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Efficacy and Safety of Lenabasum, a Cannabinoid Type 2 Receptor Agonist, in a Phase 3 Randomized Trial in Diffuse Cutaneous Systemic Sclerosis

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ABSTRACT

Introduction: Efficacy and safety of lenabasum, a cannabinoid type 2-receptor agonist, was tested in a Phase 3 study in patients with diffuse cutaneous systemic sclerosis (dcSSc).

Methods: A multi-national double-blind study was conducted in 365 dcSSc patients who were randomized and dosed 1:1:1 with lenabasum 20 mg, lenabasum 5 mg, or placebo, each twice daily and added to background treatments including immunosuppressive therapies (IST).

Results: The primary endpoint, ACR Combined Response Index in dcSSc (ACR-CRISS) score at Week 52, lenabasum 20 mg BID versus placebo, was not met, with ACR-CRISS scores of 0.888 versus 0.887, $P = 0.4972$, mixed models repeated measures (MMRM). Change in modified Rodnan Skin Score (mRSS) at Week 52 was -6.7 versus -8.1 points for lenabasum 20 mg BID versus placebo, $P = 0.1183$, MMRM. Pre-specified analyses showed higher ACR-CRISS scores, greater improvement in mRSS, and less decline in forced vital capacity in subjects on background mycophenolate and those receiving IST for ≤ 1 year duration. No deaths or excess in serious or severe adverse events related to lenabasum were observed.

Conclusions: A benefit of lenabasum in dcSSc was not demonstrated. The majority of patients were treated with background IST, and treatment with MMF in particular was associated with better outcomes. This supports the use of IST in the treatment of dcSSc, and highlights the challenge of demonstrating a treatment effect when investigational treatment is added to standard of care IST. These findings have relevance to trial design in SSc, as well as clinical care.

Analyses of Trial registration number: NCT03398837, first posted January 16, 2018

Key words: Systemic sclerosis; Autoimmune Diseases

INTRODUCTION

Patients with diffuse cutaneous SSc (dcSSc) have proximal skin thickening on the limbs or trunk and variable involvement of the lungs, heart, kidneys, gastrointestinal tract, and musculoskeletal system (1-2). The general health status of these patients is often markedly impaired, with greater chronic disease burden and increased mortality compared with the general population (3-4).

Approved treatments in North America for SSc are limited to nintedanib and tocilizumab, which are indicated for treatment of interstitial lung disease in SSc (5). Other immunosuppressants and immunomodulating drugs, including corticosteroids, are used off-label for treating overall disease or skin, musculoskeletal, or lung involvement in dcSSc (6). There remains a high unmet need for new treatments that improve overall disease, lung, and skin involvement, especially treatments that are not immunosuppressive.

The cannabinoid receptor type 2 (CB2) is a G-protein-coupled receptor which is expressed on activated immune cells, fibroblasts, and endothelial cells which when activated, reduces inflammation and fibrosis in multiple animal models of inflammatory diseases (7). Of note, a dcSSc-like illness with skin and lung fibrosis and generation of anti-topoisomerase 1 autoantibodies has been described in CB2 knock-out mice following challenge with hypochlorite to induce free radical production (8). Conversely, treatment with a CB2 agonist has been reported to alleviate dermal fibrosis in a bleomycin-induced model of skin disease in SSc (9).

Lenabasum is an oral, non-immunosuppressive CB2 agonist (10) which reduces both inflammatory and fibrotic mediators (11-14) and collagen production (15). Lenabasum also induces production of lipid mediators of the resolution phase of inflammation (11) during which inflammatory cells are cleared from tissues, wound healing is enhanced, fibrotic processes are suppressed, and endothelial cell function is restored to normal (16-20). Lenabasum reduces dermal fibrosis in a bleomycin-induced model of SSc skin disease and in mice overexpressing constitutively active transforming growth factor β . It also reduces collagen production by cultured dermal fibroblasts from SSc patients (15).

These biologic effects provided the scientific rationale for the first clinical study of efficacy and safety of lenabasum in dcSSc. In a 16-week, Phase 2 study in patients with dcSSc, lenabasum treatment provided greater improvement than placebo in the American College of Rheumatology (ACR) Combined Response Index in diffuse cutaneous

Systemic Sclerosis (CRISS) score (21), the modified Rodnan Skin Score (mRSS) (22) the Health Assessment Questionnaire-Disability Index (HAQ-DI) (23), and several other patient-reported outcomes and was safely administered and well-tolerated (24). The efficacy outcomes continued to improve over the first year of additional treatment with lenabasum in an open-label extension to this Phase 2 study and then plateaued.

Based on these encouraging Phase 2 results, efficacy, safety, and tolerability of lenabasum compared to placebo was tested in the Phase 3 RESOLVE-1 clinical trial in patients with dcSSc.

METHODS

Study design and conduct

The RESOLVE-1 clinical trial was a 52 week, double-blind, randomized, placebo-controlled study performed at 77 clinical sites in North America, Europe, Israel, and Asia-Pacific region between December 2017 and May 2020. 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. Written informed consent was obtained from all subjects before study entry. The study protocol and statistical analysis plan are provided in the **Supplemental Appendix**. An independent, unblinded Data Monitoring Committee evaluated safety data and provided periodic reports to the Sponsor (Corbus Pharmaceuticals, Inc.) with recommendations to continue, modify or terminate the study.

Study participants

Patients were eligible if they were ≥ 18 years of age, met 2013 EULAR/ACR classification criteria for SSc and had skin thickening proximal to the elbows or knees or on the trunk. 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 mRSS had to be ≥ 15 . Patients were excluded if they were medically unstable or had SSc with end-stage organ involvement (25).

Concomitant immunosuppressive therapies (IST) [Table 1] except cyclophosphamide were allowed if the IST had not started or dose increased within 8 weeks before screening, which occurred up to 4 weeks before the first dose of study drug. Chronic glucocorticoid treatment was restricted to oral prednisone \leq 10 mg per day or equivalent. Doses of concomitant IST were to remain stable during the study unless a change was in the subject's best medical interest. Concomitant use of other cannabinoids was not allowed.

Ethics approval

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.

Interventions

Patients were randomized in a 1:1:1 ratio to treatment with lenabasum 5 mg, lenabasum 20 mg or matching placebo, all administered twice daily (BID). 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 subjects were randomized at Visit 1 (baseline) from a central location. Lenabasum and placebo capsules had identical physical appearance. All subjects, the clinical site study staff, and sponsor personnel remained blinded to treatment assignment during the entire study.

