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A 24-Week, Phase IIa, Randomized, Double-Blind, Placebo-Controlled Study of Ziritaxestat in Early Diffuse Cutaneous Systemic Sclerosis

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Objective. We undertook this study to explore the efficacy, safety, and tolerability of ziritaxestat, a selective autotaxin inhibitor, in patients with early diffuse cutaneous systemic sclerosis (dcSSc).

Methods. NOVESA was a 24-week, multicenter, phase IIa, double-blind, placebo-controlled study. Adults with dcSSc were randomized to oral ziritaxestat 600 mg once daily or matching placebo. The primary efficacy end point was change from baseline in modified Rodnan skin score (MRSS) at week 24. Secondary end points assessed safety and tolerability; other end points included assessment of skin and blood biomarkers. Patients in NOVESA could enter a 104-week open-label extension (OLE).

Results. Patients were randomized to ziritaxestat (n = 21) or placebo (n = 12). Reduction in MRSS was significantly greater in the ziritaxestat group versus the placebo group (–8.9 versus –6.0 units, respectively; $P = 0.0411$). Placebo patients switching to ziritaxestat in the OLE showed similar reductions in MRSS to those observed for ziritaxestat patients in the parent study. Ziritaxestat was well tolerated; the most frequent treatment-related treatment-emergent adverse events were headache and diarrhea. Circulating lysophosphatidic acid (LPA) C18:2 was significantly reduced, demonstrating ziritaxestat target engagement, and levels of fibrosis biomarkers were reduced in the blood. No differentially expressed genes were identified in skin biopsies. Significant changes in 109 genes were identified in blood samples.

Conclusion. Ziritaxestat resulted in significantly greater reduction in MRSS at week 24 than placebo; no new safety signals emerged. Biomarker analysis suggests ziritaxestat may reduce fibrosis. Modulation of the autotaxin/LPA pathway could improve skin involvement in patients with dcSSc. A plain language summary is provided in the Supplementary Material, available on the *Arthritis & Rheumatology* website at https://onlinelibrary.wiley.com/doi/10.1002/art.42477.

INTRODUCTION

Systemic sclerosis (SSc) is a rare autoimmune disease characterized by fibrosis, immunologic dysfunction, and vasculopathy (1–4). The disease has a higher mortality rate than other rheumatologic diseases (1). Although the etiology and pathogenesis of SSc remain unclear, multifactorial processes involving genetic and environmental factors, in addition to alterations in

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immune function, are implicated (5). Characteristically, activation of fibroblasts and excessive deposition of extracellular matrix results in skin inflammation and fibrosis, which can progress to visceral organs (3). In response to vascular damage, immune activation may also be involved in SSc-associated vasculopathy (3). Although approved therapies for SSc organ involvement are available (6), there are no SSc-specific therapies for treatment of the overall disease. Treatment strategies focus on broad-spectrum immunosuppression and the reduction of skin and lung fibrosis (2,4,7).

Autotaxin is an extracellular lysophospholipase D enzyme involved in the hydrolysis of lysophosphatidylcholine to form lysophosphatidic acid (LPA) (8–10). LPA mediates inflammation and fibrosis (8,11) and has been linked to the pathogenesis of SSc (12,13). In human plasma, LPA C18:2 is the most common species, containing a fatty acid side chain of 18 carbon atoms, including 2 unsaturated bonds (14,15). In vitro and clinical studies have demonstrated that targeting the autotaxin/LPA pathway could modulate skin pathology in SSc (10,12,16,17). Ziritaxestat (GLPG1690), a small-molecule, selective autotaxin inhibitor with a novel mechanism of action, has been trialed for the treatment of idiopathic pulmonary fibrosis (IPF) (14,18–21) and SSc. Here, we present the results of a phase IIa, placebo-controlled trial assessing the efficacy, safety, and tolerability of ziritaxestat in patients with early diffuse cutaneous SSc (dcSSc). In addition, results from the corresponding open-label extension (OLE) assessing the long-term safety, tolerability, and efficacy of ziritaxestat in patients with dcSSc are reported. RNA profiling was performed to examine the effect of ziritaxestat in blood and skin to delineate its mechanism of action and to identify potential biomarkers of treatment effect.

PATIENTS AND METHODS

Study design. NOVESA (ClinicalTrials.gov identifier: NCT03798366) was a 24-week, multicenter, phase IIa, randomized, double-blind, parallel-group, placebo-controlled study. Adults meeting the 2013 American College of Rheumatology (ACR)/EULAR criteria for SSc with dcSSc involvement were randomized to oral ziritaxestat or matching placebo for 24 weeks (Supplementary Figure 1, available on the *Arthritis & Rheumatology* website at https://onlinelibrary.wiley.com/doi/10.1002/art.42477). This was in addition to any background immunosuppressant standard-of-care therapy. Patients were subsequently permitted to enter a 104-week OLE study (ClinicalTrials.gov identifier: NCT03976648). Patients entered the OLE at the rollover visit, coinciding with the week 24 visit of the parent study. The study was planned to last 116 weeks, comprising 104 weeks of ziritaxestat treatment and 12 weeks of follow-up (Supplementary Figure 2).

NOVESA was conducted at 14 clinical study centers across 5 countries (Belgium, Italy, Spain, UK, and US). The OLE was conducted at 13 study sites across the same 5 countries. Study protocols were approved by the independent ethics committee, institutional review board, or any other ethics committee according to local regulations prior to implementation. Studies were conducted in accordance with International Conference on Harmonization Guidelines for Good Clinical Practice and other local and legal requirements, consistent with the principles of the Declaration of Helsinki. All patients provided written informed consent for participation in the study. Amendments to the study are described in the Supplementary Methods at https://onlinelibrary.wiley.com/doi/10.1002/art.42477.

