Khanna Dinesh (Orcid ID: 0000-0003-1412-4453)
Denton Christopher P (Orcid ID: 0000-0003-3975-8938)
Furst Daniel E. (Orcid ID: 0000-0001-7857-2373)
Mayes Maureen D. (Orcid ID: 0000-0001-5070-2535)

A 24-Week, Phase IIa, Randomized, Double-blind, Placebo-controlled Study of Ziritaxestat in Early Diffuse Cutaneous Systemic Sclerosis (NOVESA)

Dinesh Khanna, MD, MSc;[1,*] Christopher P. Denton, PhD, FRCP;[2,*] Daniel E. Furst, MD;[3–5] Maureen D. Mayes;[6] Marco Matucci-Cerinic, MD, PhD;[7–9] Vanessa Smith;[10–12] Dick de Vries, MD;[13] Paul Ford, MD, PhD;[14,†] Yasmina Bauer, PhD;[15] Matthew J. Randall, PhD;[15] Mitra Ebrahimpoor;[13,†] Laszlo Kupcsik, PhD;[14] Pieter-Jan Stiers, PhD;[14] Liesbeth Deberdt, MSc;[14] Niyati Prasad, MBBS, MSc, DPM;[14,†] Sharlene Lim, PhD;[16] Philippe Pujuguet, PhD;[17] and Sohail Ahmed, MD, MBA[15,†,‡]

1. University of Michigan Scleroderma Program, Ann Arbor, Michigan, USA
2. Royal Free Hospital, University College London, London, UK
3. David Geffen School of Medicine at UCLA, Los Angeles, California, USA
4. University of Washington, Seattle, Washington, USA
5. University of Florence, Florence, Italy
6. University of Texas Health Science Center at Houston, Houston, Texas, USA
7. Unit of Immunology, Rheumatology, Allergy and Rare diseases (UnIRAR), IRCCS San Raffaele Hospital, Milan, Italy
8. Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy
9. Division of Rheumatology, AOUC, Florence, Italy
10. Department of Internal Medicine, Ghent University, Ghent, Belgium
11. Department of Rheumatology, Ghent University Hospital, Ghent, Belgium
12. Unit for Molecular Immunology and Inflammation, VIB Inflammation Research Center (IRC), Ghent, Belgium
13. Galapagos BV, Leiden, Netherlands

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14. Galapagos NV, Mechelen, Belgium
15. Galapagos GmbH, Basel, Switzerland
16. Gilead Sciences, Inc., Foster City, California, USA
17. Galapagos SASU, Romainville, France

*Joint first author

†Affiliation at the time of study commencement

‡Current affiliation: Kling Biotherapeutics, Amsterdam, Netherlands

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Corresponding author: Sohail Ahmed (sohail@klingbio.com). Kling Biotherapeutics, Meibergdreef 59, 1105 BA Amsterdam, Netherlands.

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Abstract

Objective

NOVESA explored 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, 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 endpoint was change from baseline in modified Rodnan skin score (mRSS) at Week 24. Secondary endpoints assessed safety and tolerability; other endpoints 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 versus placebo group (–8.9 vs. –6.0 units; $P = 0.0411$). 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; 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 reductions 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 available in the Supplement.

Introduction

Systemic sclerosis (SSc) is a rare autoimmune disease characterized by fibrosis, immunological dysfunction, and vasculopathy (1-4). The disease has a higher mortality rate than other rheumatological diseases (1). Although the etiology and pathogenesis of SSc remain unclear, multifactorial processes involving genetic and environmental factors, in addition to alterations in 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). Whereas 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). Both *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 examined 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, Phase IIa, randomized, double-blind, parallel-group, placebo-controlled, multicenter study. Adults meeting the 2013 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) criteria for SSc with dcSSc involvement were randomized to oral ziritaxestat or matching placebo for 24 weeks (**Supplementary Figure 1**). 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 follow-up (**Supplementary Figure 2**).

NOVESA was conducted at 14 clinical study centers across 5 countries (Belgium, Italy, Spain, United Kingdom, and United States of America). 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**.

Study population

NOVESA included patients aged ≥18 years 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; 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 (QD) 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 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 coronavirus disease 2019 (COVID-19) pandemic, several steps were taken to ensure patients' safety while maintaining study integrity, including extending the treatment period beyond 24 weeks for seven 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 endpoint was change from baseline in mRSS at Week 24 (Full Analysis Set [FAS]). Secondary endpoints included the incidence of adverse events (AEs), treatment-emergent AEs (TEAEs), serious TEAEs, and assessment of ziritaxestat's tolerability over 24 weeks. Blood and urine samples were collected for clinical laboratory analysis, vital signs were recorded, a standard 12-lead electrocardiogram (ECG) was performed, and physical examinations were conducted. Other endpoints included the change from baseline in FVC, high-resolution computed tomography (HRCT), Health Assessment Questionnaire Disability Index (HAQ-DI) score, and ACR Provisional Combined Response Index for Systemic Sclerosis (CRISS) score. Change in plasma LPA levels was measured as a pharmacodynamic (PD) marker of target engagement.

The OLE primary endpoint was incidence of AEs, TEAEs, and serious TEAEs over time. Change from the parent study (NOVESA) baseline in mRSS was also recorded as an OLE study endpoint.

