A randomised, double-blind, placebo-controlled phase 3 study of lenabasum in diffuse cutaneous systemic sclerosis: RESOLVE-1 design and rationale

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ABSTRACT

Objective. *The multi-systemic, heterogenous 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, randomised, double-blind, placebo-controlled trial of dcSSc patients evaluating the efficacy and safety of lenabasum. Patients ≥18 years of age with dcSSc and disease duration ≤6 years were eligible. Patients could continue stable background therapy for dcSSc, including stable immunosuppressive therapies. They were randomised 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.*

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. Eligibility criteria allowed background therapy as might occur in clinical practice. This approach also facilitated timely patient enrolment. RESOLVE-1 provides a novel study design that may be used for future Phase 3 dcSSc studies to assess the holistic efficacy of therapy.*

Introduction

Systemic sclerosis (SSc) is a life-threatening autoimmune disease characterised by thickened skin resulting from vasculopathy, inflammation, and fibrosis (1-5). Patients with diffuse cutaneous systemic sclerosis (dcSSc) experience more widespread disease with the involvement of multiple organ systems including gastrointestinal, pulmonary, musculoskeletal, cardiovascular, and kidney disease (5). Patients with SSc experience markedly impaired health status compared to the general population, as well as increased mortality (6, 7). Often, SSc patients are treated with immunosuppressives. Currently, there are no approved treatments for overall disease in SSc specifically targeting both inflammation and fibrosis, key drivers of SSc pathophysiology (8, 9). Recently, nintedanib (10) 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 (11). 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 duration that often fail to include patient-reported outcomes (PROs) (12). An unmet need remains for new treatments that meaningfully improve overall disease, affecting 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 heterogenous, displaying variable disease features, and there had been no validated outcome measures to assess the overall disease (9, 13). Recent publications called for study designs of at least 12 months duration including broad patient selection criteria and both clinical and patient focused assessments (14).

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 (15). RESOLVE-1 is a Phase 3 study designed to evaluate the efficacy, safety, and tolerability of lenabasum *versus* 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) (16) score at Week 52. The study is registered at ClinicalTrials.gov: NCT03398837.

Study design

This 52-week, randomised, double-blind, placebo-controlled study enrolled patients who satisfied 2013 American College of Rheumatology (ACR) criteria for SSc (Fig. 1) (17). The study consisted of a screening phase of up to 4 weeks and a treatment phase of 52 weeks. The study included a screening visit and 11 study visits (Visits 1-11), which occurred on 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 the UK and Israel), and the Asia-Pacific region (Fig. 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 ≥18 years of age, had to fulfil 2013 ACR classification criteria for SSc (17) and had 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 ≤6 years from the time of the first non-Raynaud's symptom; if the disease duration was >3 years and ≤6 years, then the modified Rodnan skin score (mRSS) (18) had to be ≥15 (of 51 maximum score). Enrolment of patients with a disease duration >3 years and ≤6 years and mRSS ≥15 was limited to no more than one-third of the total study enrolment. At screening, a Patient Global Assessment score ^{3}3 or physician global assessment (MDGA) score ≥3 was required. Patient were required to be on stable treatment for SSc ≥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.

Patients 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 I. The eligibility of each patient had to be reviewed and approved by a medical monitor designated by the Sponsor.

Treatment

Patients were randomised in a 1:1:1 ratio to twice daily treatment with lenabasum 5 mg, lenabasum 20 mg or matching placebo, and randomisation was stratified by location (a) United States; b) Canada, Europe, Australia; or c) Asia) and by SSc disease duration (≤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 randomised 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 II). 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 a score of zero 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 (ppFVC) by 15%, confirmed after 1 month with ppFVC <80% and confirmed diagnosis of ILD on HRCT (new or established); 3) new left ventricular failure (systolic