Study population. NOVESA included patients ≥18 years of age meeting the 2013 ACR/EULAR classification criteria for SSc and the LeRoy and Medsger classification for dcSSc (22,23). Eligible patients had their first manifestation of SSc (other than Raynaud's phenomenon) within the last 5 years, a modified Rodnan skin score (MRSS) of >10, and active disease at screening (defined as worsening of skin thickening [≥2 MRSS units], new areas of skin involvement, new-onset SSc with signs other than Raynaud's phenomenon, or ≥1 tendon friction rub). The main exclusion criterion was severe pulmonary disease with forced vital capacity (FVC) ≤45% of predicted within 6 months prior to baseline visit (day 1). Additional key exclusion criteria are listed in the Supplementary Methods.

Randomization and blinding. During the NOVESA screening period, eligible patients were randomized using an interactive web response system to receive oral ziritaxestat 600 mg once daily or matching placebo in a 2:1 ratio. Medication kits with unique numbers were provided. Patients, investigators, clinical study coordinators, and sponsor personnel were blinded with regard to the assigned treatment.

Assessments. NOVESA study visits took place during the screening period (≤28 days before day 1), on day 1 (baseline), and at weeks 2, 4, 8, 12, 16, and 24. As NOVESA was conducted during the COVID-19 pandemic, several steps were taken to ensure patients' safety while maintaining study integrity, including extending the treatment period beyond 24 weeks for 7 patients. Measurement of MRSS took place during screening, at baseline, and at weeks 4, 8, 16, and 24. The schedule of other study assessments is described in the Supplementary Methods.

Outcomes. The NOVESA primary efficacy end point was the change from baseline in MRSS at week 24 (the full analysis set). Secondary end points included the incidence of adverse events (AEs), treatment-emergent AEs (TEAEs), serious TEAEs, and assessment of ziritaxestat tolerability over 24 weeks. Blood and urine samples were collected for clinical laboratory analysis, vital signs were recorded, a standard 12-lead electrocardiogram was performed, and physical examinations were conducted. Other end points included the change from baseline in FVC,

high-resolution computed tomography, Health Assessment Questionnaire–Disability Index (HAQ-DI) score, and ACR provisional Combined Response Index in Systemic Sclerosis (CRISS) score. Change in plasma LPA levels was measured as a pharmacodynamic (PD) marker of target engagement.

The OLE primary end points were incidence of AEs, TEAEs, and serious TEAEs over time. Change from the NOVESA parent study baseline in MRSS was also recorded as an OLE study end point.

Disease biomarkers. Levels of disease biomarkers in the blood and skin were measured in the NOVESA study. Sections from skin biopsies were immunostained using antibodies against α-smooth muscle actin (α-SMA) for the detection of myofibroblasts, then scored by semiquantitative evaluation using a graded scale of 0 to 10 in a blinded fashion (24,25). Pharmaceutical Product Development performed the blinded scoring. Luminex assay or enzyme-linked immunosorbent assay (Nordic Bioscience) was used for blood biomarker assessments. For bulk RNA-sequencing analysis, blood samples were collected in PAXgene blood RNA tubes (PreAnalytiX), and skin biopsies were stored in RNAlater (Ambion). RNA isolation, library preparation, and sequencing were performed by Genewiz Germany GmbH (Leipzig, Germany). Illumina sequencing libraries were prepared using poly(A) capture (messenger RNA and long noncoding RNA) after globin messenger RNA depletion. Sequencing libraries were multiplexed and sequenced using an Illumina NovaSeq 6000 system. Gene set variation analysis was applied to the data, followed by a differential expression analysis on the enrichment scores using Limma (Differential Pathway Activation) software version 3.44.3. Differentially regulated pathways were identified using the Molecular Signatures Database Hallmark 50 collection (26).

Statistical analysis. The probability of observing a treatment effect of >4 points was determined a priori to be 63% based on 20 and 10 patients in the ziritaxestat and placebo groups, respectively, a common SD of 5 in MRSS change from baseline (27), a minimal clinically important difference of 4.7 (28,29), and a 10% dropout rate. Both the full analysis set and safety analysis set included all randomized patients receiving ≥1 dose of ziritaxestat or placebo. The OLE full analysis set included all patients receiving ≥1 dose of ziritaxestat in the OLE study. The per-protocol analysis set included all patients in the full analysis set who did not have a protocol deviation affecting the efficacy results. This set was determined prior to database lock and unblinding. The PD analysis set was a subset of the safety analysis set, including all patients who had at least 1 postbaseline PD value and excluding patients with protocol deviations that could have an effect on PD analysis. Protocol deviations that could have an effect on the PD analysis were defined prior to unblinding. The OLE full analysis set included all patients who received ≥1 dose of ziritaxestat in the OLE study.

Primary statistical analyses were performed after all patients had completed the NOVESA week 24 visit or discontinued treatment. All analyses were performed in the full analysis set unless otherwise stated. Exploratory *P* values for continuous end points (MRSS, FVC, and HAQ-DI) were calculated for the difference in least squares means at each time point, overall difference between treatment groups, and for the fixed effects included in the mixed-effects model for repeated measures. All statistical tests were 2-sided with a significance level of less than or equal to 0.05, unless otherwise stated. No formal statistical inference was performed for other efficacy end points. Efficacy and safety in the OLE were analyzed descriptively in the OLE full analysis set according to prior treatment in the parent study. Additional statistical details can be found in the Supplementary Methods, https://onlinelibrary.wiley.com/doi/10.1002/art.42477.