Endpoints and assessments

The primary efficacy endpoint was the ACR CRISS score comparing lenabasum 20 mg and placebo cohorts at Week 52. The ACR CRISS is a weighted score consisting of 5 domains including MRSS, Health Assessment Questionnaire Index (HAQ-DI), Forced Vital Capacity, HAQ-DI, and patient and physician global assessments. Secondary efficacy endpoints were change in mRSS, HAQ-DI, and forced vital capacity (FVC), percent predicted (Hankinson et al, 2010). Gut symptoms were assessed by the UCLA-SCTC GIT2.0 questionnaire and digital ulcers by a visual analogue scale. Subject safety was assessed using treatment-emergent adverse events (TEAEs), physical

examination, vital signs, 12-lead electrocardiogram (ECG), and clinical laboratory results. Intolerance to study drug was defined as study drug discontinuation because of a probably- or definitely- related TEAE.

Statistical analysis

RESOLVE-1 was expected to enroll approximately 118 subjects in each of the three cohorts, for a total of approximately 354 randomized subjects. To detect a statistically significant difference in the primary efficacy endpoint, ACR CRISS at Week 52 comparing lenabasum 20 mg versus placebo cohorts, this sample size provided > 99% power assuming a 2-sided test at $\alpha = 0.05$ and a common standard deviation (SD) of 0.41 in both cohorts for the primary efficacy outcome, and a difference in the ACR CRISS score between lenabasum and placebo of 0.33.

For primary and secondary efficacy endpoints at Week 52, 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 ACR CRISS score (primary endpoint), change from baseline in mRSS, change from baseline in HAQ-DI, and change from baseline in FVC % predicted for lenabasum 20 mg versus placebo. The same analyses in the same order were followed for lenabasum 5 mg versus placebo.

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

Data from missing visits or ACR CRISS core items due to COVID-19 were imputed using last post-baseline observation carried forward. Missing data unrelated to COVID-19 for any of the core items were imputed using Markov Chain Monte Carlo multiple imputation technique prior to calculating the score, but missing data from missing visits were not imputed.

For ACR CRISS calculations, each imputation dataset was analyzed using MMRM on the ranked ACR CRISS score with region, disease duration (≤ 24 months vs > 24 months), baseline mycophenolate (MMF) use (Yes, No), which included mycophenolate mofetil, mycophenolate sodium, and mycophenolic acid, visit, treatment, and treatment-by-visit interaction as fixed effects and baseline mRSS as a covariate. An unstructured covariance structure shared

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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. Median, 25th quartile, 75% quartile, interquartile range, mean, and SD values were calculated for each treatment group, as well as the difference in ranks and two-sided 95% and 99% confidence intervals (CI) around the difference.

Multiple subgroup analyses were pre-specified for comparison of lenabasum 20 mg versus placebo at Week 52 for ACR CRISS score and change from baseline in each of its core items and change of FVC, absolute volume (ml). These included but were not limited to subject subgroups based on baseline MMF use (Yes, No), baseline MMF use by duration prior to Visit 1 (≤ 1 year vs. > 1 year), baseline IST use (Yes, No), baseline methotrexate use (Yes, No), and baseline systemic corticosteroids (Yes, No).

Patient and public involvement

Neither patients nor the public were involved in the design, conduct, reporting or dissemination of this research other than as trial participants with informed consent.

RESULTS

Study participants

Three-hundred seventy-five subjects were randomized over 1.5 years at 76 sites in 13 countries in North America, Europe, Israel, and Asia-Pacific, and 365 subjects received ≥ 1 dose of study drug and were the safety population (**Figure 1**). One-hundred twenty subjects were treated with lenabasum 20 mg, 120 subjects with lenabasum 5 mg, and 123 subjects with placebo and had ≥ 1 post-treatment efficacy evaluation, comprising the mITT population.

In total, 47/375 (12.5%) subjects prematurely discontinued the study after randomization but before Week 52, 10 subjects (2.7%) before dosing and 37 (9.9%) subjects after dosing (**Figure 1**). Three (0.8%) dosed subjects died, 2 in the lenabasum 20 mg cohort and 1 in the placebo cohort. Two subjects in the lenabasum 5 mg cohort received a single dose of lenabasum 5 mg and then were discontinued for non-compliance from the study at Visit 1, before any efficacy evaluations were done. Reasons for discontinuation that occurred in $\geq 2\%$ of dosed subjects were

withdrawal of consent and adverse events (AEs). Ten (8.3%) dosed subjects treated with lenabasum 20 mg, 3 (2.5%) subjects treated with lenabasum 5 mg, and 1 (0.8%) subject treated with placebo withdrew consent. Five (4.2%) dosed subjects treated with lenabasum 20 mg, 1 (0.8%) treated with lenabasum 5 mg, and 6 (4.9%) treated with placebo discontinued because of AE.

At baseline, predominantly, dosed subjects were middle-aged, female, White, and non-Hispanic (**Table 1**). Demographic information was obtained by self-identification. Dosed subjects were from North America (n = 140, 38.6%), Europe (n = 110, 30.3%), Israel (n = 35, 9.6%), and Asia-Pacific (n = 78, 21.5%). Disease characteristics were well matched at baseline among the 3 cohorts (**Table 1**). Mean disease duration was < 34 months in each cohort. Among the 3 cohorts, 42.8% – 48.3% of subjects were anti-topoisomerase 1 antibody positive and 33.6% – 40.7% were anti-RNA polymerase III antibody positive. Most subjects in each cohort (68.3% – 73.3%) had interstitial lung disease at entry, identified as history of fibrosis on computerized tomography scan of the lung, fibrosis on chest X-ray, or FVC < 80% predicted on baseline spirometry.

Baseline disease measurements were similar among the 3 cohorts (**Table 1**). The modified Rodnan Skin score indicated moderately severe skin thickening on average, with range of mean mRSS of 22.0 – 23.3. Average mean FVC, % predicted in the 3 cohorts were at the lower border of normal, ranging from 78.9% – 81.3% predicted. On average, subjects had moderate functional impairment, with mean HAQ scores ranging from 1.07 – 1.16 among the lenabasum 20 mg, lenabasum 5 mg, and placebo cohorts.

Most subjects were receiving background IST (**Table 1**). The most commonly used IST was MMF, which was used in 47.5% – 56.9% of subjects among the 3 cohorts. The next most commonly used background ISTs, with ranges across the 3 cohorts, were oral glucocorticoids (29.2% – 39.8%), methotrexate (21.9% – 28.3%), and anti-malarials (13.0% – 7.2%).