Disease biomarkers

Levels of disease biomarkers in the blood and skin were measured in NOVESA. 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 Inc. performed the blinded scoring. Luminex assay or enzyme-linked immunosorbent assay (Nordic Bioscience) were used for blood biomarker assessments. For bulk RNA sequencing (RNAseq) analysis, blood samples were collected in PAXgene® blood RNA tubes, and skin biopsies were stored in RNAlater®. RNA isolation, library preparation, and sequencing were performed by Genewiz Germany GmbH (Leipzig, Germany). Illumina sequencing libraries were prepared using polyA capture (messenger RNA and long noncoding RNA) after globin mRNA depletion. Sequencing libraries were multiplexed and sequenced using Illumina Novaseq 6000. Gene set variation analysis was applied to the data, followed by a differential expression analysis on the enrichment scores using limma. 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 standard deviation (SD) of 5 in mRSS change from baseline (27); a minimal clinically important difference of 4.7 (28,29); and by taking a 10% dropout rate into account. Both the FAS and Safety Analysis Set included all randomized patients receiving ≥1 dose of ziritaxestat or placebo. The OLE FAS included all patients receiving ≥1 dose of ziritaxestat in the OLE study. The Per-

protocol Analysis Set included all patients in the FAS who did not have a protocol deviation impacting 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 subjects who had at least 1 postbaseline PD value and excluding subjects with protocol deviations that could have an impact on PD analysis. Protocol deviations that could have an impact on the PD analysis were defined prior to unblinding. The OLE FAS included all patients who received at ≥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 FAS, unless otherwise stated. Exploratory *P* values for continuous endpoints (mRSS, FVC, and HAQ-DI) were calculated for the difference in least squares (LS) means at each time point, overall difference between treatment groups, and for the fixed effects included in the mixed-effects model for repeated measures (MMRM). All statistical tests were 2-sided with a significance level of ≤0.05, unless otherwise stated. No formal statistical inference was performed for other efficacy endpoints. Efficacy and safety in the OLE were analyzed descriptively in the OLE FAS, according to prior treatment in the parent study. Additional statistical details can be found in the **Supplementary methods**.

Results

Patient disposition and baseline characteristics

Between 14 January 2019 and 20 November 2019, 33 patients were randomized to ziritaxestat 600 mg QD (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**. 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 endpoint

At Week 24, a statistically significant LS mean difference (95% confidence interval [CI]) in mRSS change from baseline of −2.8 (−5.6, −0.1) units (P = 0.0411) was observed between the ziritaxestat and placebo groups (**Figure 2**). The LS mean (95% CI) change from baseline to Week 24 in mRSS was −8.9 (−10.6, −7.1) units in the ziritaxestat group and −6.0 (−8.3, −3.8) units 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 at Week 8 (33.3% vs. 18.2%) and Week 16 (81.0% vs. 50.0%); at

Week 24, the proportion of patients with a clinically meaningful change in mRSS was similar in both treatment groups (84.2% vs. 80.0%; FAS).

Sensitivity analysis, which included patients without a Week 24 mRSS assessment within the extended window of +28 days, and analysis of the Per-protocol Analysis Set supported the primary endpoint results; a more pronounced decrease in mRSS was observed in the ziritaxestat versus placebo group (**Supplementary Table 2**).

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 (standard error) change from NOVESA baseline in mRSS was –11.6 (3.0) and –12.2 (1.6) units in the ziritaxestat-ziritaxestat and placebo-ziritaxestat groups, respectively. Premature termination of the study before pre-designated endpoints were reached resulted in a considerable drop in the number of participants after OLE Week 40.

Other efficacy endpoints

Median ACR CRISS scores were numerically higher with ziritaxestat than placebo at Week 16 (0.70 vs. 0.19) and Week 24 (0.97 vs 0.83). The proportion of patients with improvements in ACR CRISS score (i.e. score ≥0.6) was numerically higher in the ziritaxestat group than placebo group at Week 16 (52.9% vs. 20.0%), but similar in both treatment groups at Week 24 (64.7% vs. 62.5%) (**Figure 2**). One subject in the placebo group had a non-physiological change from baseline in FVC at Week 24 (+1381 mL); following exclusion of this outlier, 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 the change from baseline in FVC were evident between the ziritaxestat and placebo groups at Week 16 or 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% [20/21] and 91.7% [11/12], respectively), as were the proportions of patients with treatment-related TEAEs (57.1% [12/21] and 50.0% [6/12], respectively) (**Table 2**). The most frequent treatment-related TEAE in patients receiving ziritaxestat or placebo was headache (14.3% [3/21] vs. 16.7% [2/12] with placebo); patients receiving ziritaxestat more commonly experienced diarrhea (14.3% [3/21] vs. 0.0% [0/12] with 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 two patients in the ziritaxestat group: one patient experienced pharyngitis and sepsis and the second patient 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 due to a serious TEAE of leukopenia and one due to a TEAE of urticaria. Both events were considered to be treatment related.

There were no notable observations in vital signs or ECG 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 due to TEAEs in the parent study and no patients died in either the parent or OLE study.

Biomarkers

Target engagement

Ziritaxestat treatment resulted in a reduced percent change from baseline in circulating LPA C18:2 at each time point measured (**Figure 3**); LS mean estimates from the MMRM demonstrated that these changes were statistically significant in the ziritaxestat group versus placebo (P <0.0001 at Weeks 2, 4, 16, and 24).

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**). A higher proportion of patients in the ziritaxestat versus placebo group

had a reduction in myofibroblast score from baseline (score [SD] 4.0 [2.43] with ziritaxestat versus 1.8 [1.03] with placebo) to Week 24 of ≥1 point (52.6% and 25.0%, respectively) (**Supplementary Table 3**).

Additional skin biomarkers were assessed by RNAseq analysis. Results of the principal component analysis are shown in **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 transmembrane serine protease 4 gene (*TMPRSS4*) showed a non-significant decrease in baseline-corrected expression (log_2[fold change]= –1.4; adjusted *P* = 0.63) 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 correlation coefficient = –0.62; *P* = 0.008); greater changes in *TMPRSS4* expression were observed in patients with higher baseline myofibroblast score. Of 16 patients receiving ziritaxestat and demonstrating a reduction in mRSS at Week 24, 13 showed a reduction in *TMPRSS4* expression.