RESULTS

Patient disposition and baseline characteristics. Between January 14, 2019 and November 20, 2019, 33 patients were randomized to ziritaxestat 600 mg once daily (n = 21) or placebo (n = 12) (Figure 1). One patient receiving placebo was lost to follow-up; all remaining patients completed the parent study. Compared with placebo, patients receiving ziritaxestat had numerically shorter disease duration, higher MRSS, higher HAQ-DI scores, and were more likely to be receiving mycophenolate mofetil background therapy at baseline (Table 1). In the ziritaxestat group, 95.2% of patients received background immunosuppressant therapy versus 83.3% of patients in the placebo group. A single patient from the placebo group declined to enter the OLE study; in total, 31 patients entered the OLE (Figure 1). Baseline characteristics for the OLE study are shown in Supplementary Table 1, https://onlinelibrary.wiley.com/doi/10.1002/art.42477. Mean disease duration was 1.7 years, 77.4% of patients had an MRSS of ≥20, and 45.2% of patients reported lung disease.

Primary efficacy end point. At week 24, a statistically significant least squares mean difference in MRSS change from baseline of –2.8 units (95% confidence interval [95% CI] –5.6, –0.1) (*P* = 0.0411) was observed between the ziritaxestat and placebo groups (Figure 2). The least squares mean change from baseline to week 24 in MRSS was –8.9 units (95% CI –10.6, –7.1) in the ziritaxestat group and –6.0 units (95% CI –8.3, –3.8) in the placebo group. Clinically meaningful change in MRSS (defined as –4.7 units and/or ≥20% change in overall MRSS) was observed for a higher proportion of patients in the ziritaxestat group versus placebo group at week 8 (33.3% versus 18.2%, respectively) and week 16 (81.0% versus 50.0%, respectively); at week 24, the proportion of patients with a clinically

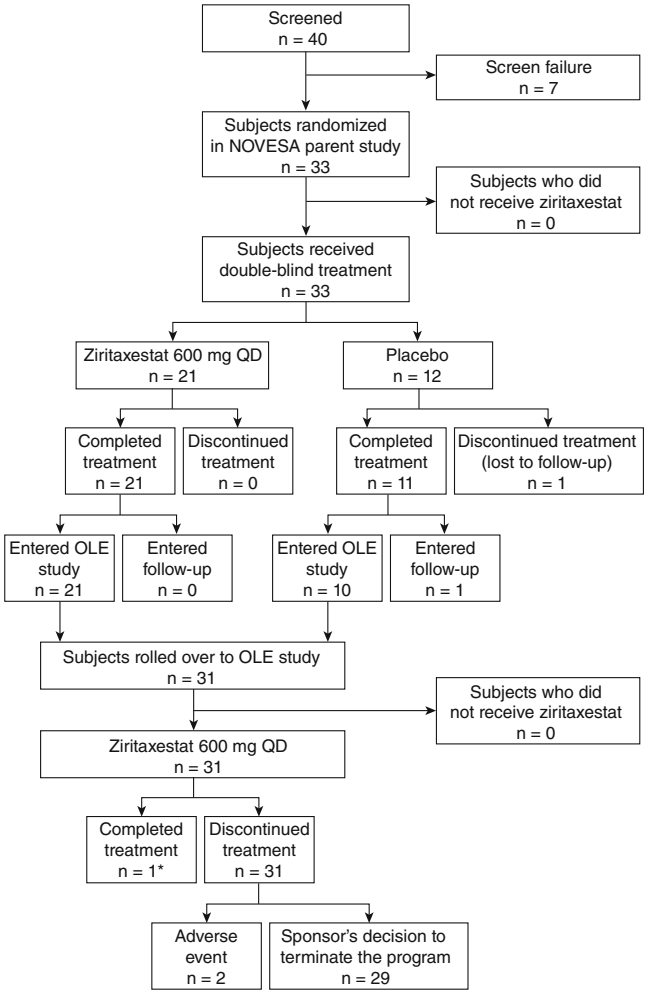

Figure 1. Study disposition of NOVESA, a 24-week, multicenter, phase IIa, double-blind, placebo-controlled study, and the open-label extension (OLE) to explore the efficacy, safety, and tolerability of ziritaxestat, a selective autotaxin inhibitor, in patients with early diffuse cutaneous systemic sclerosis. "Discontinued" refers to patients who stopped treatment. * One patient was reported as having completed the treatment although the patient had not completed the 104-week treatment period. QD = once daily.

meaningful change in MRSS was similar in both treatment groups (84.2% versus 80.0%, respectively, in the full analysis set).

Sensitivity analysis, which included patients without a week 24 MRSS assessment within the extended window of an additional 28 days, and analysis of the per-protocol analysis set supported the primary end point results; a more pronounced decrease in MRSS was observed in the ziritaxestat group versus the placebo group (Supplementary Table 2, https://onlinelibrary.wiley.com/doi/10.1002/art.42477).

In the OLE, placebo patients switching to ziritaxestat showed reductions in MRSS that were similar to those observed for ziritaxestat patients in the parent study. Reduction in MRSS continued until OLE week 28 and plateaued until OLE week 52 (Figure 2). At OLE week 52, the mean ± SEM change from NOVESA baseline in MRSS was −11.6 ± 3.0 units and −12.2 ± 1.6 units in the ziritaxestat–ziritaxestat and placebo–ziritaxestat groups, respectively. Premature termination of the study before the predesignated end points were reached resulted in a considerable drop in the number of participants after OLE week 40.