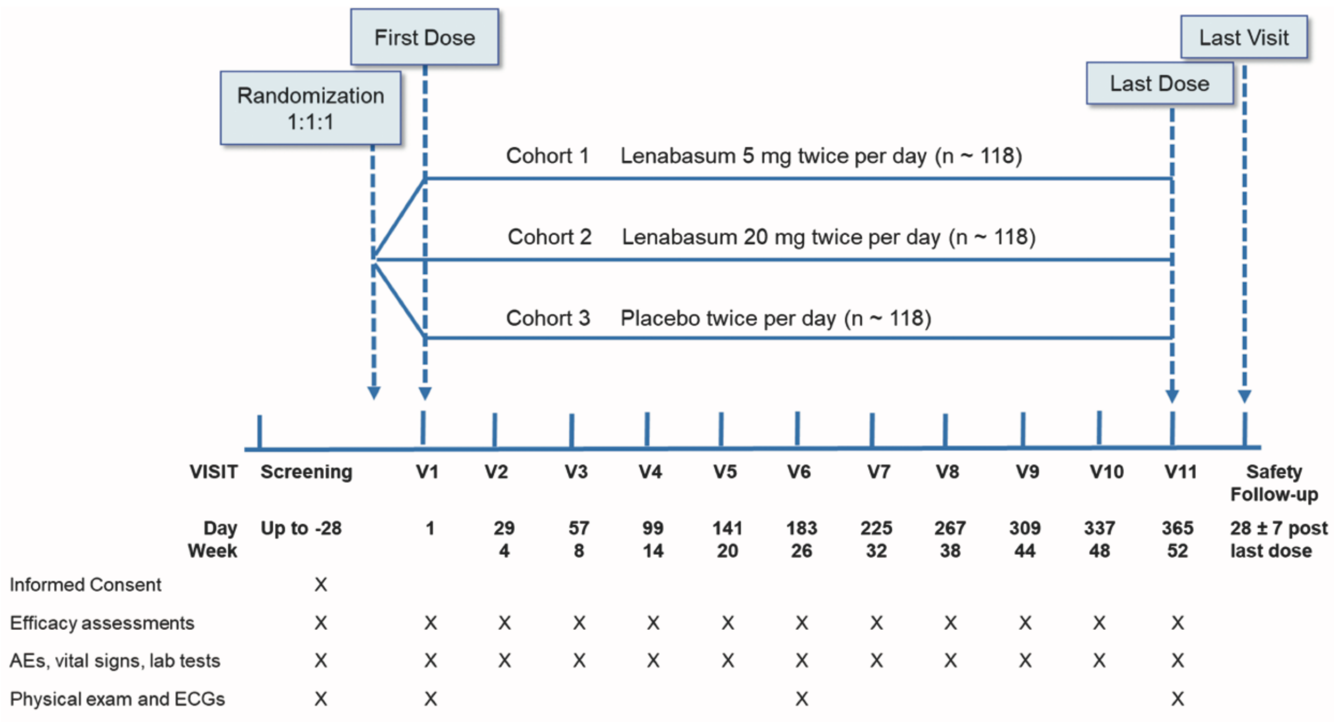

Fig. 1. Study design.