Disease biomarkers in the blood

Patients receiving ziritaxestat exhibited reductions in the blood plasma concentration of fibrosis biomarkers, including chemokine (C-C motif) ligand 18 (CCL18), markers of type III (C3M), IV (C4M), VI (C6M), and VII (C7M) collagen degradation, and a marker 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, RNAseq 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, lysophosphatidic acid receptor 2 (*LPAR2*), was observed in the ziritaxestat group as compared with placebo (adjusted $P = 0.082$) (**Supplementary Figure 5B**). Expression of the membrane-spanning 4-domains A4A gene (*MS4A4A*) increased in blood samples from placebo-treated patients and was significantly reduced in ziritaxestat-treated patients (1.9-fold reduction vs. 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 as 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** for oxidative phosphorylation and c-Myc pathway gene set heatmaps).

Discussion

In this Phase IIa, 24-week, placebo-controlled trial, ziritaxestat 600 mg QD significantly improved mRSS as 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 none were considered to be treatment related. In the OLE, although there were two discontinuations 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 endpoint. Other clinical trials of 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 beta-1 signaling (31); and lenabasum, a synthetic, orally administered cannabinoid receptor 2 agonist (32). The cytotoxic T lymphocyte-associated antigen 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-1 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% were receiving background immunosuppressive therapy. Likely, this accounts for the high placebo response rate observed (also confirmed by ACR CRISS score), with the confounding impact 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 -13, reported a significant improvement in mRSS in comparison with placebo in patients with early dcSSc. However, the proportion of patients receiving background immunosuppressive therapy was considerably lower than 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 endpoints, including ACR CRISS score. A higher proportion of patients treated with ziritaxestat improved at Week 16 as 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 towards 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-naïve patients not receiving background therapy. Together, the results from NOVESA, the Phase II trial reported by Spiera et al (2020), 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 as compared with 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 as compared with 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 anti-fibrotic and anti-inflammatory 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 ISABELA 1 and 2 (NCT03711162; NCT03733444), discontinued Phase III studies of ziritaxestat in IPF, no improvements in primary or secondary efficacy endpoints

were shown 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 impact from the higher regenerative capacity of the skin, as 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 HRCT 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 impact 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 endpoint were deemed to be minor. There were also differences in baseline characteristics between the two 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 LS mean data. Furthermore, a greater proportion of patients in the ziritaxestat vs 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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Daniel Furst (USA; 1 patient), Maureen Mayes (USA; 1 patient), Joseph Forstot (USA; 1 patient), Suzanne Kafaja (USA; 2 patients), Stanley Cohen (USA; 1 patient). The authors would also like to thank Emmanuel Karouzakis (Galapagos NV) for his contribution to the interpretation of biomarker data and Ciann|a Leatherwood (Gilead Sciences Inc.) for her involvement in reviewing the results.

Author Contributions

DK, CD, DF, MM, MMC, VS, and SA conceptualized and designed the study, were advisory board members, and endorsed the trial design. DDV, PJS, LK, ME, LD, NP, YB, MR, SL, and PP collected and analyzed data. All authors were involved in data interpretation. All authors were involved in drafting and critical revision of the article and all authors approved the final version to be published.

Role of the Study Sponsor

This study was funded by Galapagos NV (Mechelen, Belgium). Galapagos NV, the authors, and investigators designed the study. Clinical data were collected by the investigators, their teams, and Galapagos NV. Galapagos was involved in data analysis, data interpretation, and the writing, review, and approval of the article. Medical writing support (including development of a draft outline and subsequent drafts in consultation with the authors, assembling tables and figures, collating author comments, copyediting, fact checking and referencing) was provided by Iain Haslam, PhD, CMPP (Aspire Scientific Ltd, Bollington, UK), and funded by Galapagos NV (Mechelen, Belgium). All authors had full access to study data and had final responsibility for the decision to submit for publication.

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Figure Legends

Figure 1. Patient disposition (NOVESA parent study and OLE).