Efficacy

Treatment differences for lenabasum 20 mg BID and lenabasum 5 mg BID compared to placebo were not statistically significant for primary or secondary efficacy endpoints (**Table 2**). For the primary efficacy endpoint, ACR CRISS scores at Week 52 were 0.888 versus 0.887 (P = 0.4972) for lenabasum 20 mg vs. placebo. Few subjects met ACR CRISS Step 1 score = 0; n = 1 (0.8%) for lenabasum 20 mg BID (left ventricular failure); n = 4

(3.3%) for lenabasum 5 mg BID (3 interstitial lung disease, 1 left ventricular failure); and n = 4 (3.3%) for placebo (3 interstitial lung disease, 1 scleroderma renal crisis).

Because subjects in this study were allowed to take stable doses of background IST, additional prespecified analyses were done, including examining ACR CRISS scores and change in the core components of the ACR CRISS score in subjects receiving any background IST, MMF, MMF for ≤ 1 year and > 1 year duration, methotrexate, and oral glucocorticoids versus those not receiving these disease treatments. Analyses of ACR CRISS scores in subgroups of subjects showed that subjects receiving background IST had numerically higher ACR CRISS scores throughout the study (**Figure 2, Panel A, Supplementary Table 1**). Subjects started on MMF within 1 year of study start had better outcomes, achieving numerically higher ACR CRISS scores (ACR CRISS > 0.970 from Week 26 on) than subjects on longer duration of MMF at study start (> 1 year), or subjects who were being treated with methotrexate or oral glucocorticoids but not MMF at study start (**Figure 2, Panel B**). Among subjects not receiving IST at study start, those who were treated with lenabasum 20 mg BID had numerically higher ACR CRISS scores, compared to those treated with placebo (**Figure 2, Panel A**). Formal statistical analyses were not preformed for these comparisons as per the statistical analysis plan, as the primary endpoint of the study was not met.

Similar observations were made about differences in change in mRSS, depending on background IST treatment (**Figure 2**), with subjects treated with MMF for shorter duration at study start (≤ 1 year) having the best outcomes, achieving a reduction in mRSS of more than 11 points by Week 52. Among subjects not receiving IST at study start, those who were treated with lenabasum 20 mg BID had greater reduction in mRSS scores starting at Week 20, compared to those treated with placebo (**Figure 2, Panel C, Supplementary Table 2**).

Given that MMF is considered a first-line treatment for interstitial lung disease in dcSSc, pre-specified subgroup analyses were done to evaluate the effect of lenabasum on FVC in subjects who had received MMF for ≤ 1 year or greater than 1 year at study start. There was no benefit of lenabasum versus placebo on change in FVC for subjects who had MMF therapy started within 1 year of study start. However, in subjects who had been treated with MMF for > 1 year, subjects who received lenabasum added to background MMF had numerically less decline in FVC, % predicted and FVC, ml, starting at Week 8, than did subjects who received placebo added to background MMF (**Figure 3**).

Trial results did not suggest any effect of treatment with lenabasum on gastrointestinal or vascular outcome measures during the course of the study. Mean change (SD) from baseline in GIT2.0 total score at Week 52 for placebo treated patients was -0.024 (0.3798), and for patients treated with lenabasum 20 mg BID was -0.029 (0.3401). The mean change (SD) from baseline in digital ulcer VAS score at Week 52: for placebo treated patients was -0.8 (19.69) and for those treated with lenabasum 20 mg BID was - 0.7 (25.20).

Safety

The incidence of treatment emergent adverse events (TEAE) from Day 1 through Week 52 were similar among treatment groups (**Table 3**). Two deaths occurred during active treatment, one from myocarditis and hypoxia (lenabasum 20 mg), and one from renal crisis and acute respiratory failure (placebo), both unrelated to study drug. A lower proportion of subjects in the lenabasum cohorts experienced serious and severe TEAEs, compared to the placebo cohort. One placebo subject experienced study drug intolerance, with a TEAE that caused study drug discontinuation.

TEAEs that occurred in $\geq 10\%$ of subjects in the lenabasum 20 mg cohort are also shown in **Table 3**, with dizziness, diarrhea, and nasopharyngitis being the most frequent TEAEs in that cohort. There was no increased overall incidence of severe infectious TEAEs related to immunosuppression in the lenabasum 20 mg versus placebo cohorts, and none of these infectious TEAEs were serious: fungal skin infection (0% versus 0.8%); herpes zoster (0.8% versus 2.4%); oral herpes (2.5% versus 0%); and oral candidiasis (0.8% versus 0%).

TEAEs that potentially reflected cannabinoid class effects with an incidence $\geq 10\%$ in the lenabasum 20 mg group included (lenabasum 20 mg versus placebo cohort): dizziness (18.3% versus 4.9%); headache (17.0% versus 7.3%); diarrhea (17.5% versus 14.6%); nausea (14.2% versus 10.6%); and vomiting (12.5% versus 5.7%). There were no significant differences in weight change between groups during the course of the study.

DISCUSSION

This was the largest prospective randomized clinical trial in dcSSc to date, and the first Phase 3 study of a compound targeting the endocannabinoid system in a rheumatic disease. When undertaken, this was the first Phase 3 study in dcSSc that tested the efficacy of study drug versus placebo when added to background standard of care treatment with one or more IST. The study was global and involved multiple centers specializing in SSc care, whose investigators in general had participated in multiple prior clinical studies in dcSSc.

The primary efficacy endpoint was not met. Unexpectedly, remarkable improvement in CRISS and mRSS was observed both for lenabasum and placebo-treated subjects. Moreover, improvements in the placebo group were numerically greater than observed in active treatment groups in other recent clinical trials (26-27). This unexpected improvement in the placebo cohort reflected the effect of background IST, especially MMF when started within 1 year of study start, which was permitted in this study, unlike other recent trials.

The study was designed to accurately represent current clinical practice in patients with dcSSc (25), allowing for enrollment of patients with dcSSc who were receiving stable doses of background IST, with few restrictions. The present study was specifically designed to assess whether lenabasum offered incremental benefit over standard therapy in dcSSc, which is currently inadequate. This was also felt to be an ethical trial design for this group of patients with early, active dcSSc (28-29). Other recent studies in dcSSc excluded IST or allowed only glucocorticoids ≤ 10 mg (26-27, 30). The SENSICIS trial of nintedanib did allow use of a stable dose of background MMF or MTX for at least 6 months, and while active treatment with nintedanib afforded benefit in FVC, no demonstrable benefit was observed in other SSc-related outcomes, including mRSS. Of note, there was a large percentage of patients with limited cutaneous SSc enrolled in that study. In the SENSICIS trial, patients in whom background MMF was utilized demonstrated numerically better preservation of FVC than patients not treated with MMF (31).