Other efficacy end points. Median ACR CRISS scores were higher with ziritaxestat treatment than placebo at week 16 (0.70 versus 0.19, respectively) and week 24 (0.97 versus 0.83, respectively). The proportion of patients with improvements in ACR CRISS score (i.e., score ≥0.6) was higher in the ziritaxestat group than the placebo group at week 16 (52.9% versus 20.0%, respectively) but similar in both treatment groups at week 24 (64.7% versus 62.5%, respectively) (Figure 2). One patient in the placebo group had a nonphysiologic change from baseline in FVC at week 24 (increase of 1,381 ml). Following exclusion of this outlier, median ACR CRISS score decreased from 0.83 to 0.69, and the proportion of patients demonstrating ACR CRISS improvement at week 24 in the placebo group dropped to 57.1%.

No statistically significant differences in change from baseline in FVC were evident between the ziritaxestat and placebo groups at week 16 or week 24. Decreases in HAQ-DI score were also comparable in both groups (Figure 2).

Safety and tolerability. In the parent study, the proportions of patients with TEAEs were similar in the ziritaxestat and placebo groups (95.2% [20 of 21 patients] and 91.7% [11 of 12 patients], respectively), as were the proportions of patients with treatment-related TEAEs (57.1% [12 of 21 patients] and 50.0% [6 of 12 patients], respectively) (Table 2). The most frequent treatment-related TEAE in patients receiving ziritaxestat or placebo was headache (14.3% [3 of 21 patients] receiving ziritaxestat versus 16.7% [2 of 12 patients] receiving placebo); patients receiving ziritaxestat more commonly experienced diarrhea (14.3% [3 of 21 patients] receiving ziritaxestat versus 0% [0 of 12 patients] receiving placebo). All other treatment-related TEAEs were reported in ≤2 patients in either treatment group. TEAEs were largely of mild or moderate intensity. Serious TEAEs were reported in 2 patients in the ziritaxestat group, one patient who experienced pharyngitis and sepsis and another patient who experienced device-related infection and sepsis. In both patients, study treatment was interrupted, and oral and intravenous antibiotics were initiated. One patient in the placebo group experienced a serious TEAE of foreign body in the gastrointestinal tract, resulting in an interruption to study treatment. No serious TEAE was considered to be treatment related.

In the OLE study, all patients reported ≥1 TEAE, and serious TEAEs were reported in 9 (29.0%) patients. Two patients (6.5%) discontinued after switching from placebo to ziritaxestat, one patient due to a serious TEAE of leukopenia and another patient due to a TEAE of urticaria. Both events were considered to be treatment related.

Table 1. Baseline characteristics of patients with early diffuse cutaneous systemic sclerosis randomized to receive treatment with ziritaxestat or placebo (full analysis set)*

	Ziritaxestat (n = 21)	Placebo (n = 12)	Total (n = 33)
Age			
Mean ± SD years	50.4 ± 13.6	47.3 ± 18.0	49.3 ± 15.1
≤45 years	7 (33.3)	5 (41.7)	12 (36.4)
>45 years	14 (66.7)	7 (58.3)	21 (63.6)
Sex			
Female	15 (71.4)	8 (66.7)	23 (69.7)
Male	6 (28.6)	4 (33.3)	10 (30.3)
Duration of disease			
Mean ± SD years	1.5 ± 1.0	2.6 ± 2.0	1.9 ± 1.5
Range, years	0.3–4.2	0.4–5.1	0.3–5.1
<2 years	16 (76.2)	6 (50.0)	22 (66.7)
≥2 years	5 (23.8)	6 (50.0)	11 (33.3)
Total MRSS			
Mean ± SD	27.0 ± 8.8	22.5 ± 6.2	25.3 ± 8.2
Range	11.0–46.0	12.0–29.0	11.0–46.0
<20	6 (28.6)	3 (25.0)	9 (27.3)
≥20	15 (71.4)	9 (75.0)	24 (72.7)
Presence of interstitial lung disease	10 (47.6)	5 (41.7)	15 (45.5)
Forced vital capacity, ml			
Mean ± SD	3,561.3 ± 909.9	3,441.1 ± 1,464.2	3,524.0 ± 1,085.1
Range	2,579–6,470	1,393–5,805	1,393–6,470
Percent predicted forced vital capacity, %			
Mean ± SD	94.0 ± 14.8	87.6 ± 18.4	92.0 ± 15.9
Range	70–125	57–111	57–125
HAQ-DI score			
Mean ± SD	1.24 ± 0.70	0.84 ± 0.89	1.10 ± 0.78
Range	0.00–2.38	0.00–2.75	0.00–2.75
Background immunosuppressive therapy			
Methotrexate (no prednisone)	2 (9.5)	2 (16.7)	4 (12.1)
Methotrexate + prednisone	4 (19.0)	2 (16.7)	6 (18.2)
Mycophenolate mofetil (no prednisone)	9 (42.9)	2 (16.7)	11 (33.3)
Mycophenolate + prednisone	4 (19.0)	4 (33.3)	8 (24.2)
Prednisone alone	1 (4.8)	0	1 (3.0)
None	1 (4.8)	2 (16.7)	3 (9.1)
Any systemic glucocorticoids at baseline†	9 (42.9)	6 (50.0)	15 (45.5)
≤7.5 mg once daily	7 (33.3)	5 (41.7)	12 (36.4)
>7.5 mg once daily	2 (9.5)	1 (8.3)	3 (9.1)

* Except where otherwise indicated, data are the no. (%) of patients. MRSS = modified Rodnan skin score; HAQ-DI = Health Assessment Questionnaire–Disability Index.
† Includes prednisone, prednisolone, and methylprednisolone.

There were no notable observations in vital signs or electrocardiogram parameters, and no differences were observed between the ziritaxestat and placebo groups. Physical examination abnormalities were identified in most patients receiving ziritaxestat or placebo; these were largely attributed to underlying disease. One patient from each treatment group experienced a mild TEAE of weight increase. This was considered to be potentially treatment related for the ziritaxestat patient. No patients discontinued treatment due to TEAEs in the parent study, and no patients died in either the parent or OLE study.

