006) for mRSS. In more recent trials in which the mRSS was used as the primary endpoint, treatment of patients with early dcSSc with tolicizumab (Khanna et al, 2018c; Khanna et al, 2020a; Khanna et al, 2020b), did not demonstrate a statistically significant improvement comparing active drug vs. placebo, despite implementation of various cohort enrichment criteria (shorter disease duration, defined range of baseline mRSS, elevated CRP requirement and indicator of worsening skin in the previous 6 months prior to screening) to increase subjects with active progressive skin disease. Using ACR CRISS score as a secondary (abatacept) or exploratory (tolilizumab) efficacy outcome in 2 of these trials (Khanna et al, 2018a; Khanna et al, 2018b), however, was able to discriminate active drug from placebo. These results underscore the potential limitation of selecting mRSS as the primary endpoint, since skin thickness has a relatively high coefficient of variation, is

heterogeneous and measures one aspect of SSc disease which typically peaks and then regresses early in the disease. Further it often improves in both the placebo and treated groups in the context of clinical trials. This can result in an unpredictable degree of improvement in the placebo group (Kuwanna, 2020). The mean changes in mRSS from baseline in one year in the placebo group in these studies were -4.4 (tocilizumab), -4.5 (abatacept), and -0.8 (riociguat). Another limitation to mRSS includes inter- and intra-rater variability, although much of this variability can be minimized by study training certification for skin assessment and the use of experienced investigators (Khanna 2017) as was done for RESOLVE-1.

Further, the mRSS captures one clinical feature of SSc and may not adequately capture the heterogeneous features that can contribute to patient quality of life and function in SSc. It therefore is important to consider the role and value of PROs in evaluating clinical burden and treatment benefit to patients in SSc studies (Pauling, 2020). SSc has a substantial burden on the health-related quality of life (QoL) of affected patients (Hudson et al, 2009a; Fischer et al, 2017). The QoL of SSc patients is substantially lower than that in the general population (Li et al, 2018; Fischer et al, 2017; Morrisroe et al, 2018), is worse than in patients with other rheumatic diseases (Park et al, 2019), and is worse in patients with dcSSc than in patients with primarily local cutaneous disease (Frantz et al, 2016). Work disability occurs early in the course of the disease and worsens with the severity of SSc and the patient's functional status (Hudson et al, 2009b). Both functional disability and anxiety have a significant impact on QoL in patients with SSc (Sierakowska et al, 2019).

In this Phase 3 study with lenabasum, we wanted to select a primary efficacy outcome that would reflect clinically meaningful treatment benefit--that is- how the patient feels, functions, or survives (FDA, 2009). RESOLVE-1 is the first Phase 3 study in dcSSc where the primary efficacy outcome is ACR-CRISS. The ACR-CRISS is a composite score consisting of testing for major organ decrements followed by examination of 5 clinical and patient-reported outcomes (PROs) developed to assess the likelihood of improvement in how the patient feels and functions from baseline in clinical studies. RESOLVE-1's study design, utilizing ACR-CRISS as the primary endpoint and multiple other SSc specific and non-specific PROs as secondary endpoints, represents an important advance in evaluating new pharmacological therapies for dcSSc. The ACR-CRISS score was developed to address the limitations of mRSS by providing a multiple domain scoring system that includes assessment of skin changes, pulmonary function, daily function, and patient and physician global assessments (Khanna et al, 2016a). In a Phase 2 study of lenabasum in 42 patients with dcSSc, where ACR-CRISS was used as the primary outcome, improvement was observed in the lenabasum group starting at Week 8 and increasing over time. The ACR-CRISS reached a maximum of 0.33 probability of improvement compared to 0.00 at Week 16 in the placebo group. This was consistent with improvement across multiple physician- and patient-reported outcomes that spanned overall disease, skin involvement, and patient function (Spiera et al, 2020). Through 2 years of the lenabasum Phase 2 open-label extension study, additional analyses show: ACR-CRISS score positively correlates with improvements in multiple PROs; ACR-CRISS score correlates more strongly with these PROs than