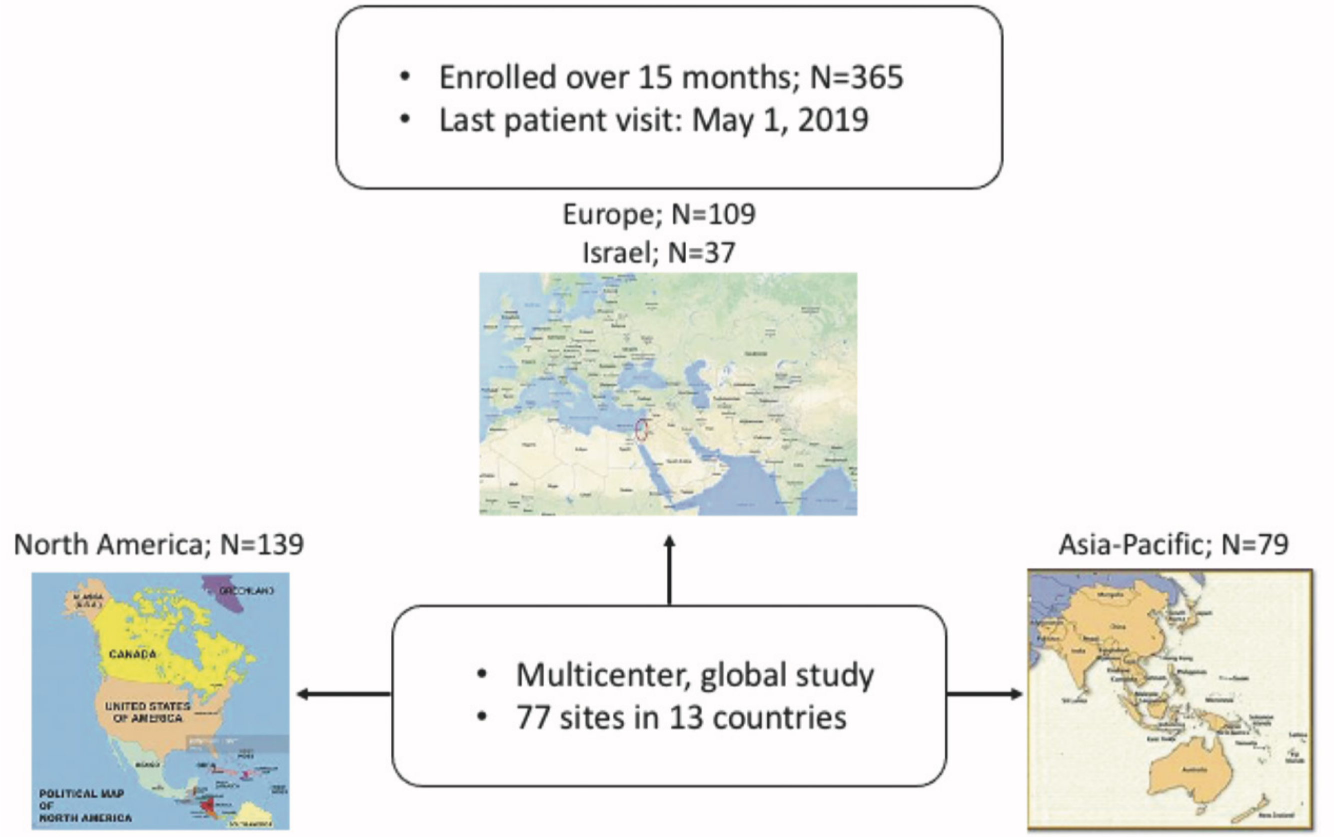

Fig. 2. Patient enrolment.

ejection fraction <45%); or 4) new pulmonary arterial hypertension on right heart catheterisation requiring treatment. For remaining patients, mean changes from baseline for the 5 CRISS components were assessed at Week 52 for the mRSS, ppFVC, Patient Global Assessment (PTGA) of Overall Health (100 mm horizontal VAS), Physician Global Assessment (MDGA) of Overall Health (100 mm horizontal VAS), and Health Assessment Questionnaire-

Table I. Inclusion/exclusion criteria.

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

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. ≥18 years of age at the time Informed Consent is signed
4. Written informed consent from the subject
5. Disease duration ≤6 years from the first non-Raynaud's symptom. If disease duration is >3 years and ≤6 years, then mRSS ≥15. Subjects with disease duration >3 years and ≤6 years and mRSS ≥15 will be limited to no more than 1/3rd of the subjects.
6. Patient Global Assessment ≥3 or MDGA ≥3
7. Stable treatment for SSc ≥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 enrolment:

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 hospitalisation 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, localised 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. Haemoglobin <9 g/dL in males and <8 g/dL in females
   c. Neutrophils <1.0 X 10^9/L
   d. Platelets <75 X 10^9/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.

Disability Index (HAQ-DI) (0-3). The CRISS is 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 (18).

Other secondary efficacy outcomes were the HAQ-DI (19); ppFVC (20); Functional Assessment of Chronic Illness Therapy (FACIT) (21); MDGA of Over-

all Health; European Quality of Live Five-domain questionnaire (EQ-5D-3L) (22); Patient-Reported Outcomes Measurement Information System-29 item (PROMIS-29) questionnaire (23); Medical Outcomes Study Short Form-36 (SF-36) (24); Scleroderma Skin Patient Reported Outcome (SSPRO) (25); The University of California at Los Angeles Scleroderma Clinical Trials (UCLA SCTC) Consortium Gastrointestinal Tract symptoms questionnaire (GIT 2.0) (26); 5-Dimension Itch Scale (5-D Itch Scale) (27); and Digital Ulcer Visual Analogue Scale (28).
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 (AEs), 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 PRO questionnaires on depression, including suicidality. They will be instructed that if they experience feelings of depression or suicidality at any time, 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) (29); Cannabis Withdrawal Scale (CWS) (30); and Addiction Research Center Inventory – Marijuana (ARCI-M) (31) questionnaire (Table II).