Biomarkers. In target engagement analysis, ziritaxestat treatment resulted in a reduced percent change from baseline in circulating LPA C18:2 at each time point measured (Figure 3). Least squares mean estimates from the model for repeated measures demonstrated that these changes were statistically significant in the ziritaxestat group versus placebo ($P < 0.0001$ at weeks 2, 4, 16, and 24).

To assess disease biomarkers in the skin, skin biopsies from ziritaxestat- and placebo-treated patients were immunostained for α-SMA, showing the presence of myofibroblasts in the dermis (Supplementary Figure 3, https://onlinelibrary.wiley.com/doi/10.1002/art.42477). The mean ± SD myofibroblast score at baseline was 4.0 ± 2.43 for the ziritaxestat group versus 1.8 ± 1.03 for the placebo group. A higher proportion of patients in the ziritaxestat group had a reduction in myofibroblast score from baseline to week 24 of ≥1 point versus the placebo group (52.6% versus 25.0%, respectively) (Supplementary Table 3).

Additional skin biomarkers were assessed by RNA-sequencing analysis. Results of the principal components analysis are shown in

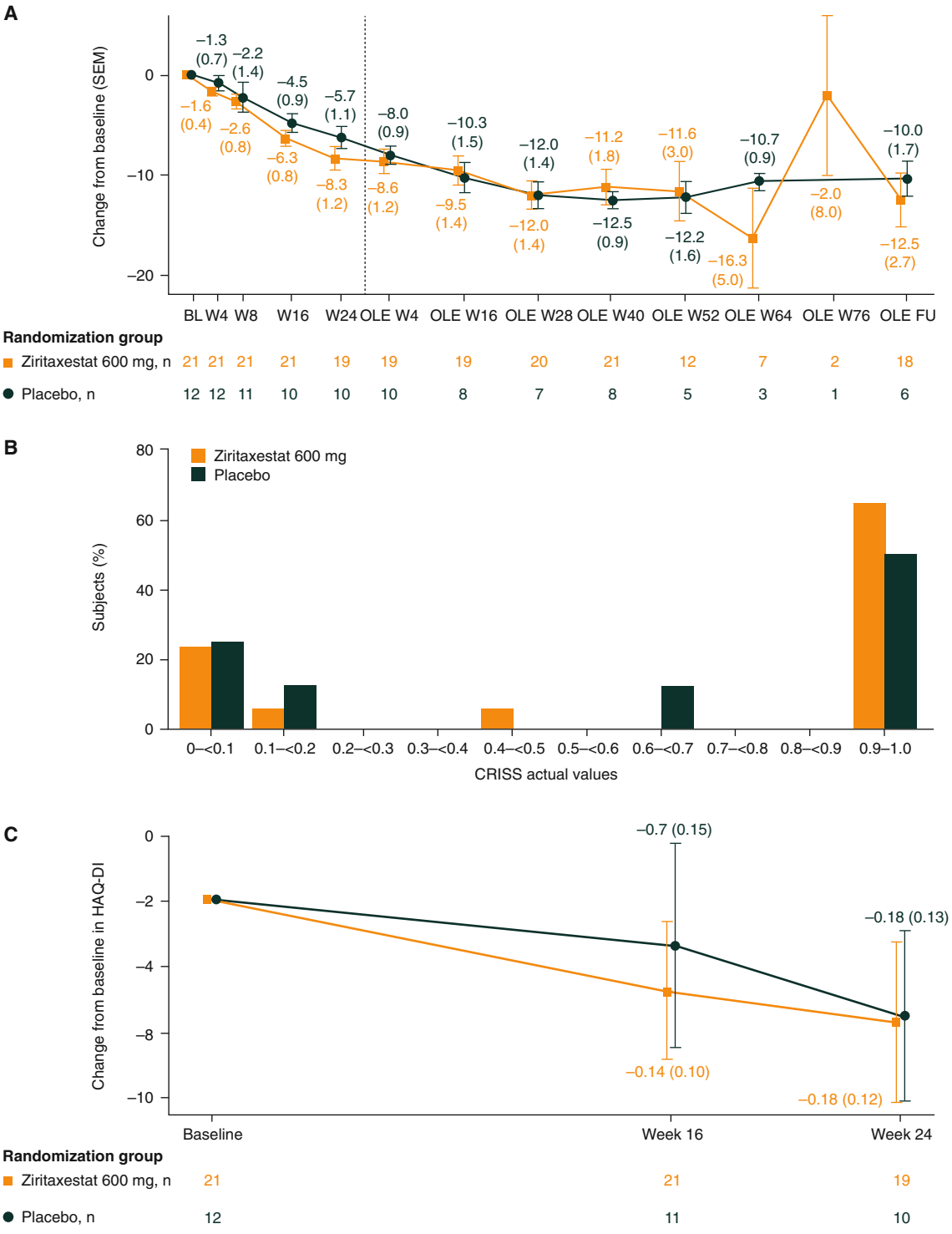

Figure 2. Primary and other efficacy end points of a phase IIa, double-blind, placebo-controlled study and the open-label extension (OLE) to assess ziritaxestat for the treatment of early diffuse cutaneous systemic sclerosis. **A**, Mean ± SEM change from baseline in modified Rodnan skin score (full analysis set and OLE full analysis set). Placebo patients in the NOVESA parent study received 600 mg ziritaxestat once daily in the OLE. Dashed line indicates the start of the OLE. **B**, Frequency of American College of Rheumatology Combined Response Index in Systemic Sclerosis (CRISS) actual values at week 24 (full analysis set). **C**, Mean ± SEM change from baseline in Health Assessment Questionnaire–Disability Index (HAQ-DI) score (full analysis set). BL = baseline; FU = follow-up; W = week.