change in mRSS; and improvement in the two PROs [Health Assessment Questionnaire-Disability Index (HAQ-DI) and Patient Global Assessment (PtGA)] included in the composite ACR CRISS score themselves correlate with multiple other PROs [Scleroderma Skin Patient Reported Outcome (SSPRO) and Patient-Reported Outcomes Measurement Information System-29 item (PROMIS-29) questionnaire] (Spiera et al, 2020). Together, these data show that the ACR CRISS score broadly reflects changes from baseline in how patients feel and function. In addition, Step 1 captures survival as it assesses clinically meaningful cardio-pulmonary-renal involvement. Since the completion of the lenabasum Phase 2 randomized, double-blind, placebo-controlled trial, ACR CRISS was selected as a primary outcome for a number of currently active Phase 2 dcSSc clinical trials: MT-7117 (dersimelargon; ClinicalTrials.gov: NCT04440592), KD025 (belumosudil; ClinicalTrials.gov: NCT03919799), IgPro10 (IVIG; ClinicalTrials.gov: NCT04137224) and belimumab / rituximab (ClinicalTrials.gov: NCT03844061).

One unique feature of RESOLVE-1 was the inclusive eligibility criteria. It allowed background treatment including immunosuppressives and low dose corticosteroids and even allowed changes in immunosuppressive dosing if needed; this facilitated timely, full enrollment into the study. Consequently, the study population would be expected to be more representative of SSc patients who are managed in clinical practice. In patients with dcSSc, this study is evaluating improvement in overall disease burden, rather than effects on a single domain of the disease, which may provide valuable information on health outcomes as well as the efficacy and tolerability of lenabasum. This study design

was chosen to demonstrate that a new pharmacologic therapy for dcSSc has incremental benefit over and beyond what is achieved with the traditionally used immunosuppressive strategies. A strong argument can be made to allow background therapy in clinical trials in early dcSSc recognizing how devastating the disease can be with the potential for incurring irreversible skin or organ damage which is generally most progressive in that early phase. (Khanna et al, 2015). Although there are no proven “disease modifying” therapies for dcSSc or clear definitions as to what would constitute disease modification, most clinicians and patients opt for therapy in early disease in clinical practice. Unlike several of the recent aforementioned studies, we allowed background immunosuppressive therapy at the risk of blunting a more subtle treatment effect of lenabasum that might have been seen in a study that did not allow background immunosuppressives. With this design, we hope to find a meaningful incremental advance in the pharmacological therapy of dcSSc, rather than merely demonstrating a drug-placebo difference in efficacy. By choosing a 52-week study that allowed background therapy, we also avoided the ethical dilemma of including a placebo-controlled arm for a long-duration study (Khanna et al, 2015).

Conclusion:

RESOLVE-1 is the first Phase 3 interventional study to date in dcSSc to prospectively use the ACR CRISS as the primary efficacy outcome. The study design incorporated some unique features including ACR CRISS as the primary endpoint, broad eligibility criteria, and concomitant use of stable background immunosuppressive therapy. These features facilitate rapid recruitment of a large placebo controlled study in 1.5 years.

RESOLVE-1 may provide a template for the design of future Phase 3 dcSSc studies to demonstrate meaningful improvement in overall disease activity.

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Table 1. Inclusion/Exclusion criteria

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

1. Fulfills the 2013 ACR criteria for systemic sclerosis (van den Hoogen, 2013)
2. Diffuse cutaneous SSc (skin thickening on upper arms proximal to the elbows, upper legs proximal to the knees, or trunk)
3.  $\geq 18$  years of age at the time Informed Consent is signed
4. Written informed consent from the subject
5. Disease duration  $\leq 6$  years from the first non-Raynaud's symptom. If disease duration is  $> 3$  years and  $\leq 6$  years, then mRSS  $\geq 15$ . Subjects with disease duration  $> 3$  years and  $\leq 6$  years and mRSS  $\geq 15$  will be limited to no more than 1/3rd of the subjects.
6. Patient Global Assessment  $\geq 3$  or MDGA  $\geq 3$
7. Stable treatment for SSc  $\geq 28$  days before Visit 1
8. Willing to not start or stop any immunosuppressive medications for SSc from Visit 1 through Visit 11, unless a change is considered in the subject's best medical interest by the site investigator or another physician who has primary responsibility for treating the subject's SSc.
9. Willing not to use any cannabinoids including recreational marijuana, medical marijuana and other prescription cannabinoids from Screening through Visit 11
10. Women of childbearing potential (WOCBP) must not be pregnant or breastfeeding at Screening or Visit 1 and must be using at least one highly effective method of contraception (failure rate  $< 1\%$  per year) for at least 28 days before Visit 1 and be willing to continue to use at least one highly effective method of contraception throughout the study and for at least 28 days after discontinuation of study product.
11. Male participants must be willing to follow contraceptive requirements and should not get anyone pregnant while they are taking the study product or within 28 days after taking the last dose of the study product, during which time period they or their partner must be willing to use at least one highly effective method of contraception.
12. Able to adhere to the study visit schedule and other protocol requirements.

