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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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Objective. This phase 3 study was undertaken to investigate the efficacy and safety of lenabasum, a cannabinoid type 2 receptor agonist, in patients with diffuse cutaneous systemic sclerosis (dcSSc).

Methods. A multinational 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 end point, the American College of Rheumatology combined response index in dcSSc (CRISS) at week 52 for lenabasum 20 mg twice a day versus placebo, was not met, with CRISS score of 0.888 versus 0.887 (P = 0.4972, using mixed models repeated measures [MMRM]). The change in the modified Rodnan skin thickness score (MRSS) at week 52 for lenabasum 20 mg twice a day versus placebo was −6.7 versus −8.1 (P = 0.1183, using MMRM). Prespecified analyses showed higher CRISS scores, greater improvement in MRSS, and lower decline in forced vital capacity in patients on background mycophenolate and those who were taking IST for ≤1 year. No deaths or excess in serious or severe adverse events related to lenabasum were observed.

Conclusion. A benefit of lenabasum in dcSSc was not demonstrated. Most patients were treated with background IST, and treatment with mycophenolate mofetil in particular was associated with better outcomes. These findings support the use of IST in the treatment of dcSSc and highlight 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 to clinical care.

INTRODUCTION

Patients with diffuse cutaneous systemic sclerosis (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

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and immunomodulating drugs, including glucocorticoids, are for off-label use in treatment of overall disease or skin, musculoskeletal, or lung involvement in dcSSc (6). A high unmet need remains for new treatments that improve overall disease and lung and skin involvement, especially treatments that are not immunosuppressive.

The cannabinoid receptor type 2 (CB_2) is a G protein–coupled receptor that 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 I autoantibodies has been described in CB_2 knockout mice following challenge with hypochlorite to induce free radical production (8). Conversely, treatment with a CB_2 agonist has been reported to alleviate dermal fibrosis in a bleomycin-induced model of skin disease in SSc (9).

Lenabasum is an oral, nonimmunosuppressive CB_2 agonist (10) that 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. Lenabasum 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 the 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) provisional combined response index in dcSSc (CRISS) for clinical trials (21), the modified Rodnan skin thickness 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 the phase 2 study and then plateaued.

With these encouraging phase 2 results, the efficacy, safety, and tolerability of lenabasum compared to placebo were tested in the phase 3 RESOLVE-1 clinical trial in patients with dcSSc.

PATIENTS AND 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. Details of the study protocol and statistical analysis plan can be viewed at ClinicalTrials.gov (identifier: NCT03398837). 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 subjects. Patients were eligible if they were ≥18 years of age, met the 2013 ACR/EULAR classification criteria for SSc (25), 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 phenomenon 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 (26).

Concomitant immunosuppressive therapies (ISTs) (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 ≤10 mg/day or equivalent. Doses of concomitant ISTs were to remain stable during the study unless a change was in the

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The investigators of the RESOLVE-1 Study Group are shown in Appendix A.

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Table 1. Baseline demographic and disease characteristics of subjects (aged ≥18 years) with diffuse cutaneous systemic sclerosis in the phase 3 RESOLVE-1 clinical trial*

Characteristic	Safety population (mITT population)		
	Lenabasum 20 mg (n = 120)	Lenabasum 5 mg (n = 122)	Placebo (n = 123)
Age, mean ± SD years	49.7 ± 12.87	49.7 ± 13.51	51.9 ± 12.38
Female	96 (80.0)	88 (73.3)	91 (74.0)
Race			
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)
Multiracial, all other races	6 (5.0)	8 (6.7)	5 (4.1)
Hispanic	14 (11.7)	6 (5.0)	10 (8.1)
BMI, mean ± SD kg/m^2	25.0 ± 5.61	24.5 ± 4.96	25.1 ± 5.25
Disease duration, mean ± SD months	33.2 ± 20.32	32.6 ± 17.95	30.6 ± 17.15
Scl-70 autoantibody positive†	58 (48.3)	52 (42.8)	55 (44.7)
RNA polymerase 3 autoantibody positive†	48 (40.0)	41 (33.6)	50 (40.7)
Interstitial or restrictive lung disease‡	82 (68.3)	89 (73.0)	89 (72.4)
MRSS (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
HAQ DI (0–3), mean ± SD	1.12 ± 0.782	1.07 ± 0.765	1.16 ± 0.768
FVC%, mean ± SD	81.3 ± 18.83	79.5 ± 16.13	78.9 ± 15.23
Immunosuppressive/modulating therapies	107 (89.2)	94 (78.3)	103 (83.7)
Mycophenolate§	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¶	20 (16.7)	21 (17.2)	16 (13.0)
Biologics#	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**	2 (1.6)	1 (0.8)	2 (1.6)