Supplementary Figure 4. No differentially expressed genes were identified when comparing skin samples from ziritaxestat- and placebo-treated patients. In 5 of 7 skin samples categorized as having a high myofibroblast score at baseline (i.e., score of ≥5), the *TMPRSS4* gene showed a nonsignificant decrease in baseline-corrected expression (log_2 fold change −1.4; adjusted P = 0.63)

Table 2. Summary of TEAEs in early diffuse cutaneous systemic sclerosis patients who received ziritaxestat or placebo (safety analysis set)*

	Ziritaxestat (n = 21)	Placebo (n = 12)
Patients with TEAEs	20 (95.2)	11 (91.7)
Most frequently reported TEAEs†		
Diarrhea	7 (33.3)	2 (16.7)
Headache	5 (23.8)	2 (16.7)
Skin lesion	4 (19.0)	0
Patients with treatment-related TEAEs	12 (57.1)	6 (50.0)
Most frequently reported treatment-related TEAEs‡		
Headache	3 (14.3)	2 (16.7)
Diarrhea	3 (14.3)	0
Patients with serious TEAEs	2 (9.5)	1 (8.3)
TEAEs by worst severity		
Mild	4 (19.0)	4 (33.3)
Moderate	14 (66.7)	7 (58.3)
Severe	2 (9.5)	0
Deaths	0	0
Patients with TEAEs leading to discontinuation	0	0

* Values are the no. (%) of patients.
† Most frequently reported treatment-emergent adverse events (TEAEs) are defined as those reported in >3 patients in the ziritaxestat group or >2 patients in the placebo group.
‡ Most frequently reported treatment-related TEAEs are defined as those reported in ≥3 patients in the ziritaxestat group or >2 patients in the placebo group.

in ziritaxestat-treated patients compared with that in placebo-treated patients (Supplementary Figure 5A). High myofibroblast scores were only recorded in skin samples from ziritaxestat-treated patients. At baseline, a significant correlation between *TMPRSS4* expression and skin myofibroblast score was observed (Spearman's correlation coefficient = –0.62; P = 0.008); greater changes in *TMPRSS4* expression were observed in patients with higher baseline myofibroblast score. Among the 16 patients receiving ziritaxestat who demonstrated a reduction in MRSS at week 24, 13 patients showed a reduction in *TMPRSS4* expression.

In the analysis of disease biomarkers in the blood, we observed that patients receiving ziritaxestat exhibited reductions in the blood plasma concentration of fibrosis biomarkers, including chemokine (C-C motif) ligand 18 (CCL18), biomarkers of type III (C3M), IV (C4M), VI (C6M), and VII (C7M) collagen degradation, and a biomarker of type IV (PRO-C4) collagen synthesis. Levels of these biomarkers increased in patients given placebo, with significant differences between the ziritaxestat and placebo groups observed at week 24 (Table 3).

At week 24, RNA-sequencing analysis identified 768 differentially expressed genes (adjusted $P \leq 0.1$) between blood samples from ziritaxestat-treated and placebo-treated patients, with significant changes in 109 genes ($\log_2$ fold change >0.68; mean normalized count >128). A significant 1.4-fold increase in the autotaxin-related gene *LPAR2* was observed in the ziritaxestat group compared with the placebo group (adjusted P = 0.082) (Supplementary Figure 5B). Expression of the *MS4A4A* gene increased in blood samples from placebo-treated patients and was significantly reduced in ziritaxestat-treated patients (1.9-fold reduction versus placebo; adjusted P = 0.03); however, as the normalized count for this gene was below the arbitrary empirical cutoff of 128, it was not included in the shortlist of differentially expressed genes.

The metabolic pathway of oxidative phosphorylation was inhibited in the ziritaxestat group compared with the placebo group (adjusted $P < 0.01$) (see Supplementary Table 4). Alterations in the c-Myc pathway were also observed in samples from ziritaxestat-treated patients (adjusted $P < 0.1$) (see Supplementary Figure 6, available at https://onlinelibrary.wiley.com/doi/10.1002/art.42477, for oxidative phosphorylation and c-Myc pathway gene set heatmaps).

DISCUSSION

In this 24-week, phase IIa, placebo-controlled trial, ziritaxestat 600 mg once daily significantly improved MRSS compared with placebo when administered with standard-of-care immunosuppressive therapy in patients with early dcSSc. Ziritaxestat was generally well tolerated, with largely mild or moderate TEAEs, none of which resulted in study drug discontinuation. The incidence of serious TEAEs was low, and no TEAEs were considered to be treatment related. In the OLE, although 2 patients discontinued due to AEs considered related to ziritaxestat treatment, there were no changes from baseline over time that raised concerns regarding the safety of ziritaxestat. There were no deaths in the parent study or OLE study.

As the main objective of NOVESA was to assess, in a proof-of-concept setting, the impact of ziritaxestat on the skin, MRSS was selected as the primary end point. Other clinical trials of

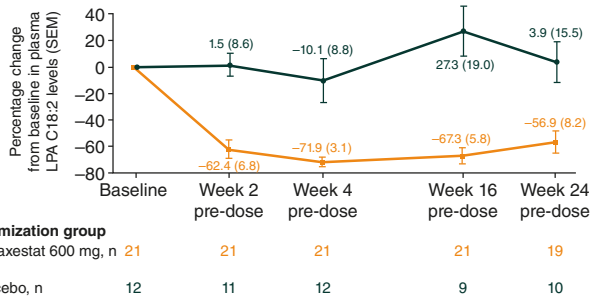

Figure 3. Mean ± SEM percent change from baseline in plasma lysophosphatidic acid (LPA) C18:2 levels (pharmacodynamic analysis set) in patients with early diffuse cutaneous systemic sclerosis who received ziritaxestat 600 mg once daily versus those who received placebo. Pre-dose is defined as samples collected within 30 minutes of study drug dosing. Baseline is defined as the last non-missing measurement prior to dosing. Values below the detection limit were input as 0. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/art.42477/abstract.