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

1. Unstable SSc or SSc with end-stage organ involvement from SSc at screening or Visit 1 (baseline), including:
  - a. On an organ transplantation list or has received an organ transplant (previous autologous bone marrow/stem cell transplantation is permitted, but such cases should be discussed individually with the medical monitor).
  - b. Renal crisis within 1 year before Visit 1
  - c. Interstitial lung disease requiring constant oxygen therapy. This excludes oxygen used to aid sleep or exercise.
  - d. Pulmonary hypertension requiring constant oxygen therapy. This excludes oxygen used to aid sleep or exercise.
  - e. Gastrointestinal dysmotility requiring total parenteral nutrition or hospitalization within 6 months before Visit 1.
2. Certain medications at Screening or Visit 1, including:
  - a. Treatment with any oral prednisone  $> 10$  mg per day or equivalent within 28 days before Visit 1. Treatment with intravenous corticosteroids within 28 days

- before Visit 1 is not allowed, and treatment with intra-articular corticosteroids within 28 days before Visit 1 is allowed (topical corticosteroids are allowed).
- b. New or increase in doses of any non-corticosteroid immunosuppressive medication within 8 weeks before Screening
  - c. Treatment with cyclophosphamide within 3 months before Visit 1
3. Concomitant inflammatory myositis, rheumatoid arthritis, or systemic lupus erythematosus when definite classification criteria for those diseases are met (Bohan and Peter criteria for polymyositis and dermatomyositis [Bohan and Peter, 1975a; 1975b]; 2010 rheumatoid arthritis classification criteria of ACR/EULAR [Aletaha, 2010]; ACR revised criteria for the classification of systemic lupus erythematosus [Hochberg, 1997]).
  4. SSc-like illnesses related to exposures or ingestions
  5. A positive test for anti-centromere antibody at Screening.
  6. Significant diseases or conditions other than SSc that may influence response to the study product or safety, such as:
    - a. A new bacterial or viral infection that was treated with oral or intravenous antibiotics or anti-viral treatments within 28 days before Visit 1. This does not include prophylactic antibiotic or anti-viral treatments, or treatment for gastrointestinal bacterial overgrowth.
    - b. Acute or chronic hepatitis B or C infection
    - c. Human immunodeficiency virus (HIV) infection
    - d. History of active tuberculosis or positive tuberculosis test without a completed course of appropriate treatment or already completed at least 1 month of ongoing appropriate treatment
    - e. Evidence of required treatment for cancer (except for treated, localized basal or squamous cell carcinoma of the skin or cervical carcinoma in situ) within 3 years of Visit 1
  7. Any of the following values for laboratory tests at Screening:
    - a. A positive pregnancy test in WOCBP (also at Visit 1)
    - b. Hemoglobin <9 g/dL in males and <8 g/dL in females
    - c. Neutrophils <1.0 X 10<sup>9</sup>/L
    - d. Platelets <75 X 10<sup>9</sup>/L
    - e. Creatinine clearance in blood < 50 mL/min according to the Modification of Diet in Renal Disease (MDRD) Study equation. Creatinine clearance may be assessed in a 24-hour urine collection to confirm eligibility (creatinine clearance ≥50 ml/min) if screening blood test is <50 mL/min.
    - f. Aspartate aminotransferase or alanine aminotransferase >2.0 X upper limit of normal
  8. Any investigational agent within 30 days or 5 therapeutic half-lives of that agent, whichever is longer, before Visit 1
  9. Prior exposure to lenabasum
  10. Significant diseases or conditions other than SSc or concurrent medical therapies at Screening or Visit 1, including a history of non-compliance with medical treatments, that may put the subject at greater safety risk, influence response to study product, or interfere with study assessments.