* Except where otherwise indicated, values are the number (%) of subjects. mITT = modified intent-to-treat; BMI = body mass index; MRSS = modified Rodnan skin score; FVC% = forced vital capacity, percent predicted; HAQ DI = Health Assessment Questionnaire Disability Index.
† History of positive antibody test or positive antibody test at baseline.
‡ History of fibrosis on chest radiography or computed tomography of lungs or FVC% <80% at baseline.
§ Includes mycophenolate mofetil, mycophenolic acid, and mycophenolate sodium.
¶ Includes hydroxychloroquine, hydroxychloroquine sulfate, and chloroquine phosphate.
# Monoclonal antibodies include tocilizumab, etanercept, and rituximab.
** Other immunosuppressive therapies include cyclosporin, abatacept, apremilast, and paclitaxel.

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 Institutional Review Boards/Ethics Committees at 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. Randomization was stratified by locations in 1) United States; 2) Canada, Europe, and Australia; or 3) Asia and by SSc disease duration (≤24 months or >24 months). An interactive web-based response system (IWRS) was used to assign a unique identification number to each subject 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.

End points and assessments. The primary efficacy end point 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 (FVC), and patient and physician global assessments. Secondary efficacy end points were change in MRSS, HAQ DI, and FVC percent predicted (FVC%). Gut symptoms were assessed by the University of California Los Angeles Scleroderma Clinical Trial Consortium Gastrointestinal Tract 2.0 (UCLA-SCTC GIT 2.0) questionnaire, and digital ulcers were assessed by a visual analog

scale. To assess patient safety, we analyzed treatment-emergent adverse events (TEAEs) and physical examination, vital sign, 12-lead electrocardiogram, and clinical laboratory results. Intolerance to study drug was defined as study drug discontinuation because of probably or definitely related TEAEs.

Statistical analyses. RESOLVE-1 was expected to enroll approximately 118 subjects in each of the 3 cohorts, for a total of ~354 randomized subjects. To detect a statistically significant difference in the primary efficacy end point (ACR CRISS at week 52 comparing lenabasum 20 mg versus placebo cohorts), this sample size provided >99% power assuming a 2-sided test with significance level 0.05, a common SD of 0.41 in both cohorts for the primary efficacy outcome, and a difference in the ACR CRISS score for lenabasum versus placebo of 0.33.

For primary and secondary efficacy end points 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 end point), change from baseline in MRSS, change from baseline in HAQ DI, and change from baseline in FVC% for lenabasum 20 mg versus placebo. The same analyses in the same order were followed for lenabasum 5 mg versus placebo.

The modified intent-to-treat population was used for efficacy analyses and included all randomized subjects who received at least 1 dose of study drug and had at least 1 postbaseline 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 postbaseline 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 calculation of the score, but missing data from missing visits were not imputed.

For ACR CRISS calculations, each imputation data set was analyzed using mixed models repeated measures on the ranked ACR CRISS score with region, disease duration (≤24 months versus >24 months), baseline mycophenolate mofetil (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 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 and 75th percentile interquartile range, mean, and SD values were calculated for each treatment group, as well as the difference in ranks and 2-sided 95% and 99% confidence intervals (CI) around the difference.

Multiple subgroup analyses were prespecified 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 versus no), baseline MMF use by duration before visit 1 (≤1 year versus >1 year), baseline IST use (yes versus no), baseline methotrexate use (yes versus no), and baseline systemic glucocorticoid use (yes versus no).