The improvements seen in CRISS and mRSS in RESOLVE-1 exceeded the natural history of disease or improvements usually seen in mRSS in other dcSSc clinical trials (32). In our study, the mean improvement in mRSS in placebo treated patients was 8.1, whereas improvements in mRSS at 48 weeks in a Phase 3 trial of tocilizumab [Khanna Lancet Resp Med 2020] and in a Phase 2 trial of abatacept in early dcSSc [Khanna, A&R 2020]

were 4.41 and 4.49 respectively in placebo treated patients. In the subgroup of subjects not treated with background IST in RESOLVE-1, lenabasum treatment provided numerically greater improvement from baseline than placebo for ACR-CRISS score and mRSS. In this subgroup, the magnitude of treatment effect was comparable or larger to the effect observed with active treatment in other clinical studies in dcSSc (26-27, 30).

In pre-specified analyses, we assessed the potential treatment effect of monotherapy or combination therapies using IST (including MMF, methotrexate without MMF, and oral glucocorticoids without MMF) on ACR CRISS, mRSS, FVC% predicted and FVC, ml. Results showed the greatest numerical improvement in these outcomes in subjects on background MMF, compared to those treated with methotrexate and/or steroids. We further explored the effect of duration of MMF treatment at the time of randomization, reasoning that an effect of MMF may have diminished or plateaued after 12 or 24 months of treatment. Results suggested that MMF treatment was associated with high levels of benefit in all patients, and that MMF-associated improvements were more striking in subjects who had more recently initiated that therapy.

In patients who received MMF for > 1 year at study start, lenabasum provided numerically greater improvement in ACR-CRISS scores and mRSS and less decline in FVC than placebo, suggesting some treatment effect of lenabasum in dcSSc. In subjects with longer mean disease duration and high rates of background IST, lenabasum 20 mg BID resulted in stabilized FVC, % predicted and FVC, ml compared to worsening in the placebo group. The effect predominated in subjects who had been treated with MMF for > 1 year, but not \leq 1 year. Treatment differences were observed as early as 8 weeks.

ACR CRISS Improvements seen in this trial who were receiving background IST has implications for clinical practice. These results suggest that treatment with IST provides robust benefit. Treatment with MMF was associated with greater improvement than other IST. The relative benefit waned over time, suggesting a benefit to instituting MMF early in patients with dcSSc. Importantly however, use of MMF or other background IST was not randomized but rather was at the discretion of the investigators, so conclusions about efficacy of background IST should be approached with caution.

The improvements in clinical outcomes observed in the placebo group in the setting of background IST also has implications for clinical trial design, Although background IST may decrease effect size, background IST is

appropriate on ethical grounds and probably should be the standard clinical trial design. Treatment with MMF afforded benefit in FVC in the SENSICIS trial, and post hoc analyses of other trials have suggested benefit of MMF on mRSS. . Results of this study suggest future Phase 2/3 trial designs in dcSSc might be restricted to subjects who have received MMF for a certain minimum period of time, perhaps > 1 year; this would satisfy ethical concerns while decreasing the confounding effects of MMF. Our study also was the first to use the ACR-CRIS as the primary efficacy outcome, and demonstrated that when background IST is allowed, there is a ceiling effect which makes it difficult to distinguish a treatment benefit. Newer outcome measures in clinical trials in dcSSc, including the revised CRIS (34) will hopefully be able discriminate active therapy from placebo in the presence of background therapy in future studies.

The primary efficacy end point in this trial was not met. An unanticipated high level of improvement in the placebo cohort limited the potential to demonstrate significant differences with lenabasum treatment, if such an effect exists. This exceptionally high level of improvement was likely related to background IST and exceeded what had been observed with active treatment in many previous dcSSc studies that excluded subjects treated with significant background IST, making it difficult to discern a differential treatment response. The absence of a treatment benefit could also be due to lack of adequate efficacy of lenabasum for treatment of dcSSc, although treatment effects could be discerned in subjects not receiving background IST and in subjects who had been on MMF for > 1 year at study start. Moreover, nominal benefit observed in pre-specified subgroups of subjects treated with lenabasum versus placebo is intriguing, especially given the favorable safety profile when lenabasum was added to potent background IST This may warrant further investigation in future studies.

The primary analysis of this study does not show efficacy for lenabasum in dcSSc. While this may reflect lack of efficacy of the drug, analyses that considered the effect of background IST on outcomes did suggest a possible treatment effect, perhaps obscured by the greater than anticipated efficacy of IST in this population. Results from the pre-specified subgroup analyses will require confirmation in additional studies to determine the potential of lenabasum for treating patients with dcSSc. The safety profile of lenabasum was consistent with other studies with lenabasum and may have implications for strategies targeting the endocannabinoid system in rheumatic diseases more broadly.

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Figure 1. Subject Disposition

Figure 2: Effect of Background Immunosuppressive Therapies on ACR CRISS Scores and Change in Modified Rodnan Skin Score

IST = immunosuppressant therapy; MMF = mycophenolate; mRSS = modified Rodnan skin score. The primary analysis population is presented.

A; C. Solid square = all placebo subjects, placebo and background treatments. Week 2 n = 123, Week 52 n = 115. Solid circle = all placebo subjects, any background IST. Week 2 n = 103, Week 52 n = 98. Open circle = all placebo subjects, no background IST. Week 2 n = 20, Week 52 n = 17. Solid diamonds = lenabasum 20 mg, no background IST. Week 2 n = 13, Week 52 n = 10.

B; D. All subjects in this figure received placebo added to specified background treatments. Solid circle = background MMF. n = 61 Week 2, n = 61 Week 52. Solid square = background MMF ≤ 1 year duration. n = 39 Week 2, n = 41 Week 52. Solid triangles = background MMF > 1 year duration. n = 23 Week 2, n = 21 Week 52. Open circle = background methotrexate, no background MMF. n = 15 Week 2, n = 15 Week 52. Open square = background steroids, no background MMF. n = 17 Week 2, n = 16 Week 52.

Figure 3. Change from Baseline in Forced Vital Capacity in Subjects Receiving Mycophenolate for > 1 Year

Legend: All subjects were receiving background mycophenolate > 1 year duration at baseline. Data from the primary analysis population are presented as change from baseline, mean ± SEM.