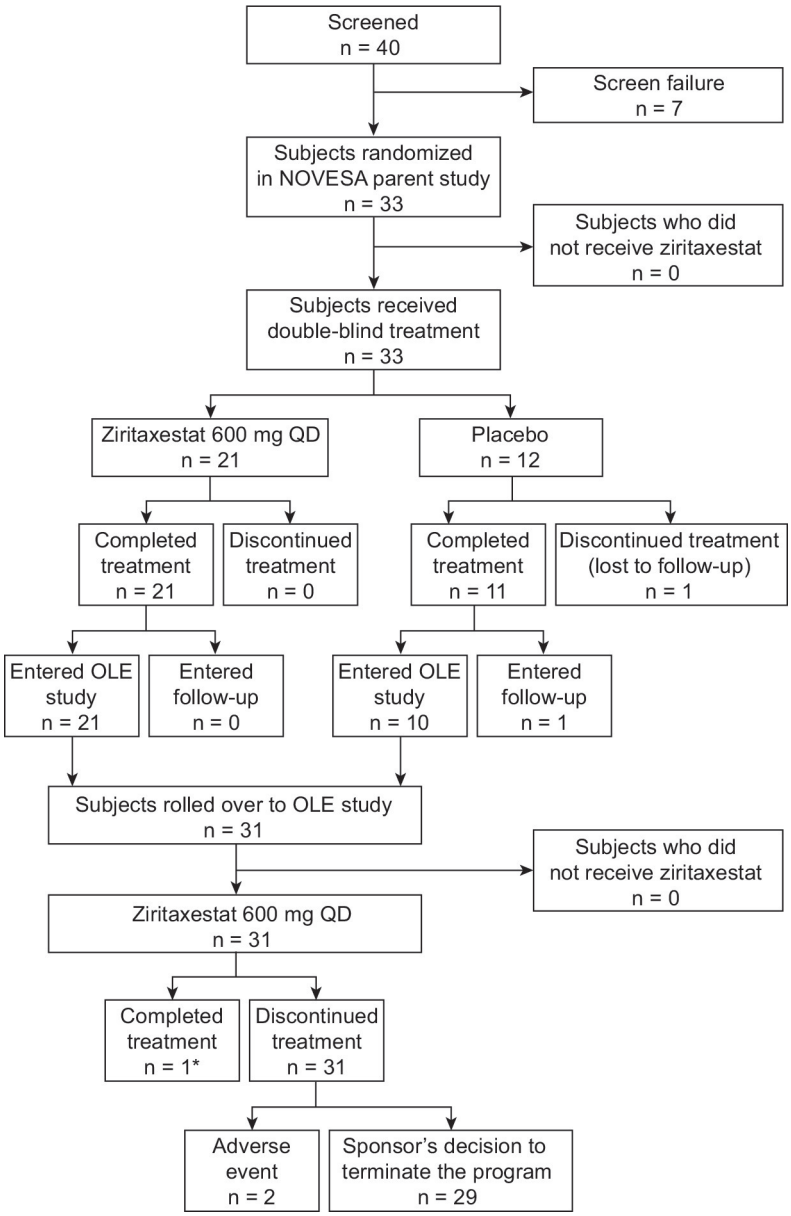
'Discontinued' applies to subjects who stopped treatment. *One subject was reported as having completed the treatment although the subject had not completed the 104-week treatment period. OLE, open-label extension; QD, once daily

Figure 2. (A) Mean (±SE) change from baseline in modified Rodnan skin score (Full Analysis Set, OLE Full Analysis Set), (B) Frequency of American College of Rheumatology CRISS actual values at Week 24 (Full Analysis Set), (C) Mean (± standard error) change from baseline in HAQ-DI (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. BL, baseline; CRISS, Combined Response Index for Systemic Sclerosis; FU, follow-up; HAQ-DI, Health Assessment Questionnaire Disability Index; OLE, open-label extension; SE, standard error; W, week

Figure 3. Mean (±SE) percent change from in plasma LPA C18:2 levels (Pharmacodynamic Analysis Set).

Pre-dose is defined as samples collected within 30 minutes of study drug dosing. Baseline is defined as last non-missing measurement prior to dosing. Values below the detection limit are regarded as 0. LPA, lysophosphatidic acid; SE, standard error



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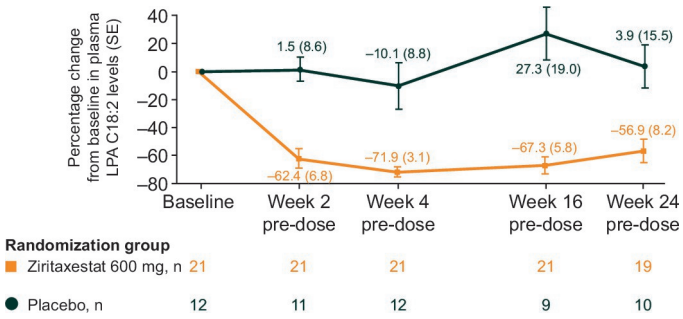

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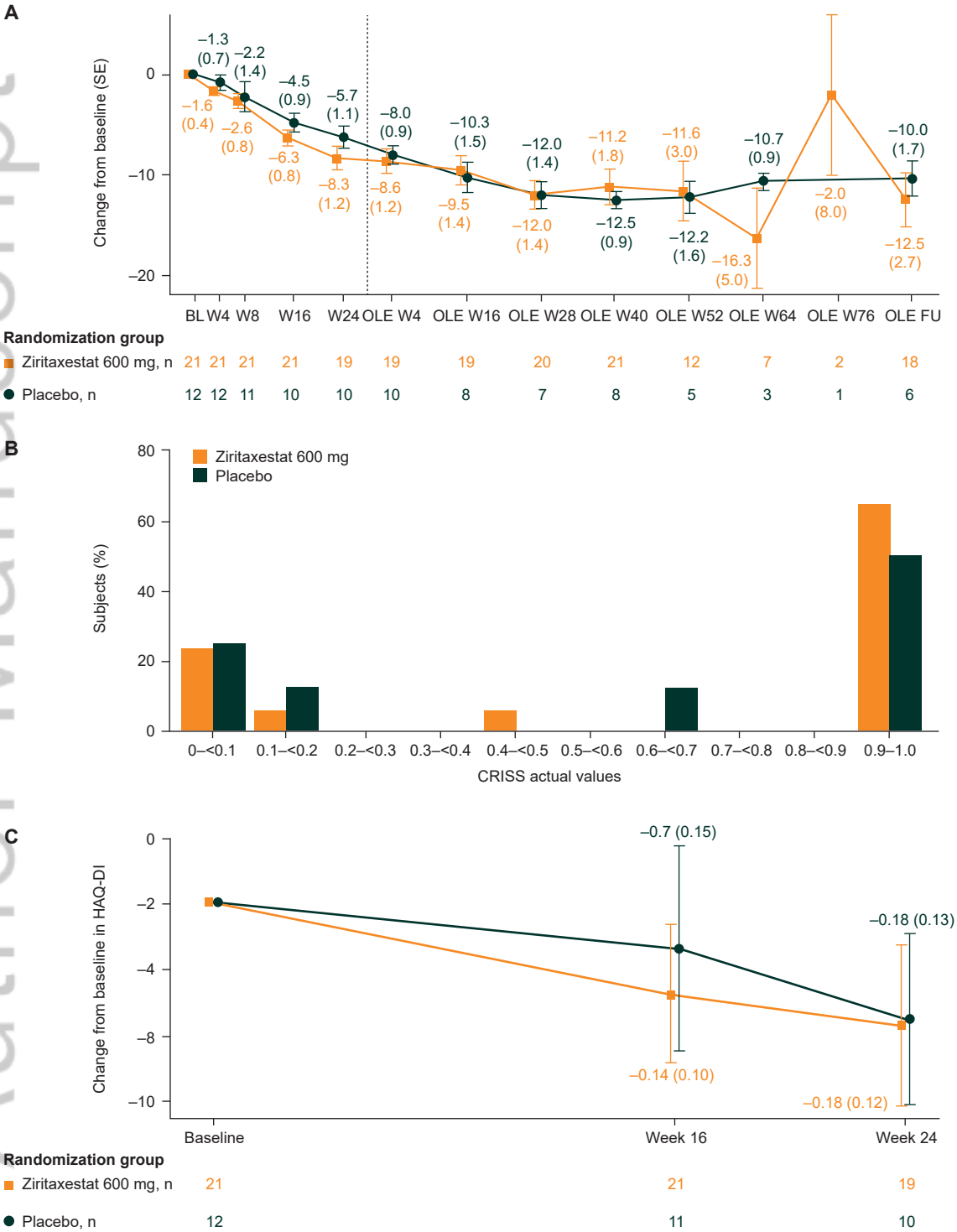