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

RESULTS

Study subject treatment groups and characteristics. Over 1.5 years, 375 subjects were randomized at 76 sites in 13 countries in North America, Europe, Israel, and Asia-Pacific; 365 subjects received ≥1 dose of study drug and were the safety population (Figure 1). In total, 120 subjects were treated with lenabasum 20 mg, 120 subjects were treated with lenabasum 5 mg, and 123 subjects were treated with placebo and had ≥1 post-treatment efficacy evaluation, comprising the modified intent-to-treat population.

In total, 47 of 375 subjects (12.5%) prematurely discontinued the study after randomization but before week 52, with 10 subjects (2.7%) before dosing and 37 subjects (9.9%) after dosing (Figure 1). Three dosed subjects (0.8%) 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 from the study for noncompliance at visit 1, before any efficacy evaluations were conducted. Reasons for discontinuation that occurred in ≥2% of dosed subjects were withdrawal of consent and adverse events. Ten of 120 subjects (8.3%) treated with lenabasum 20 mg, 3 of 120 subjects (2.5%) treated with lenabasum 5 mg, and 1 of 123 subjects (0.8%) treated with placebo withdrew consent. Five of 120 subjects (4.2%) treated with lenabasum 20 mg, 1 of 120 subjects (0.8%) treated with lenabasum 5 mg, and 6 of 123 subjects (4.9%) treated with placebo discontinued because of adverse events.

At baseline, dosed subjects were predominantly middle-aged, female, White, and non-Hispanic (Table 1). Demographic information was self-reported by subjects. 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% to 48.3% of subjects were anti–topoisomerase I antibody positive and 33.6% to 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 by history of fibrosis

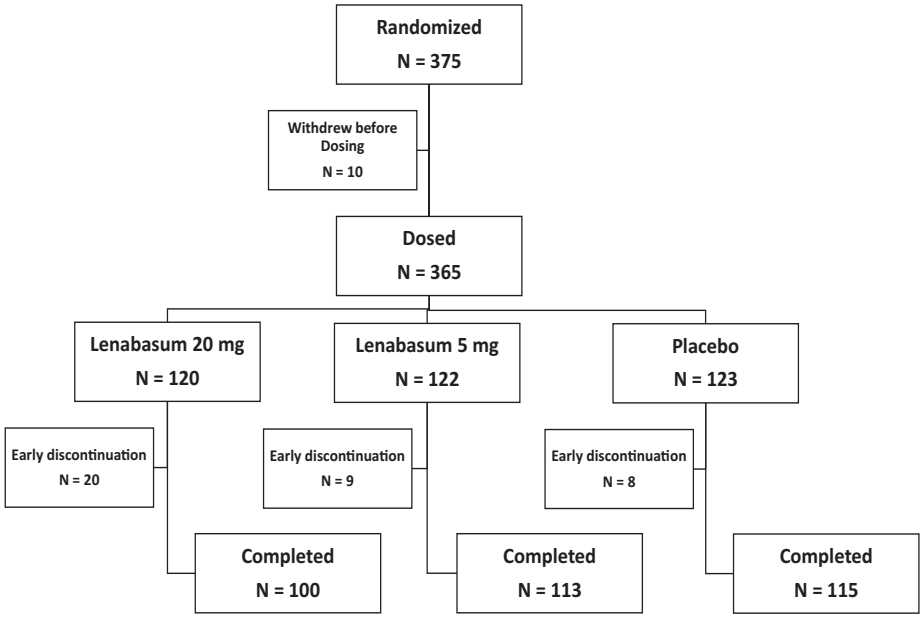

Figure 1. Disposition of subjects in the phase 3 RESOLVE-1 clinical trial of patients with diffuse cutaneous systemic sclerosis.

on computed tomography of the lung, fibrosis on chest radiography, or FVC% <80% on baseline spirometry.

Baseline disease measurements were similar among the 3 cohorts (Table 1). The MRSS indicated moderately severe skin thickening on average, with range of mean MRSS from 22.0 to 23.3. Average mean FVC% results in the 3 cohorts were at the lower border of normal, ranging from 78.9% to 81.3%. On average, subjects had moderate functional impairment, with mean HAQ DI scores ranging from 1.07 to 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 taken by 47.5%–56.9% of subjects among the 3 cohorts. The next most common background ISTs taken by subject across the 3 cohorts were oral glucocorticoids (29.2%–39.8%), methotrexate (21.9%–28.3%), and antimalarials (7.2%–13.0%).