Table 3. Change from baseline to week 24 in blood biomarkers of fibrosis for which there was a significant treatment effect with ziritaxestat*

	Ziritaxestat (n = 21)		Placebo (n = 11)		Ziritaxestat versus placebo	
Biomarker	Baseline, mean ± SD	Change from baseline at week 24†	Baseline, mean ± SD	Change from baseline at week 24‡	Treatment effect	*P*
C3M, μg/ml	12.7 ± 2.9	−0.4 (−1.2, 0.4)	14.2 ± 4.9	1.1 (0.0, 2.1)	−1.5 (−2.7, −0.2)	0.0208
C4M, μg/ml	32.3 ± 6.3	−0.9 (−3.1, 1.2)	33.5 ± 9.9	3.6 (0.9, 6.3)	−4.6 (−7.8, −1.3)	0.0074
C6M, μg/ml	20.9 ± 7.9	−1.8 (−3.6, −0.0)	22.6 ± 8.8	3.2 (0.9, 5.4)	−5.0 (−7.7, −2.3)	0.0006
C7M, μg/ml	10.5 ± 5.6	−0.3 (−1.4, 0.8)§	10.5 ± 5.4	1.5 (0.2, 2.9)	−1.8 (−3.5, −0.2)	0.0328
PRO-C4, μg/ml	214.1 ± 79.2	−5.5 (−29.7, 18.7)	235.7 ± 110.3	40.3 (10.9, 69.8)	−45.8 (−81.5, −10.2)	0.0135
CCL18, pg/ml	84,842.9 ± 40,513.4¶	−9,580.1 (−19,183.4, 23.2)§	60,169.6 ± 23,057.3	6,256.4 (−4,491.5, 17,004.4)	−15,836.6 (−29,991.2, −1,681.9)	0.0295

* Except where otherwise indicated, data are the least squares mean estimate (95% confidence interval). C3M = matrix metalloproteinase-9 (MMP-9) degradation of type III collagen; C4M = MMP-2,9,12 degradation of type IV collagen; C6M = MMP-2 degradation of type VI collagen; C7M = MMP-13 degradation of type VII collagen; PRO-C4 = procollagen type IV N-terminal propeptide; CCL18 = chemokine (C-C motif) ligand 18.
† Change from baseline data are for 19 patients in the ziritaxestat group.
‡ Change from baseline data are for 10 patients in the placebo group.
§ For 18 patients at week 24.
¶ For 20 patients at baseline.

compounds in development for the treatment of dcSSc have failed to report any significant impact on MRSS compared with placebo. These include the LPA receptor 1 antagonist SAR100842 (10); belimumab, a monoclonal antibody designed to inhibit the activity of B lymphocyte stimulator and reduce autoantibody production (30); the soluble guanylate cyclase inhibitor riociguat, which attenuates transforming growth factor β1 signaling (31); and lenabasum, a synthetic, orally administered cannabinoid receptor 2 agonist (32). The CTLA-4 immunoglobulin fusion protein abatacept improved MRSS in patients stratified into inflammatory and normal-like intrinsic skin gene expression subsets, with no improvement in patients with the fibroproliferative intrinsic expression profile (33,34). Analysis of molecular differences between dcSSc subgroups characterized by antinuclear autoantibody (ANA) profile (33) reported that anti–topoisomerase I and anti–RNA polymerase III subgroups were associated with longitudinal changes in markers of fibrosis, displaying differential gene expression profiles. Stratifying patients by either intrinsic gene expression or hallmark ANA profiles may help explain response to specific treatments and should be considered in future trial designs.

The significant improvement in MRSS with ziritaxestat as compared with placebo is reported in a total patient population in which >90% of patients were receiving background immunosuppressive therapy. Likely, this accounts for the high placebo response rate observed (also confirmed by ACR CRISS score), with the confounding effect of background mycophenolate mofetil demonstrating an overlap with the mechanism of action of ziritaxestat. A phase II trial of romilkimab (SAR156597), a humanized IgG4 antibody that neutralizes interleukin-4 and interleukin-13, reported a significant improvement in MRSS compared with placebo in patients with early dcSSc. However, the proportion of patients receiving background immunosuppressive therapy was considerably lower than that in NOVESA (~50%) (35).

In the OLE, improvement in MRSS continued for patients remaining on ziritaxestat. From OLE week 4, patients switching from placebo to ziritaxestat showed improvements in MRSS similar to patients remaining on ziritaxestat. The magnitude of the MRSS treatment responses in patients switching to ziritaxestat in the OLE resulted in both groups from the parent study having comparable MRSS at OLE week 52. Beyond OLE week 52, the number of patients remaining in the OLE was too low for conclusions to be drawn.