A. Change from baseline in FVC, % predicted, mean ± SEM. Solid triangles = placebo BID. Week 4 n = 23, Week 52 n = 21. Solid diamonds = lenabasum 20 mg BID. Week 4 n = 35, Week 52 n = 31.

B. Change from baseline in FVC, ml, mean ± SEM. Solid triangles = placebo BID. Week 4 n = 23, Week 52 n = 21. Solid diamonds = lenabasum 20 mg BID. Week 4 n = 35, Week 52 n = 31.

Supplemental Figure 1. ACR CRISS Score and Its Core Components Over Time

A. ACR CRISS score. Solid square = all placebo subjects. Week 2 n = 123, Week 52 n = 115. Open circle = all lenabasum 20 mg BID subjects. Week 2 n = 119, Week 52 n = 100. Median values are presented.

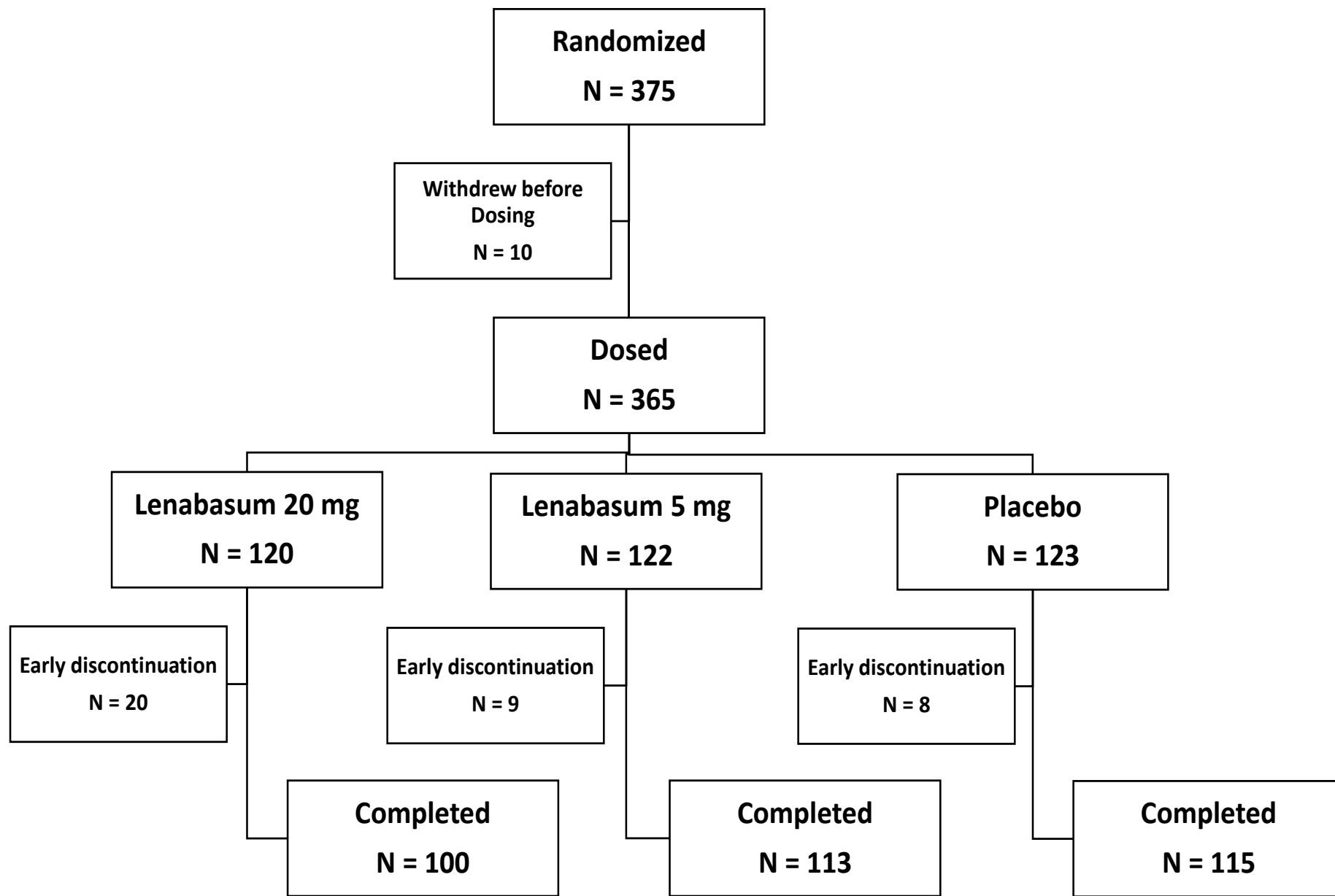
B. Change in mRSS. Solid square = all placebo subjects. Week 2 n = 123, Week 52 n = 115. Open circle = all lenabasum 20 mg BID subjects. Week 2 n = 119, Week 52 n = 100. Mean \pm SEM values are presented.