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Manuscript Title: A 24-Week, Phase IIa, Randomized, Double-blind, Placebo-controlled Study of Ziritaxestat in Early Diffuse Cutaneous Systemic Sclerosis (NOVESA)

Manuscript Number (if known): ar-22-0805

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		ERN-ReCONNET	Steering committee member, unpaid
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Your Name: Dick de Vries
Manuscript Title: A 24-Week, Phase IIa, Randomized, Double-blind, Placebo-controlled Study of Ziritaxestat in Early Diffuse Cutaneous Systemic Sclerosis (NOVESA)
Manuscript number (if known): ar-22-0805

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The following questions apply to the author's relationships/activities/interests as they relate to the current manuscript only.

The author's relationships/activities/interests should be defined broadly. For example, if your manuscript pertains to the epidemiology of hypertension, you should declare all relationships with manufacturers of antihypertensive medication, even if that medication is not mentioned in the manuscript.

In item #1 below, report all support for the work reported in this manuscript without time limit. For all other items, the time frame for disclosure is the past 36 months.

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
Time frame: Since the initial planning of the work			
1	All support for the present manuscript (e.g., funding, provision of study materials, medical writing, article processing charges, etc.) **No time limit for this item.**	Galapagos	
Time frame: past 36 months			
2	Grants or contracts from any entity (if not indicated in item #1 above).	__X__None	
3	Royalties or licenses	__X__None	
4	Consulting fees	__X__None	

5	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	__X__None	
6	Payment for expert testimony	__X__None	
7	Support for attending meetings and/or travel	__X__None	
8	Patents planned, issued or pending	__X__None	
9	Participation on a Data Safety Monitoring Board or Advisory Board	_X___None	
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	__X__None	
11	Stock or stock options	Galapagos	warrant holder
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	__X__None	
13	Other financial or non-financial interests	__X__None	

Please place an "X" next to the following statement to indicate your agreement:

_X_ I certify that I have answered every question and have not altered the wording of any of the questions on this form.

ICMJE DISCLOSURE FORM

Date: 08 December 2022
Your Name: Liesbeth Deberdt
Manuscript Title: A 24-Week, Phase IIa, Randomized, Double-blind, Placebo-controlled Study of Ziritaxestat in Early Diffuse Cutaneous Systemic Sclerosis (NOVESA)
Manuscript number (if known): ar-22-0805

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3	Royalties or licenses	__X__None	
4	Consulting fees	__X__None	

5	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	__X__None	
6	Payment for expert testimony	__X__None	
7	Support for attending meetings and/or travel	__X__None	
8	Patents planned, issued or pending	__X__None	
9	Participation on a Data Safety Monitoring Board or Advisory Board	_X___None	
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	__X__None	
11	Stock or stock options	Galapagos	warrant holder
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	__X__None	
13	Other financial or non-financial interests	__X__None	

Please place an "X" next to the following statement to indicate your agreement:

_X_ I certify that I have answered every question and have not altered the wording of any of the questions on this form.

ICMJE DISCLOSURE FORM

Date: 06 December 2022
Your Name: Christopher P. Denton
Manuscript Title: A 24-Week, Phase IIa, Randomized, Double-blind, Placebo-controlled Study of Ziritaxestat in Early Diffuse Cutaneous Systemic Sclerosis (NOVESA)
Manuscript number (if known): ar-22-0805

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Time frame: past 36 months			
2	Grants or contracts from any entity (if not indicated in item #1 above).	Acceleron Actelion Arxx Therapeutics Bayer Boehringer Ingelheim BMS Corbus CSL Behring	Less than $10000 each

		Galapagos GlaxoSmithKline Horizon Inventiva Leadiant Biosciences Roche Sanofi	
3	Royalties or licenses	__X__None	
4	Consulting fees		
5	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	_X___None	
6	Payment for expert testimony	_X___None	
7	Support for attending meetings and/or travel	__X__None	
8	Patents planned, issued or pending	_X___None	
9	Participation on a Data Safety Monitoring Board or Advisory Board	_X___None	
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	_X___None	
11	Stock or stock options		
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	__X__None	
13	Other financial or non-financial interests		

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_X_ I certify that I have answered every question and have not altered the wording of any of the questions on this form.