Efficacy. Treatment differences for lenabasum 20 mg twice a day and lenabasum 5 mg twice a day compared to placebo were not statistically significant for primary or secondary efficacy end points (Table 2). For the primary efficacy end point, ACR CRISS scores at week 52 were 0.888 versus 0.887 ($P = 0.4972$) for lenabasum 20 mg versus placebo. Few subjects met ACR CRISS step 1 score of zero (n = 1 [0.8%] for lenabasum 20 mg twice a day [left ventricular failure], n = 4 [3.3%] for lenabasum 5 mg twice a day [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, included examination of 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 taking background IST had numerically higher ACR CRISS scores throughout the study (Figure 2A, Supplementary Table 1, available on the *Arthritis & Rheumatology* website at https://onlinelibrary.wiley.com/doi/10.1002/art.42510). Subjects who started taking 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 who were taking MMF for a longer duration at study start (>1 year), or subjects who were receiving methotrexate or oral glucocorticoids but not MMF at study start (Figure 2B). Among subjects not receiving IST at study start, those who were treated with lenabasum 20 mg twice a day had numerically higher ACR CRISS scores, compared to those treated with placebo (Figure 2A). Formal statistical analyses were not performed for these comparisons as per the statistical analysis plan, as the primary end point of the study was not met. Other examinations of ACR CRISS and its core components over time are shown in Supplementary Figure 1, available on the *Arthritis & Rheumatology* website at https://onlinelibrary.wiley.com/doi/10.1002/art.42510.

Similar observations were made about differences in change in MRSS, depending on background IST treatment (Figure 2), with subjects taking MMF for shorter durations at study start (≤1 year) having the best outcomes and achieving a reduction in MRSS of more than 11 points by week 52. Among subjects who were not taking IST at study start, those who were treated with lenabasum 20 mg twice a day had greater reduction in MRSS

Table 2. ACR CRISS score and its core items at week 52 by cohort, mITT population, phase 3 RESOLVE-1 clinical trial*

Efficacy end point	Lenabasum 20 mg (n = 99–100)	Lenabasum 5 mg (n = 111–113)	Placebo (n = 112–115)
ACR CRISS score, median (IQR)	0.8880 (0.0610–0.9970)	0.8270 (0.0700–0.9880)	0.8870 (0.0710–0.990)
P versus placebo, ranked score, MMRM	0.4972	0.3486	
Change in MRSS, mean ± SD	−6.7 ± 6.59	−7.1 ± 6.24	−8.1 ± 7.72
P versus placebo, MMRM	0.1183	0.5036	–
Change in FVC%, mean ± SD	−1.6 ± 6.9	−2.2 ± 6.2	−1.0 ± 8.7
P versus placebo, MMRM	0.539	0.516	–
Change in HAQ DI, mean ± SD	−0.13 ± 0.44	−0.06 ± 0.39	−0.13 ± 0.47
P versus placebo, MMRM	0.745	0.322	–
Change in MDGA, mean ± SD	−1.7 ± 1.7	−1.9 ± 1.9	−1.8 ± 1.7
P versus placebo, MMRM	0.649	0.406	–
Change in PtGA, mean ± SD	−1.4 ± 2.7	−0.3 ± 2.4	−1.1 ± 2.2
P versus placebo, MMRM	0.598	0.015	–

* ACR = American College of Rheumatology; CRISS = combined response index in diffuse cutaneous systemic sclerosis (dcSSc); IQR = interquartile range; MMRM = mixed models for repeated measures; MDGA = physician global assessment of health related to dcSSc; PtGA = patient global assessment of health related to dcSSc (see Table 1 for other definitions).

starting at week 20 compared to those treated with placebo (Figure 2C, Supplementary Table 2, available on the *Arthritis & Rheumatology* website at https://onlinelibrary.wiley.com/doi/10.1002/art.42510).