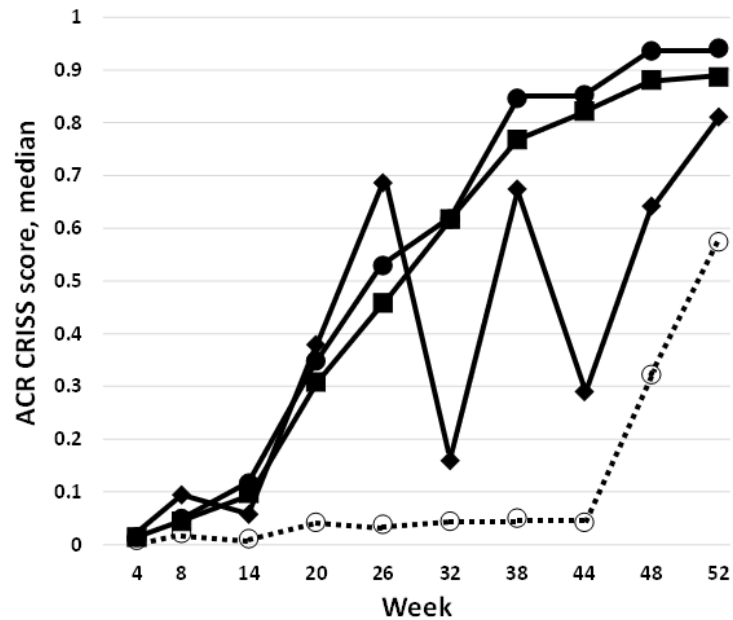
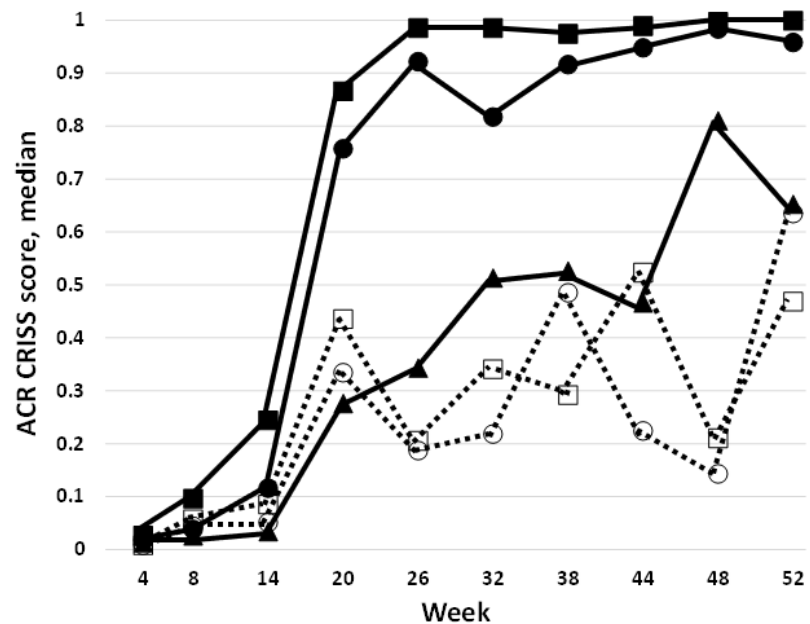
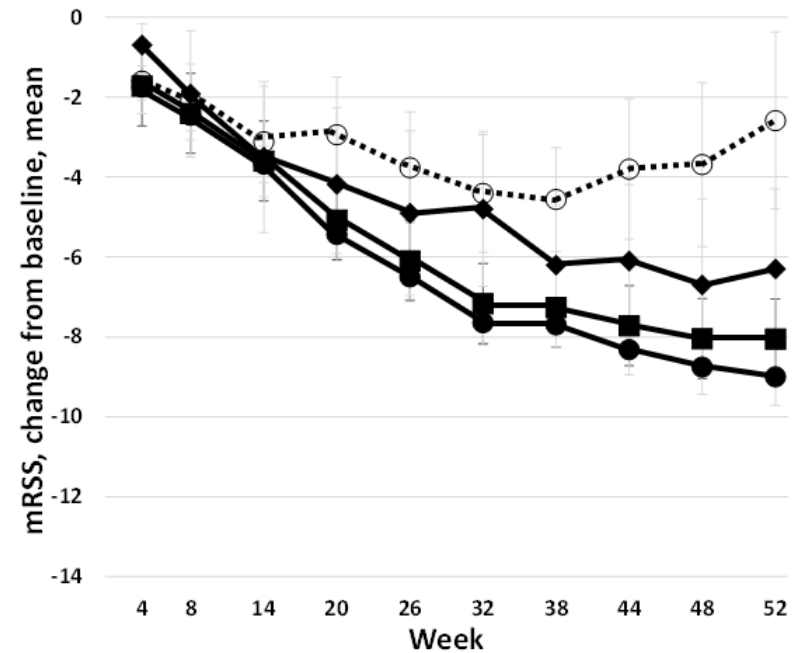
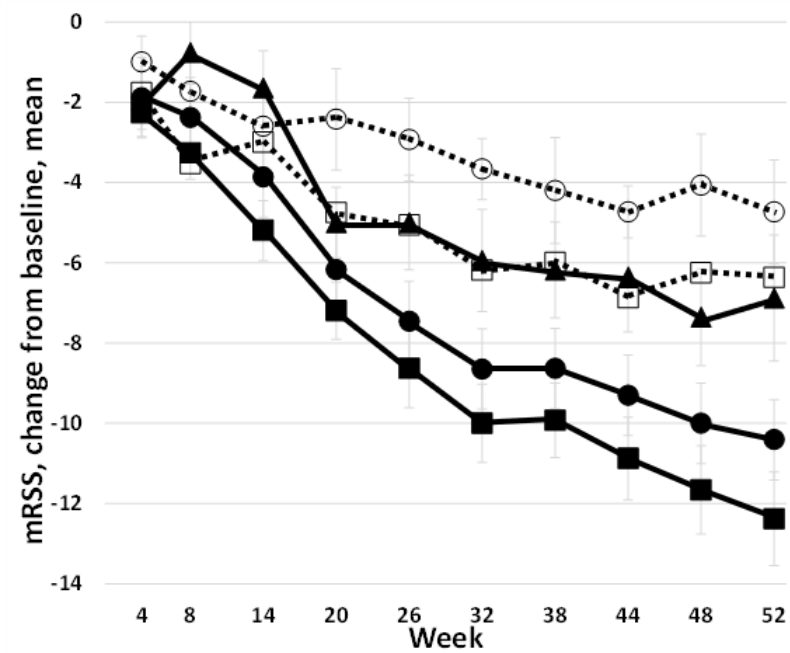
C. Change in FVC, % predicted. Solid square = all placebo subjects. Week 2 n = 118, Week 52 n = 112. Open circle = all lenabasum 20 mg BID subjects. Week 2 n = 116, Week 52 n = 99. Mean \pm SEM values are presented.

D. Change in HAQ-DI. Solid square = all placebo subjects. Week 2 n = 123, Week 52 n = 114. Open circle = all lenabasum 20 mg BID subjects. Week 2 n = 119, Week 52 n = 99. Mean \pm SEM values are presented.

E. Change in MDGA. Solid square = all placebo subjects. Week 2 n = 123, Week 52 n = 114. Open circle = all lenabasum 20 mg BID subjects. Week 2 n = 119, Week 52 n = 100. Mean \pm SEM values are presented.

F. Change in PtGA. Solid square = all placebo subjects. Week 2 n = 123, Week 52 n = 114. Open circle = all lenabasum 20 mg BID subjects. Week 2 n = 119, Week 52 n = 101. Mean \pm SEM values are presented.