ICMJE DISCLOSURE FORM

Date: 08 December 2022
Your Name: Mitra Ebrahimpoor
Manuscript Title: A 24-Week, Phase IIa, Randomized, Double-blind, Placebo-controlled Study of Ziritaxestat in Early Diffuse Cutaneous Systemic Sclerosis (NOVESA)
Manuscript number (if known): ar-22-0805

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3	Royalties or licenses	__X__None	
4	Consulting fees	__X__None	

5	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	__X__None	
6	Payment for expert testimony	__X__None	
7	Support for attending meetings and/or travel	__X__None	
8	Patents planned, issued or pending	__X__None	
9	Participation on a Data Safety Monitoring Board or Advisory Board	_X___None	
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	__X__None	
11	Stock or stock options	Galapagos	warrant holder
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	__X__None	
13	Other financial or non-financial interests	__X__None	

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_X_ I certify that I have answered every question and have not altered the wording of any of the questions on this form.

ICMJE DISCLOSURE FORM

Date: 08 December 2022
Your Name: Paul Ford
Manuscript Title: A 24-Week, Phase IIa, Randomized, Double-blind, Placebo-controlled Study of Ziritaxestat in Early Diffuse Cutaneous Systemic Sclerosis (NOVESA)
Manuscript number (if known): ar-22-0805

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Time frame: past 36 months			
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3	Royalties or licenses	__X__None	
4	Consulting fees	__X__None	

5	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	__X__None	
6	Payment for expert testimony	__X__None	
7	Support for attending meetings and/or travel	__X__None	
8	Patents planned, issued or pending	__X__None	
9	Participation on a Data Safety Monitoring Board or Advisory Board	_X___None	
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	__X__None	
11	Stock or stock options	Galapagos	warrant holder
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	__X__None	
13	Other financial or non-financial interests	__X__None	

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_X_ I certify that I have answered every question and have not altered the wording of any of the questions on this form.

ICMJE DISCLOSURE FORM

Date: 06 December 2022
Your Name: Dinesh Khanna
Manuscript Title: A 24-Week, Phase IIa, Randomized, Double-blind, Placebo-controlled Study of Ziritaxestat in Early Diffuse Cutaneous Systemic Sclerosis (NOVESA)
Manuscript number (if known): ar-22-0805

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Time frame: past 36 months			
2	Grants or contracts from any entity (if not indicated in item #1 above).	Bayer BMS Horizon Immune Tolerance Network NIH Pfizer	
3	Royalties or licenses	__X__None	

4	Consulting fees	AbbVie Acceleron Actelion Amgen Bayer Chemomab CSL Behring Galapagos Genentech/Roche Horizon Merck Mitsubishi Tanabe Pharma	Less than $10000 each
		Boehringer Ingelheim	Greater than $10000
5	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	_X___None	
6	Payment for expert testimony	__X__None	
7	Support for attending meetings and/or travel	__X__None	
8	Patents planned, issued or pending	__X__None	
9	Participation on a Data Safety Monitoring Board or Advisory Board	__X__None	
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	__X__None	
11	Stock or stock options	__X__None	
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	__X__None	
13	Other financial or non-financial interests	__X__None	

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ICMJE DISCLOSURE FORM

Date: 08 December 2022
Your Name: Laszlo Kupcsik
Manuscript Title: A 24-Week, Phase IIa, Randomized, Double-blind, Placebo-controlled Study of Ziritaxestat in Early Diffuse Cutaneous Systemic Sclerosis (NOVESA)
Manuscript number (if known): ar-22-0805

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Time frame: past 36 months			
2	Grants or contracts from any entity (if not indicated in item #1 above).	__X__None	
3	Royalties or licenses	__X__None	
4	Consulting fees	__X__None	

5	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	__X__None	
6	Payment for expert testimony	__X__None	
7	Support for attending meetings and/or travel	__X__None	
8	Patents planned, issued or pending	__X__None	
9	Participation on a Data Safety Monitoring Board or Advisory Board	_X___None	
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	__X__None	
11	Stock or stock options	Galapagos	warrant holder
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	__X__None	
13	Other financial or non-financial interests	__X__None	

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_X_ I certify that I have answered every question and have not altered the wording of any of the questions on this form.

ICMJE DISCLOSURE FORM

Date: 08 December 2022
Your Name: Sharlene Lim
Manuscript Title: A 24-Week, Phase IIa, Randomized, Double-blind, Placebo-controlled Study of Ziritaxestat in Early Diffuse Cutaneous Systemic Sclerosis (NOVESA)
Manuscript number (if known): ar-22-0805

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Time frame: past 36 months			
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3	Royalties or licenses	__X__None	
4	Consulting fees	__X__None	

5	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	__X__None	
6	Payment for expert testimony	__X__None	
7	Support for attending meetings and/or travel	__X__None	
8	Patents planned, issued or pending	__X__None	
9	Participation on a Data Safety Monitoring Board or Advisory Board	_X___None	
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	__X__None	
11	Stock or stock options	Gilead Sciences	shareholder
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	__X__None	
13	Other financial or non-financial interests	__X__None	

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_X_ I certify that I have answered every question and have not altered the wording of any of the questions on this form.