Given that MMF is considered a first-line treatment for interstitial lung disease in dcSSc, prespecified subgroup analyses were done to evaluate the effects of lenabasum on FVC in subjects who had received MMF for ≤1 year or >1 year at study start. There was no benefit of lenabasum versus placebo on change in FVC in subjects who were taking MMF therapy within 1 year of study start. However, in subjects who were taking MMF for >1 year, subjects who received lenabasum added to background MMF had numerically less decline in FVC% 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. The mean ± SD change from baseline in GIT 2.0 total score at week 52 was –0.024 ± 0.3798 for patients treated with placebo and –0.029 ± 0.3401 for patients treated with lenabasum 20 mg twice a day. The mean ± SD change from baseline in digital ulcer visual analog scale at week 52 was –0.8 ± 19.69 for patients treated with placebo and –0.7 ± 25.20 for patients treated with lenabasum 20 mg twice a day.

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

TEAEs that occurred in ≥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 ≥10% in the lenabasum 20 mg group included, for the 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 1 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 end point was not met. Unexpectedly, remarkable improvements in ACR CRISS and MRSS were observed for both lenabasum-treated and placebo-treated subjects. Moreover, improvements in the placebo group were numerically greater than observed in active treatment groups in other recent clinical trials (27,28). This unexpected improvement in the placebo cohort reflected the effect of background IST, especially