Table 2. Study Assessments and Definitions

Assessment	Definition
ACR CRISS	Continuous variable score between 0.0 and 1.0 (0 – 100%). A higher score indicates greater improvement. Patients were not considered improved (ACR CRISS score = 0) if they developed new: 1) renal crisis; 2) decline in FVC% predicted by 15% (relative) to baseline and confirmed after 1 month; 3) left ventricular failure (systolic ejection fraction <45%); or 4) new pulmonary artery hypertension on right heart catheterization requiring treatment
Modified Rodnan Skin Score (mRSS)	Evaluation of skin thickness rated by clinical palpation using a 0–3 scale for each of 17 surface anatomic areas of the body: face, anterior chest, abdomen, and, with right and left sides of the body separately evaluated, the fingers, forearms, upper arms, thighs, lower legs, dorsum of hands and feet where 0 = normal skin; 1 = mild thickness; 2 = moderate thickness; and 3 = severe thickness with inability to pinch the skin into a fold. Individual values are added and the sum is defined as the total skin score, with a maximum score of 51; a lower score indicates less skin thickness.
Health Assessment Questionnaire-Disability Index (HAQ-DI)	Patient-reported assessment of functional disability that includes 8 sections: dressing, arising, eating, walking, hygiene, reach, grip, and activities. Scoring within each section is from 0 (without any difficulty) to 3 (unable to do), and scores are adjusted for use of aides, devices, or help from others. The individual scores of the 8 sections are summed and divided by 8. A higher score indicates more functional disability.
Forced vital capacity (FVC)	Forced vital capacity (FVC) actual and % predicted were obtained by staff properly trained in spirometry
Functional Assessment of Chronic Illness Therapy (FACIT)	13-item patient-reported questionnaire that assesses tiredness, weakness, and difficulty conducting everyday activities due to fatigue in the last 7 days. Items are scored on a 5-point scale (0 – not at all, 4 = very much) with a total score (range 0-52). A higher score indicates less fatigue.
Physician Global Assessment (MDGA)	Visual analog scale in which the physician selects a whole number (0 through 10 integers) that best reflects overall health. A higher score indicates worse overall health. The Patient Global Assessment (PtGA) of overall health uses a visual analog scale in which the patient selects a whole number (0 through 10 integers) that best reflects overall health. A higher score indicates worse overall health.
European Quality of Live Five-domain questionnaire (EQ-5D-3L)	Patient-reported health questionnaire that assesses five domains of health quality. In SSc, the minimal important difference is 0.08 for improvement and -0.13 for deterioration
Patient-Reported	Measures what patients are able to do and how they feel by asking questions. These questions can focus on a mental health topic

Outcomes Measurement Information System-29 item (PROMIS-29) questionnaire	such as fatigue, anxiety, or physical health topics such as pain, sleep impairment, or topics related to social health such as ability to participate in roles and activities, or a mixture of these.
Medical Outcomes Study Short Form-36 (SF-36)	36-item, patient-reported survey of patient health
Scleroderma Skin Patient Reported Outcome (SSPRO)	Patient-reported answers to 18 questions about how scleroderma affects the skin and how those skin problems affect how the person feels and does things. A higher score indicates worse skin symptoms
The University of California at Los Angeles Scleroderma Clinical Trial (UCLA SCTC) Consortium Gastrointestinal Tract symptoms questionnaire (GIT 2.0)	Assesses patients with gastrointestinal disorders including irritable bowel syndrome, inflammatory bowel disease, other common gastrointestinal disorders, SSc, and a census-based US general population control sample (Khanna, 2009). The scale consists of eight domains relating to gastroesophageal reflux, disrupted swallowing, diarrhea, bowel incontinence/soilage, nausea and vomiting, constipation, belly pain, and gas/bloat/flatulence.
5-Dimension Itch Scale (5-D Itch Scale)	Patient-reported assessment of itch in skin diseases that assesses five dimensions of itch - degree, duration, direction, disability and distribution. Total 5-D Itch scores can range between 5 (no itch) and 25 (most severe itch). A higher score indicates worse itch.
Digital Ulcer Visual Analog Scale	Assesses digital ulcer severity
Beck Depression Inventory (BDI)	21-item scale that facilitates a self-evaluation of clinical depression. The final composite score correlates to a level of depression: 1-10 = ups and downs that are considered normal; 11-16 = mild mood disturbance; 17-20 = borderline clinical depression; 21-30 = moderate depression; 31-40 = severe depression; and over 40 = extreme depression. The maximum score for the BDI is 63.
Cannabis Withdrawal Scale (CWS)	Evaluates cannabis withdrawal symptoms. Patients are asked about the intensity and how each of 19 symptom has negatively impacted normal daily activities by grading on a 10-point scale, ranging from not at all (0) to extremely (10). The maximum withdrawal score is 190.