ICMJE DISCLOSURE FORM

Date: 06 December 2022
Your Name: Marco Matucci-Cerinic
Manuscript Title: A 24-Week, Phase IIa, Randomized, Double-blind, Placebo-controlled Study of Ziritaxestat in Early Diffuse Cutaneous Systemic Sclerosis (NOVESA)
Manuscript number (if known): ar-22-0805

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Time frame: past 36 months			
2	Grants or contracts from any entity (if not indicated in item #1 above).	__X__None	
3	Royalties or licenses	__X__None	
4	Consulting fees	Acceleron Actelion	less than $10,000 each

		Bayer Boehringer Ingelheim Chemomab CSL Behring Corbus Galapagos Janssen Inventiva Lilly Mitsubishi MSD Pfizer Regeneron Roche Samsung	
5	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	__X__None	
6	Payment for expert testimony	__X__None	
7	Support for attending meetings and/or travel	__X__None	
8	Patents planned, issued or pending	__X__None	
9	Participation on a Data Safety Monitoring Board or Advisory Board	_X___None	
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	__X__None	
11	Stock or stock options	__X__None	
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	__X__None	
13	Other financial or non-financial interests	__X__None	

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_X__ I certify that I have answered every question and have not altered the wording of any of the questions on this form.

ICMJE DISCLOSURE FORM

Date: 08 December 2022
Your Name: Niyati Prasad
Manuscript Title: A 24-Week, Phase IIa, Randomized, Double-blind, Placebo-controlled Study of Ziritaxestat in Early Diffuse Cutaneous Systemic Sclerosis (NOVESA)
Manuscript number (if known): ar-22-0805

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Time frame: past 36 months			
2	Grants or contracts from any entity (if not indicated in item #1 above).	__X__None	
3	Royalties or licenses	__X__None	
4	Consulting fees	__X__None	

5	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	__X__None	
6	Payment for expert testimony	__X__None	
7	Support for attending meetings and/or travel	__X__None	
8	Patents planned, issued or pending	__X__None	
9	Participation on a Data Safety Monitoring Board or Advisory Board	_X___None	
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	__X__None	
11	Stock or stock options	Galapagos	warrant holder
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	__X__None	
13	Other financial or non-financial interests	__X__None	

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_X_ I certify that I have answered every question and have not altered the wording of any of the questions on this form.

ICMJE DISCLOSURE FORM

Date: 08 December 2022
Your Name: Philippe Pujuguet
Manuscript Title: A 24-Week, Phase IIa, Randomized, Double-blind, Placebo-controlled Study of Ziritaxestat in Early Diffuse Cutaneous Systemic Sclerosis (NOVESA)
Manuscript number (if known): ar-22-0805

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Time frame: past 36 months			
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3	Royalties or licenses	__X__None	
4	Consulting fees	__X__None	

5	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	__X__None	
6	Payment for expert testimony	__X__None	
7	Support for attending meetings and/or travel	__X__None	
8	Patents planned, issued or pending	__X__None	
9	Participation on a Data Safety Monitoring Board or Advisory Board	_X___None	
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	__X__None	
11	Stock or stock options	Galapagos	warrant holder
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	__X__None	
13	Other financial or non-financial interests	__X__None	

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ICMJE DISCLOSURE FORM

Date: 08 December 2022
Your Name: Matthew Randall
Manuscript Title: A 24-Week, Phase IIa, Randomized, Double-blind, Placebo-controlled Study of Ziritaxestat in Early Diffuse Cutaneous Systemic Sclerosis (NOVESA)
Manuscript number (if known): ar-22-0805

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6	Payment for expert testimony	__X__None	
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10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	__X__None	
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ICMJE DISCLOSURE FORM

Date: 08 December 2022
Your Name: Pieter-Jan Stiers
Manuscript Title: A 24-Week, Phase IIa, Randomized, Double-blind, Placebo-controlled Study of Ziritaxestat in Early Diffuse Cutaneous Systemic Sclerosis (NOVESA)
Manuscript number (if known): ar-22-0805

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Time frame: Since the initial planning of the work			
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Time frame: past 36 months			
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3	Royalties or licenses	__X__None	
4	Consulting fees	__X__None	

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6	Payment for expert testimony	__X__None	
7	Support for attending meetings and/or travel	__X__None	
8	Patents planned, issued or pending	__X__None	
9	Participation on a Data Safety Monitoring Board or Advisory Board	_X___None	
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	__X__None	
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ICMJE DISCLOSURE FORM

Date: 09 December 2022
Your Name: Maureen D. Mayes
Manuscript Title: A 24-Week, Phase IIa, Randomized, Double-blind, Placebo-controlled Study of Ziritaxestat in Early Diffuse Cutaneous Systemic Sclerosis (NOVESA)
Manuscript number (if known): ar-22-0805

In the interest of transparency, we ask you to disclose all relationships/activities/interests listed below that are related to the content of your manuscript. "Related" means any relation with for-profit or not-for-profit third parties whose interests may be affected by the content of the manuscript. Disclosure represents a commitment to transparency and does not necessarily indicate a bias. If you are in doubt about whether to list a relationship/activity/interest, it is preferable that you do so.

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Time frame: Since the initial planning of the work			
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Time frame: past 36 months			
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3	Royalties or licenses	_x___None	

4	Consulting fees	Actelion Astellas Medtelligence Mitsubishi Tanabe	Less than $10000 each
5	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	__x__None	
6	Payment for expert testimony	__x__None	
7	Support for attending meetings and/or travel	__x__None	
8	Patents planned, issued or pending	_x___None	
9	Participation on a Data Safety Monitoring Board or Advisory Board	_x___None	
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	__x__None	
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ICMJE DISCLOSURE FORM

Date: 06 December 2022
Your Name: Daniel E. Furst
Manuscript Title: A 24-Week, Phase IIa, Randomized, Double-blind, Placebo-controlled Study of Ziritaxestat in Early Diffuse Cutaneous Systemic Sclerosis (NOVESA)
Manuscript number (if known): ar-22-0805

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Time frame: past 36 months			
2	Grants or contracts from any entity (if not indicated in item #1 above).	Actelion GSK Roche/Genentech Sanofi	Less than $10000 each
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4	Consulting fees	Amgen	Less than $10000 each