A: Effect of IST on ACR CRISS Scores**B: Effect of Specific ISTs in Placebo Subjects on ACR CRISS Scores****C: Effect of IST on Change in mRSS****D: Effect of Specific ISTs in Placebo Subjects on Change in mRSS**

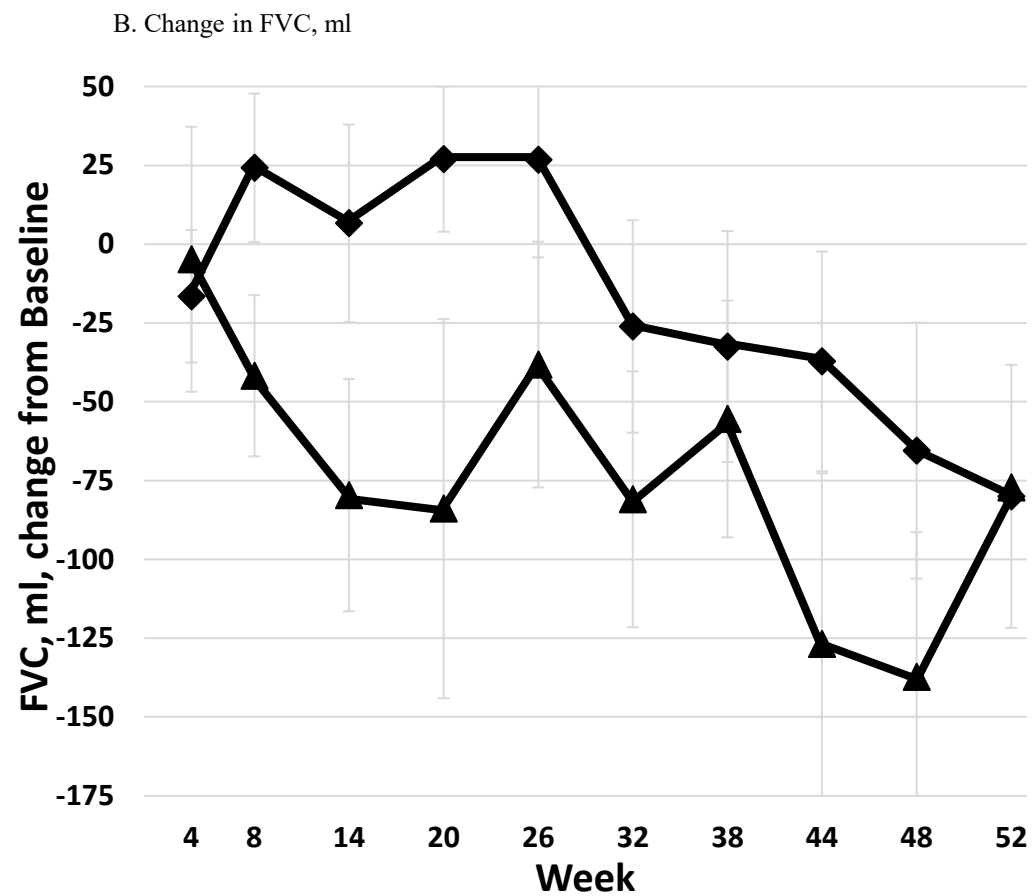
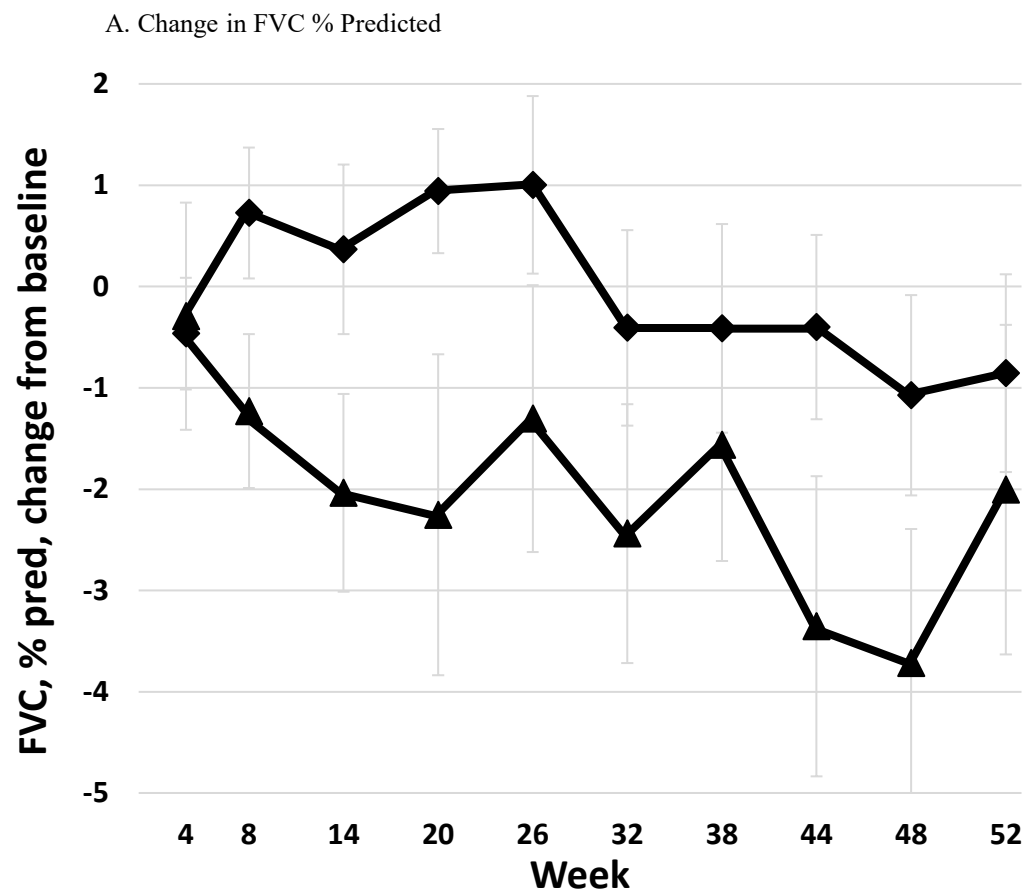