NOVESA reports a high placebo response rate for other end points, including ACR CRISS score. A higher proportion of patients treated with ziritaxestat improved at week 16 compared with placebo; by week 24, improvements were similar between treatment groups. A phase II trial of lenabasum in patients with dcSSc demonstrated a trend toward improved ACR CRISS scores at week 16 (P = 0.07) (32), whereas the phase III RESOLVE-1 trial failed to demonstrate any significant improvement in ACR CRISS score at week 52 (36). As in NOVESA, patients included in RESOLVE-1 received background immunosuppressive therapy. Importantly, ACR CRISS was developed and validated in a cohort of treatment-naive patients not receiving background therapy. Together, the results from NOVESA, the phase II trial reported by Spiera et al, and RESOLVE-1 suggest that ACR CRISS score may have a ceiling effect with background immunosuppressive therapy (32,36).

Blood analysis demonstrated a reduction in biomarkers of collagen degradation and synthesis in ziritaxestat-treated patients compared with those who received placebo. This is noteworthy in the context of the improvement in MRSS reported in both treatment groups and may suggest that these blood biomarkers are associated with changes in fibrosis more generally, rather than specifically reflecting changes in skin fibrosis. Also, the reduction in collagen degradation markers may reflect reduced collagen turnover associated with ziritaxestat treatment.

Biomarker data from blood samples demonstrated changes in the expression of genes related to immune activation and inflammation in ziritaxestat-treated patients compared with those who received placebo. *MS4A4A*, an M2 macrophage marker

gene, has previously been incorporated into weighted modeling of a longitudinal, PD skin biomarker for SSc (2GSSc skin biomarker), which exhibited a high correlation with MRSS (37). In NOVESA, analysis of blood samples detected reductions in *MS4A4A* expression in ziritaxestat-treated patients that were linked to significant improvements in MRSS. A similar reduction in expression of the 2GSSc skin biomarker has been reported in skin biopsies from patients with SSc receiving fresolimumab (38) and tocilizumab (39).

Recent in vitro evidence has demonstrated a dual function for autotaxin, as both a producer and chaperone of LPA (40–42), allowing diffusion and release of LPA and activation of LPA receptors over a greater distance. Downstream of autotaxin-mediated LPA production, signaling via LPA receptors intersects with diverse cellular processes, from cell proliferation and motility to apoptosis and inflammation (43). The role of autotaxin as a master regulator and chaperone could mean that, in some patients, the impact of antagonism goes beyond the anticipated antifibrotic and antiinflammatory activity. Results from NOVESA show that ziritaxestat-mediated inhibition of autotaxin increased the expression of LPA receptor 2 in the blood and reduced the levels of fibrosis markers. As *LPAR2* deletion is linked to protection against bleomycin-induced lung fibrosis in mice (44), increased *LPAR2* expression in patients with reduced fibrosis in NOVESA may seem counterintuitive; however, induction of receptor expression in the absence of ligand (in this instance, LPA) is commonly observed in feedback loops. Unexpected changes in the expression of genes linked to the development of fibrosis have been reported previously, including transforming growth factor β downstream signaling where there is suppression of canonical Smad transcripts (45) associated with attenuation of fibroblast activation.

In discontinued phase III studies of ziritaxestat in IPF, ISABELA 1 and 2 (ClinicalTrials.gov identifiers: NCT03711162 and NCT03733444), no improvements in primary or secondary efficacy end points were observed versus placebo (manuscript in preparation). Results from NOVESA are not in agreement with those of ISABELA. A possible explanation for the ziritaxestat efficacy observed in NOVESA may be the prominent role of autotaxin in the pathogenesis of early SSc. It is postulated that ziritaxestat could target immune activation, inflammation, and downstream fibrosis. There may also be an effect from the higher regenerative capacity of the skin compared with the lung. A trend was observed suggesting a larger reduction in MRSS in patients with SSc of shorter duration, which could suggest that earlier intervention is more effective in the treatment of fibrotic diseases. Of note, ziritaxestat development was discontinued following results from ISABELA. This included termination of the NOVESA OLE study.

A number of limitations were identified for the NOVESA study, including the small size of the patient cohort; this, alongside insufficient skin sampling, prevented molecular stratification of patients (by genetic signature or ANA profile) as seen in other studies (33,46). As high-resolution computed tomography was only performed for patients with a documented SSc-associated diagnosis of lung disease, there was no opportunity to assess interstitial lung disease involvement and the effect on lung function in NOVESA. As such, evidence for the presence or absence of interstitial lung disease at baseline was lacking for some patients. As a result of the COVID-19 pandemic, several study procedures could not be performed or were postponed to safeguard vulnerable patients with SSc. The impact of these changes on the primary end point were deemed to be minor. There were also differences in baseline characteristics between the 2 treatment groups, with shorter disease duration and higher skin scores in patients randomized to ziritaxestat compared with placebo. To an extent, this was corrected for in the primary efficacy analysis by using least squares mean data. Furthermore, a greater proportion of patients in the ziritaxestat versus placebo group were receiving treatment with mycophenolate mofetil. It is possible that these differences may have contributed to the apparent efficacy of ziritaxestat compared with placebo, somewhat confounding the interpretation of results.

This phase IIa trial in patients with dcSSc demonstrated that ziritaxestat is significantly more effective than placebo in improving MRSS after 24 weeks of treatment. Longer-term data indicated that switching from placebo to ziritaxestat results in a similar improvement in MRSS to that experienced by patients receiving ziritaxestat in the parent study. Blood biomarker analysis suggested that ziritaxestat lowers the circulatory level of fibrosis markers and also has potentially beneficial effects in reducing the expression of genes associated with inflammation, oxidative phosphorylation, and mitochondrial function. Ziritaxestat was generally well tolerated, and no new safety signals emerged in this small population. Results from NOVESA support a possible role for the autotaxin/LPA pathway in modulating immune activation and inflammation in patients with dcSSc, which may promote improvement of MRSS, and should be confirmed in a larger, adequately powered clinical trial.

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AUTHOR CONTRIBUTIONS

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

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