		BMS Horizon Corbus Prometheus Galapagos Talaris Novartis Pfizer	
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8	Patents planned, issued or pending	_X___None	
9	Participation on a Data Safety Monitoring Board or Advisory Board	__X__None	
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	__X__None	
11	Stock or stock options	None	
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	_X___None	
13	Other financial or non-financial interests	None	

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

Study design

NOVESA parent study
Phase IIa, randomized, placebo-controlled double-blind, proof-of-concept

Primary end point: change in modified Rodnan skin score (MRSS) at week 24

Open-label extension

Primary end point: incidence of adverse events, treatment-emergent adverse events (TEAEs) and serious TEAEs

Study Population

Adults with early diffuse cutaneous systemic sclerosis (dcSSc)

- **70%** Female
- Mean age: **49.3** years
- Mean disease duration: **1.9** years

NOVESA parent study:
n = 21 **ziritaxestat** 600 mg
n = 12 placebo

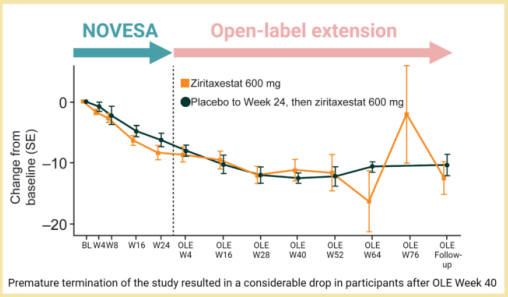
Open-label extension:
n = 31 **ziritaxestat** 600 mg

Efficacy

NOVESA

Significantly greater reduction in MRSS for **ziritaxestat** versus placebo-treated patients at **week 24**

Least squares mean:
Ziritaxestat: −8.9 units
Placebo: −6.0 units
P = 0.0411



Premature termination of the study resulted in a considerable drop in participants after OLE Week 40

Open-label extension

Patients who switched from placebo to **ziritaxestat** showed similar reductions in mRSS to those receiving **ziritaxestat** in the parent study

Safety

Treatment-emergent adverse events in the parent study were largely mild or moderate; none resulted in discontinuation

Target engagement and disease biomarkers

Ziritaxestat reduced plasma LPA C18:2 at each time point up to week 24, confirming target engagement. Circulatory markers of fibrosis were reduced at week 24 in the **ziritaxestat** group and increased in the placebo group

Summary

At 24 weeks, improvements in mRSS were significantly greater in the **ziritaxestat** treatment group versus placebo; biomarker analysis suggested that **ziritaxestat** reduces circulatory markers of fibrosis. **Ziritaxestat** was generally well-tolerated.

Khanna D, Denton CP, Furst DE, et al. A 24-week, phase IIa, randomized, double-blind, placebo-controlled study of ziritaxestat in early diffuse cutaneous systemic sclerosis (NOVESA). Arthritis Rheumatol 2023.

Arthritis & Rheumatology ACR American College of Rheumatology

ART_42477_Khanna_GraphicalAbstract_ar-22-0805.png

Table 1. Baseline characteristics (Full Analysis Set).

Characteristic	**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)
FVC			
Mean (SD), mL	3561.3 (909.9)	3441.1 (1464.2)	3524.0 (1085.1)

Range, mL	2579–6470	1393–5805	1393–6470
Percent predicted FVC			
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)			
Methotrexate + prednisone	2 (9.5)	2 (16.7)	4 (12.1)
Mycophenolate mofetil (no prednisone)	4 (19.0)	2 (16.7)	6 (18.2)
Mycophenolate + prednisone	9 (42.9)	2 (16.7)	11 (33.3)
Prednisone alone	4 (19.0)	4 (33.3)	8 (24.2)
None	1 (4.8)	0	1 (3.0)
	1 (4.8)	2 (16.7)	3 (9.1)
Any systemic corticosteroids at baseline*	9 (42.9)	6 (50.0)	15 (45.5)
≤7.5 mg QD	7 (33.3)	5 (41.7)	12 (36.4)
>7.5 mg QD	2 (9.5)	1 (8.3)	3 (9.1)

Data are presented as n (%), unless otherwise stated. *Includes prednisone, prednisolone, and methylprednisolone. FVC, forced vital capacity; HAQ-DI, Health Assessment Questionnaire Disability Index; mRSS, modified Rodnan skin score; QD, once daily; SD, standard deviation

Table 2. Summary of TEAEs (Safety Analysis Set).

Characteristic, n (%)	**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
Patient 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

*>3 patients in the ziritaxestat group and/or >2 patients in the placebo group.

†≥3 patients in the ziritaxestat group and/or >2 patients in the placebo group.

TEAE, treatment-emergent adverse event

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 vs. placebo	
Biomarker	**Baseline**	**Change from baseline at Week 24*,†**	**Baseline**	**Change from baseline at Week 24†,‡**	**Treatment effect†**	***P* value**
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	84842.9 ± 40513.4¶	−9580.1 (−19183.4, 23.2)	60169.6 ± 23057.3	6256.4 (−4491.5, 17004.4)	−15836.6 (−29991.2, −1681.9)	0.0295

Data are presented as mean ± standard deviation or LS mean (95% confidence interval). *n = 19. †LS mean estimates. ‡n = 10. §n = 18 at Week 24. ¶n = 20 at baseline. C3M, matrix metalloproteinase-9 degradation of type 3 collagen; C4M, matrix metalloproteinase-2,9,12 degradation of type 4 collagen; C6M, matrix metalloproteinase-2 degradation of type 6 collagen; C7M, matrix metalloproteinase-

13 degradation of type 7 collagen; CCL18, chemokine (C-C motif) ligand 18; LS, least squares; PRO-C4, procollagen 4 N-terminal propeptide