Table 1. Baseline Demographic and Disease Characteristics

Characteristic (range)	Safety Population, Results by Cohort N (%) or mean (SD)		
	Lenabasum 20 mg N = 120	Lenabasum 5 mg N = 122	Placebo N = 123
Age (\geq 18 years), years, mean (SD)	49.7 (12.87)	49.7 (13.51)	51.9 (12.38)
Female, n (%)	96 (80.0)	88 (73.3)	91 (74.0)
Race, n (%)			
White	84 (70.0)	80 (66.7)	88 (71.5)
Asian	24 (20.0)	24 (20.0)	26 (21.1)
Black or African American	6 (5.0)	8 (6.7)	4 (3.3)
Multi-racial, all other races	6 (5.0)	8 (6.7)	5 (4.1)
Hispanic, n (%)	14 (11.7)	6 (5.0)	10 (8.1)
BMI, kg/m ² mean (SD)	25.0 (5.61)	24.5 (4.96)	25.1 (5.25)
Disease duration, months, mean (SD)	33.2 (20.32)	32.6 (17.95)	30.6 (17.15)
Scl-70 autoantibody positive, ² n (%)	58 (48.3)	52 (42.8)	55 (44.7)
RNA polymerase 3 autoantibody positive, ² n (%)	48 (40.0)	41 (33.6)	50 (40.7)
Interstitial or restrictive lung disease, ³ n (%)	82 (68.3)	89 (73.0)	89 (72.4)
Modified Rodnan Skin Score (0-51), mean (SD)	22.1 (8.55)	22.0 (7.35)	23.3 (8.68)
Physician Global Assessment (0-10), mean (SD)	5.3 (1.46)	5.4 (1.58)	5.6 (1.71)
Patient Global Assessment (0-10), mean (SD)	5.0 (2.10)	4.8 (2.16)	5.0 (2.10)
Health Assessment Questionnaire - Disability Index (0-3), mean (SD)	1.12 (0.782)	1.07 (0.765)	1.16 (0.768)
Forced vital capacity, % predicted, mean (SD)	81.3 (18.83)	79.5 (16.13)	78.9 (15.23)
Immunosuppressive/modulating therapies, n (%)	107 (89.2)	94 (78.3)	103 (83.7)
Mycophenolate ⁴	66 (54.2)	58 (47.5)	70 (56.9)
Glucocorticoids	35 (29.2)	36 (29.5)	49 (39.8)
Methotrexate	34 (28.3)	28 (22.9)	27 (21.9)
Antimalarials ⁵	20 (16.7)	21 (17.2)	16 (13.0)
Biologics ⁶	13 (10.9)	8 (6.5)	10 (8.2)

Immunoglobulin	6 (4.9)	4 (3.3)	6 (4.9)
Azathioprine	5 (4.2)	4 (3.3)	3 (2.4)
Other ⁷	2 (1.6)	1 (0.8)	2 (1.6)

¹ Modified intent-to-treat population

² History of positive antibody test or positive antibody test at baseline

³ History of fibrosis on chest x-ray or CT of lungs or FVC% predicted < 80% at baseline testing

⁴ Includes mycophenolate mofetil, mycophenolic acid, and mycophenolate sodium

⁵ Includes hydroxychloroquine, hydroxychloroquine sulfate, and chloroquine phosphate

⁶ Monoclonal antibodies include tocilizumab, etanercept, and rituximab

⁷ Other IST includes ciclosporin, abatacept, apremilast, and paclitaxel.

Sources: T14.1.3, T14.3.1.2, T14.1.5.1.1.1

Table 2. American College of Rheumatology Combined Response Index in Cutaneous Systemic Sclerosis Score and Its Core Items at Week 52 by Cohort, mITT Population

Efficacy Endpoint	Lenabasum 20 mg N = 99-100	Lenabasum 5 mg N = 111-113	Placebo N = 112-115
ACR CRISS score, median (Q1, Q3) p-value vs. placebo, ranked score, MMRM	0.8880 (0.0610, 0.9970) 0.4972	0.8270 (0.0700, 0.9880) 0.3486	0.8870 (0.0710, 0.990)
Change in mRSS, mean (SD) p-value vs. placebo, MMRM	-6.7 (6.59) 0.1183	-7.1 (6.24) 0.5036	-8.1 (7.72)
Change in FVC % predicted, mean (SD) p-value vs. placebo, MMRM	-1.6 (6.9) 0.539	-2.2 (6.2) 0.516	-1.0 (8.7)
Change in HAQ-DI, mean (SD) p-value vs. placebo, MMRM	-0.13 (0.44) 0.745	-0.06 (0.39) 0.322	-0.13 (0.47)
Change in MDGA, mean (SD) p-value vs. placebo, MMRM	-1.7 (1.7) 0.649	-1.9 (1.9) 0.406	-1.8 (1.7)
Change in PtGA, mean (SD) p-value vs. placebo, MMRM	-1.4 (2.7) 0.598	-0.3 (2.4) 0.015	-1.1 (2.2)

ACR = American College of Rheumatology; CRISS = Combines Response Index in diffuse cutaneous Systemic Sclerosis; FVC = forced vital capacity; HAQ-DI = Health Assessment Questionnaire-Disability Index; MDGA = Physician Global Assessment of Health related to dcSSc; mITT = modified intent-to-treat; MMRM = mixed models for repeated measures; mRSS = modified Rodnan Skin Score; PtGA = Patient Global Assessment of Health related to dcSSc; SD = standard deviation

Sources: T14.2.1.1, T14.2.2.1

Table 3. Treatment-Emergent Adverse Events by Safety Population Cohort

Treatment-Emergent Adverse Events (TEAE)	Number (%) of Subjects, by Treatment Cohort		
	Lenabasum 20 mg N = 120	Lenabasum 5 mg N = 122	Placebo N = 123
Any TEAE	110 (91.7)	110 (90.2)	106 (86.2)
Any TEAE Leading to Death	1 (0.8)	0	1 (0.8)
Any Serious TEAE	11 (9.2)	10 (8.2)	18 (14.6)
Any Severe TEAE	7 (5.8)	4 (3.3)	16 (13.0)
TEAE Leading to Drug Discontinuation	5 (4.2)	2 (1.6)	7 (5.7)
TEAE probably-or definitely-related to study drug and leading to study drug withdrawal	0	0	1 (0.8)
Individual TEAEs in $\geq 10\%$ subjects in the lenabasum 20 mg cohort			
Dizziness	22 (18.3)	11 (9.0)	6 (4.9)
Diarrhea	21 (17.5)	16 (13.1)	18 (14.6)
Nasopharyngitis	18 (15.0)	25 (20.5)	10 (8.1)
Upper respiratory tract infection	17 (14.2)	18 (14.8)	20 (16.3)
Nausea	17 (14.2)	5 (4.1)	13 (10.6)
Headache	17 (14.2)	14 (11.5)	9 (7.3)
Scleroderma-associated digital ulcer	15 (12.5)	23 (18.9)	19 (15.4)
Vomiting	15 (12.5)	7 (5.7)	7 (5.7)
Urinary tract infection	13 (10.8)	10 (8.2)	6 (4.9)
Arthralgia	12 (10.0)	15 (12.3)	20 (16.3)
Pruritus	12 (10.0)	10 (8.2)	9 (7.3)

Source: T 14.3.1.1.1, T14.3.1.2.1, Table 14.3.1.3.1