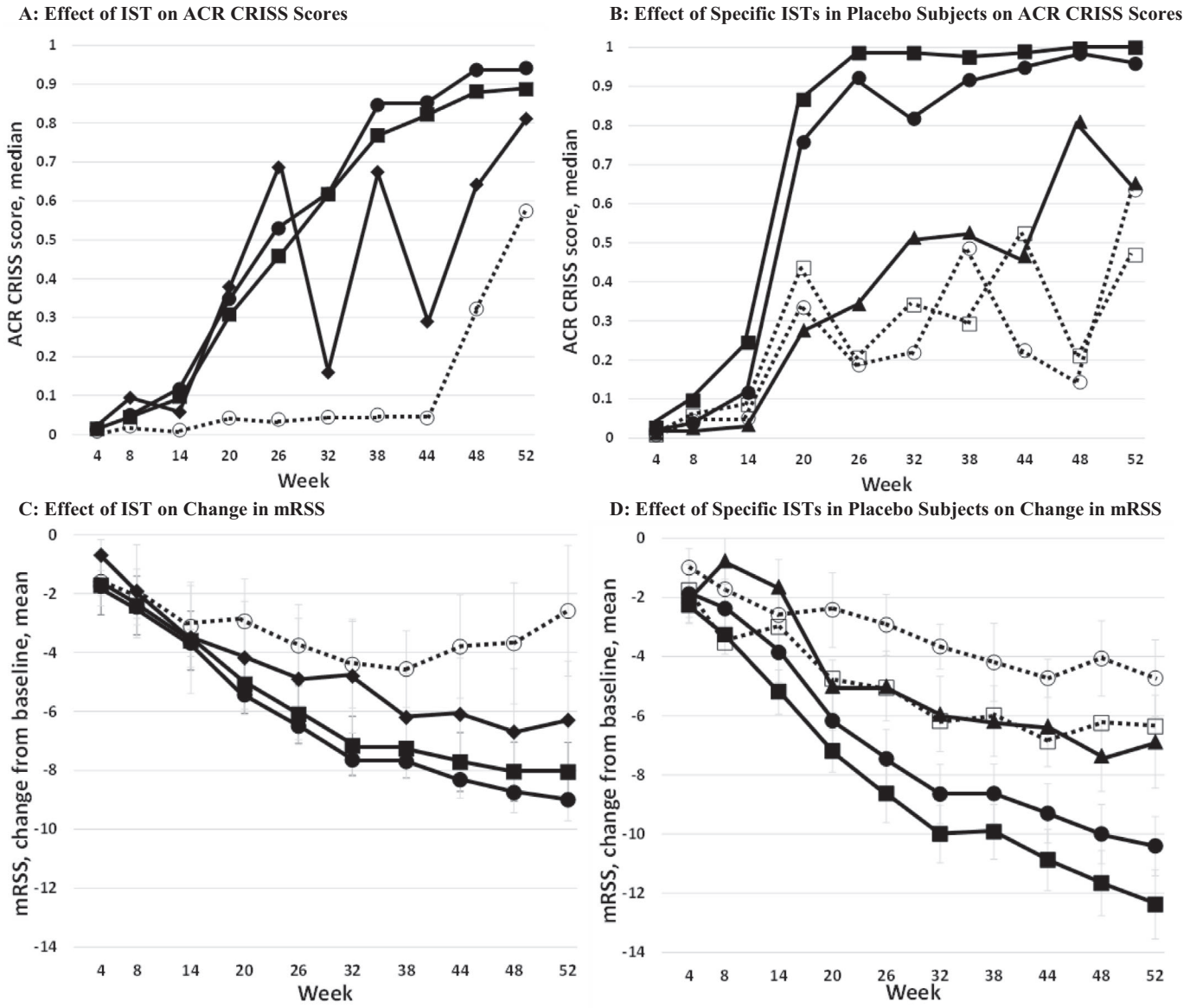

Figure 2. Effect of background immunosuppressive therapies (ISTs) on American College of Rheumatology (ACR) combined response index in diffuse cutaneous systemic sclerosis (CRISS) scores and change in modified Rodnan skin score (MRSS) in the primary analysis population. **A** and **C**, Effect of IST on ACR CRISS (**A**) and MRSS (**C**) in placebo subjects with placebo and background treatments (■; n = 123 at week 2, n = 115 at week 52), in all placebo subjects with any background IST (●; n = 103 at week 2, n = 98 at week 52), in all placebo subjects with no background IST (○; n = 20 at week 2, n = 17 at week 52), and in subjects treated with lenabasum 20 mg and no background IST (◆; n = 13 at week 2, n = 10 at week 52). **B** and **D,** effect of specific ISTs on ACR CRISS (**B**) and MRSS (**D**) in subjects who received placebo added to the following specified background treatments: mycophenolate mofetil (MMF) (●; n = 61 at week 2, n = 61 at week 52), MMF ≤1 year duration (■; n = 39 at week 2, n = 41 at week 52), MMF >1 year duration (▲; n = 23 at week 2, n = 21 at week 52), methotrexate, no MMF (○; n = 15 at week 2, n = 15 at week 52), and steroids, no MMF (□; n = 17 at week 2, n = 16 at week 52).

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 (26), 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 trial design was also felt to be an ethical design for this group of patients with early, active dcSSc (29,30). Other recent studies in dcSSc excluded IST or allowed only glucocorticoids ≤10 mg (27,28,31). The SENSCIS trial of nintedanib did allow use of a stable dose of background MMF or methotrexate for at least 6 months, and, although active treatment with nintedanib afforded benefit in FVC, no demonstrable benefit was observed in other SSc-related outcomes, including MRSS. Of