Statistical analysis
Sample size calculations were based on results from a Phase 2 study (15). RESOLVE-1 was expected to enrol approximately 118 patients in each of the three treatment arms, for a total of approximately 354 randomised 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 ≥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 (mRSS) was 99% with a corresponding treatment difference of -5.0, SD of 7.0.
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 ppFVC for lenabasum 20 mg twice daily *versus* placebo, and ACR CRISS, mRSS, HAQ-DI, and ppFVC for lenabasum 5 mg twice daily *versus* 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 III. 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 not missing at random.
The modified intent-to-treat (mITT) population was used for efficacy analyses and included all randomised 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 the 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 (32). Prior studies suggested a possible benefit of immunosuppressive strategies including methotrexate (33, 34), cyclophosphamide (35) and mycophenolate mofetil (36) for mRSS. In more recent trials in which the mRSS was used as the primary endpoint, treatment of patients with early dcSSc with abatacept, riociquat, and tocilizumab (37-39), did not demonstrate a statistically significant improvement comparing active drug *versus* placebo. Two trials used ACR CRISS score as a secondary (abatacept) or exploratory (tocilizumab) efficacy outcome (40, 41). In both trials, ACR CRISS 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 coef-

Table II. 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 catheterisation 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 analogue 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 Outcomes Measurement Information System-29 item (PROMIS-29) questionnaire	Measures what patients are able to do and how they feel by asking questions. These questions can focus on a mental health topic 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 Analogue 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 symptoms 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).

Table III. Study outcomes.

Primary efficacy outcome	Change from baseline to week 52
ACR CRISS	Lenabasum 20 mg BID *vs.* placebo
Secondary efficacy outcomes	
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
Tertiary efficacy outcomes	**Change from baseline to week 26**
ACR CRISS	
mRSS	
HAQ-DI	
FVC% predicted	
	Change from baseline to week 26 and 52
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	

ficient of variation 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 (42). Despite implementation of various cohort enrichment criteria (shorter disease duration, defined range of baseline mRSS, elevated C-reactive protein, and evidence of worsening skin in the previous 6 months prior to screening) to increase enrolment of patients with active progressive skin disease, the mean changes in mRSS from baseline in one year in the placebo group were -4.4 (tocilizumab) and -4.5 (abatacept). In the RISE-SSc trial ofriociguat, enrichment for progressors (worsening) of skin fibrosis using evidence-based criteria (43) was successful, but even then, the number of progressors was relatively low and the regressors still outweighed the progressors (mean change in mRSS in placebo from baseline -0.8). Another limitation of the mRSS, which is the component most weighed in the ACR CRISS score, includes inter- and intra-rater variability, although much of this variability can be minimised by study training certification for skin assessment and the use of experienced investigators (44) as was done for RESOLVE-1.

Further, the mRSS captures one clinical feature of SSc and may not adequately capture the heterogenous 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 (32). SSc has a substantial burden on the health-related quality of life (QoL) of affected patients (45). The QoL of SSc patients is substantially lower than that in the general population (7, 45), is worse than in patients with other rheumatic diseases (46), and is worse in patients with dcSSc than in patients with limited cutaneous disease (47). Work disability occurs early in the course of the disease and worsens with the severity of SSc and the patient's functional status (47). Both functional disability and anxiety have a significant impact on QoL in patients with SSc (48).

The ACR CRISS score was developed to assess the likelihood of improvement by providing a multiple domain scoring system that includes assessment of skin changes, pulmonary function, daily function, and patient and physician global assessments (16). In an early dcSSc population where there is mRSS regression and improvement, ACR CRISS score can serve as a trial endpoint that measures the likelihood of overall SSc improvement. In trials (SENCSIS and RISE-SSc) designed for the prevention of worsening for a specific disease outcome with inclusion criteria adapted accordingly, ACR CRISS would likely not be an appropriate trial endpoint (11, 39).

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 and functions. 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 overall SSc improvement. RESOLVE-1's study design, utilising ACR CRISS as the primary endpoint and multiple other SSc specific and non-specific PROs as secondary endpoints, represents another important path in prospectively evaluating new pharmacological therapies for early dcSSc.

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 (15). Through 2 years of the lenabasum Phase 2 open-label extension study, additional analyses showed: ACR CRISS score positively correlated 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] (49). Together, these data show that the ACR CRISS score broadly reflects changes from baseline in how patients feel and function in this patient population. In addition, Step 1 captures survival or disease features associated with survival as it assesses clinically meaningful cardiopulmonary-renal involvement. Since the completion of the lenabasum Phase 2 randomised, 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 enrolment 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 recognising 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 (50, 51). 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 (50).

In 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.

Take home messages

- An unmet need still exists for pharmacological therapy of SSc which 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 SSc, including allowance of background therapy with immunosuppressives.

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