Addiction Research Center Inventory – Marijuana (ARCI-M)	12-item questionnaire developed by the National Institute on Drug Abuse to detect the full range of subjective responses experienced by marijuana users and has been validated by subjects following marijuana smoking. Evidence of psychotropic effects of the study product in subjects are identified by an increase in score indicating more symptoms (scale 0 – 10).
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Table 3. Study Outcomes

<b>Primary Efficacy Outcome</b>	<b>Change from Baseline to Week 52</b>
ACR CRISS	Lenabasum 20 mg BID vs. placebo
<b>Secondary Efficacy Outcomes</b>	
ACR CRISS	Lenabasum 5 mg BID vs. placebo
mRSS	Lenabasum 20 mg BID vs. placebo
	Lenabasum 5 mg BID vs. placebo
HAQ-DI	Lenabasum 20 mg BID vs. placebo
	Lenabasum 5 mg BID vs. placebo
FVC % predicted	Lenabasum 20 mg BID vs. placebo
	Lenabasum 5 mg BID vs. placebo
<b>Tertiary Efficacy Outcomes</b>	<b>Change from Baseline to Week 26</b>
ACR CRISS	
mRSS	
HAQ-DI	
FVC % predicted	
	<b>Change from Baseline to Week 26 and 52</b>
MDGA	
PtGA	
SSPRO	
5-D Itch	
PROMIS-29	
FACIT-fatigue	
EQ-5D	
UCLA SCTC GIT 2.0	
Digital Ulcer VAS	
Responders – mRSS, HAQ-DI, FVC % predicted, MDGA, PtGA	

Figure 1. Study Design

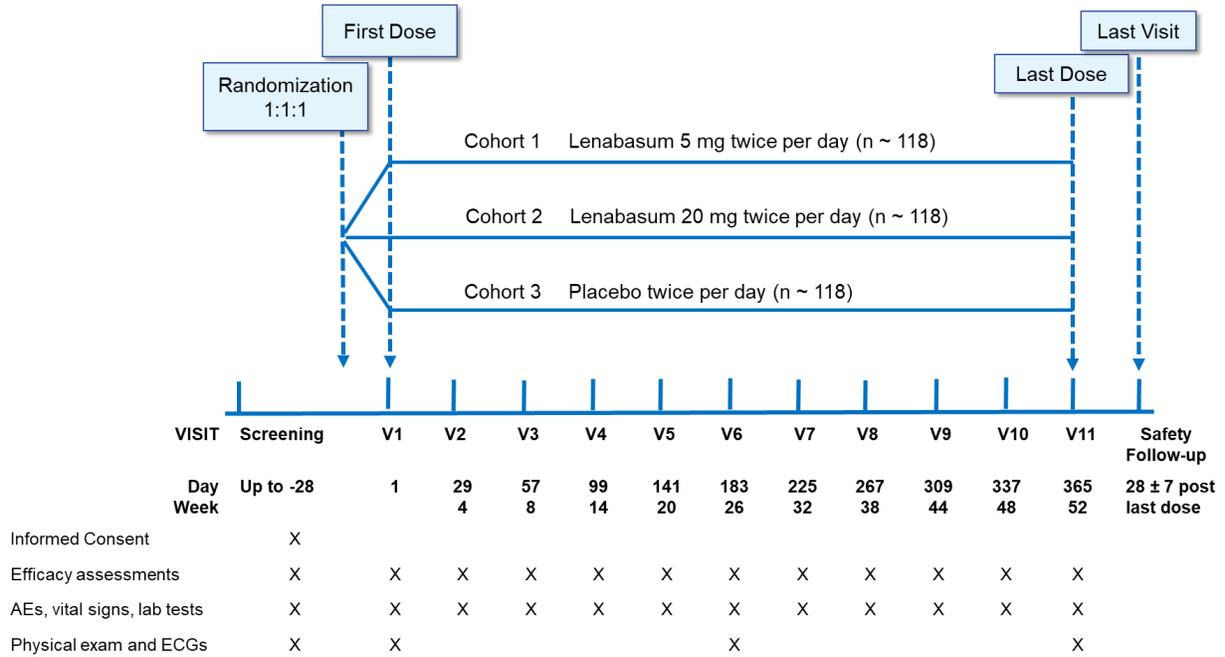


Figure 2. Patient enrollment [high resolution graphics in progress]