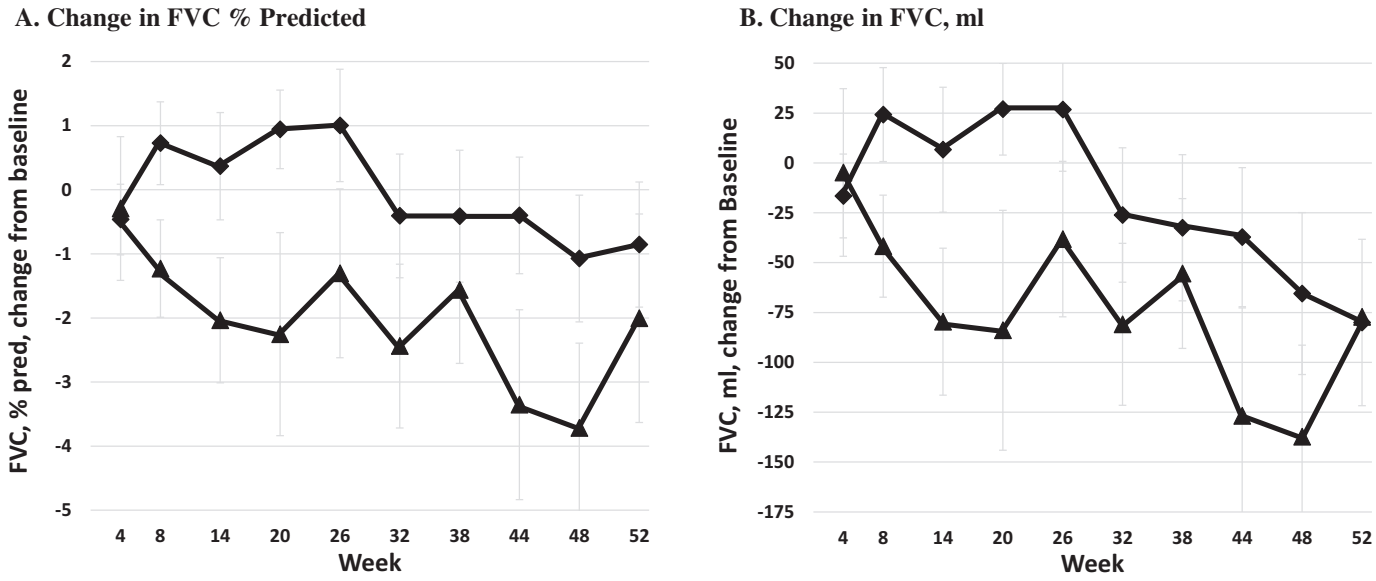

Figure 3. Change from baseline in forced vital capacity percent predicted (FVC%) in subjects in the primary analysis population receiving mycophenolate for >1 year at baseline. **A,** Mean ± SEM change from baseline in FVC% in subjects who received placebo twice a day (▲; n = 23 at week 4, n = 21 at week 52) or lenabasum 20 mg twice a day (◆; n = 35 at week 4, n = 31 at week 52). **B,** Mean ± SEM change from baseline in FVC (ml) in subjects who received placebo twice a day (▲; n = 23 at week 4, n = 21 at week 52) or lenabasum 20 mg twice a day (◆; n = 35 at week 4, n = 31 at week 52).

note, there was a large percentage of patients with limited cutaneous SSc enrolled in that study. In the SENSCIS trial, patients who had background MMF treatment demonstrated numerically better preservation of FVC than patients not treated with MMF (32).

The improvements seen in ACR CRISS and MRSS in RESOLVE-1 exceeded the natural history of disease or improvements usually seen in MRSS in other dcSSc clinical trials (33). 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 (28) and in a phase 2 trial of abatacept in early dcSSc (27) 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

Table 3. Treatment-emergent adverse event by safety population cohort, phase 3 RESOLVE-1 clinical trial*

	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 ≥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)

* Values are the number (%) of subjects. TEAE = treatment-emergent adverse event.

placebo for ACR CRISS score and MRSS. In this subgroup, the magnitude of treatment effect was comparable to or larger than the effect observed with active treatment in other clinical studies in dcSSc (27,28,31,34).

In prespecified 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%, and FVC (ml). The greatest numerical improvements in these outcomes were shown 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 twice a day resulted in stabilized FVC% 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 ≤1 year. Treatment differences were observed as early as 8 weeks.

The finding of improvements in ACR CRISS in this trial in subjects 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; thus, conclusions about efficacy of background IST should be approached with caution.

The finding of 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 SENSCIS 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 ACR CRISS as the primary efficacy outcome and demonstrated that, when background IST is allowed, there is a ceiling effect that makes it difficult to distinguish a treatment benefit. Newer outcome measures in clinical trials in dcSSc, including the revised CRISS (35), may be able to 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, the nominal benefit observed in prespecified 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 prespecified 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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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Spiera had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Spiera, Kuwana, Khanna, Constantine, Dgetluck, Dinh, Bloom, Furst, White, Denton.

Acquisition of data. Spiera, Kuwana, Khanna, Hummers, Frech, Stevens, Matucci-Cerinic, Kafaja, Distler, Jun, Levy, Leszczyński, Gordon, Steen, Lee, Jankowski, Litinsky, Chung, Hsu, Mayes, Sandorfi, Simms, Finzel, de Vries-Bouwstra.

Analysis and interpretation of data. Spiera, Kuwana, Khannam, Constantine, Dgetluck, Dinh, Bloom, Furst, White, Denton.

ROLE OF THE STUDY SPONSOR

Corbus Pharmaceuticals Inc. was involved in the study design and in the collection, analysis, and interpretation of the data, the writing of the manuscript, and the decision to submit the manuscript for publication. Publication of this article was contingent upon approval by Corbus Pharmaceuticals Inc.

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APPENDIX A:

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