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Assessment of the Impact of RNase in Patients With Severe Fatigue Related to Post-Acute Sequelae of SARS-CoV-2 Infection (PASC): A Randomized Phase 2 Trial of RSLV-132

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Background. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA and RNA debris persist in viral reservoirs for weeks to months following infection, potentially triggering interferon production and chronic inflammation. RSLV-132 is a biologic drug composed of catalytically active human RNase1 fused to human IgG1 Fc and is designed to remain in circulation and digest extracellular RNA. We hypothesized that removal of SARS-CoV-2 viral RNA from latent reservoirs may improve inflammation, neuroinflammation, and fatigue associated with post-acute sequelae of SARS-CoV-2 infection (PASC).

Methods. This was a phase 2, double-blind, placebo-controlled randomized clinical trial in participants with a 24-week history of PASC and severe fatigue. The primary endpoint of the trial assessed the impact of 6 intravenous doses of RSLV-132 on the mean change from baseline at day 71 in the Patient-Reported Outcomes Measurement Information System Fatigue Short Form 7a (PROMIS Fatigue SF 7a).

Results. A statistically significant difference on day 71 was not observed with respect to the primary or secondary endpoints. This was likely due to a placebo response that increased during the trial. Statistically significant improvement in fatigue as measured by the PROMIS Fatigue SF 7a, Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-Fatigue), and Physicians Global Assessment (PGA) instruments were observed earlier in the trial, with women demonstrating greater responses to RSLV-132 than men.

Conclusion. While fatigue was not statistically significantly improved at Day 71, earlier timepoints revealed statistically significant improvement in fatigue and physician global assessment. The data suggest eliminating latent viral RNA by increasing serum RNase activity may improve fatigue in PASC patients. Women may respond better to this approach than men. Future studies will aim to confirm these findings.

Keywords. PASC; RNase; RSLV-132; COVID-19; fatigue.

Of the estimated 770 million patients infected worldwide with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), approximately 20% experience severe, debilitating symptoms that persist for months to years following the acute illness. Patients with long coronavirus disease 2019 (COVID-19) or post-acute sequelae of SARS-CoV-2 infection (PASC) have a complex constellation of symptoms involving major organ systems, such as immune system dysregulation with a break in self-tolerance and the development of autoantibodies, cognitive impairment, severe fatigue, and pulmonary, cardiovascular, renal, and gastrointestinal symptoms [1, 2]. While the symptoms of PASC vary considerably among patients, severe debilitating fatigue is one of the few that is shared by the majority of patients [3, 4]. PASC shares many symptoms with another post-viral illness, myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), prompting some investigators to suggest there may be common underlying biological abnormalities between the 2 diseases [5].

Numerous studies have described the persistence of SARS-CoV-2 RNA for up to several months following infection. Although not detectable by typical diagnostic methods, viral RNA and RNA debris have been found in reservoirs within the body for long periods of time following initial diagnosis [6–11]. These reservoirs of viral RNA may drive chronic inflammation and neuroinflammation responsible for some of the symptoms of PASC.

One of the most fundamental and crucial functions of the human immune system is the detection of and response to viral infection. Given the importance of rapid detection and elimination of viral RNA, the immune system has evolved multiple, sensitive mechanisms to detect and respond to extracellular

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RNA. At least 5 known receptors bind to different forms of RNA, resulting in receptor activation and the production of type I interferons. These include the retinoic acid–inducible gene I (RIG-I), melanoma differentiation-associated gene 5 (MAD5), and Toll-like receptors (TLR) 3, 7, and 8 [12–16]. Of these RNA receptors, TLR7 has been extensively studied in autoimmune diseases such as systemic lupus erythematosus (SLE), where its overexpression appears to be causally associated with the disease [17–20]. Persistent, increased expression of type I interferons has also been observed in PASC [21].

Several autoimmune diseases such as SLE and Sjögren's, as well as some post-viral illnesses such as ME/CFS, affect primarily women; studies suggest they are also at increased risk for PASC relative to men [22]. The prevailing view of the mechanism accounting for this sex difference in female-biased autoimmune diseases is incomplete X chromosome inactivation (XCI), which has been shown to lead to overexpression of TLR7, increased interferon signaling, and chronic inflammation [23, 24]. Xist is a long-noncoding RNA (lncRNA) transcribed only in females that initiates and maintains XCI [25]. A recent discovery demonstrates that Xist is associated with several protein autoantigens in patients with autoimmune diseases, and when expressed in transgenic male animals, worsens SLE-like disease pathology [26].

Clinical trials in SLE and Sjögren's syndrome with RSLV-132 that increased serum RNase catalytic activity resulted in reduced fatigue and a reduction in other disease symptoms [27, 28]. Therefore, we hypothesized that increasing serum RNase enzymatic activity in patients with PASC may lead to the digestion and removal of viral RNA, and possibly decreased inflammation, and improve clinical symptoms, such as fatigue. We evaluated this hypothesis through a placebo-controlled, randomized clinical trial of RSLV-132, a catalytically active RNase Fc fusion protein.

METHODS

Patients

Participants aged 18 to 75 years with COVID-19 and diagnosed with SARS-CoV-2 by polymerase chain reaction (PCR) test of a nasal swab at least 24 weeks prior to baseline were enrolled in the trial. Participants were required to have a history of COVID-19 symptoms from diagnosis to screening and severe fatigue at screening as documented by the Patient-Reported Outcomes Measurement Information System Fatigue Short Form 7a (PROMIS Fatigue SF 7a) raw score of 21 or greater (standardized to a T-score of 58), with a medical history confirming that the onset of fatigue was postinfection and not preexisting. History of 24 weeks of persistent severe fatigue was determined based on participant self-report of severe fatigue symptoms beginning at the time of index COVID-19 infection and persisting until the time of eligibility assessment. Study investigators reviewed participant medical history to confirm that severe fatigue was due to index COVID-19 infection as opposed to another alternative etiology.

Trial Design

The present trial was a phase 2, double-blind, placebo-controlled randomized clinical trial in participants with at least a 24-week history of PASC and severe fatigue. The first trial treatment was administered on 4 August 2021, and the last follow-up visit occurred on 12 January 2023. Randomization was conducted by computer algorithm and transmitted to an unblinded pharmacist at each of the 4 trial sites. Participants were randomized 2:1 to receive 6 intravenous doses of 10 mg/kg RSLV-132 or matched placebo, respectively, on days 1, 8, 15, 29, 43, and 57. The volume of placebo infusions corresponded to the participant's equivalent weight-based RSLV-132 infusion volume. Placebo infusions were administered using the same supplies as RSLV-132 infusions. Placebo and RSLV-132 infusions were of similar clear, colorless appearance and indistinguishable to study staff and participants. The primary endpoint in the trial was the mean change from baseline at day 71 in the PROMIS Fatigue SF 7a T-score, comparing the placebo and RSLV-132 groups. Secondary endpoints included the Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-Fatigue), and the Physicians Global Assessment (PGA), the Digit Symbol Substitution Test (DSST), long COVID-19–related symptom patient assessment, and the Patient Global Assessment of Change (PGIC). Exploratory endpoints included SARS-CoV-2 RNA real-time reverse transcriptase-polymerase chain reaction (RT-PCR), measurement of serum antinuclear antibodies (ANAs), antiphospholipid antibodies, C-reactive protein (CRP), and serum ferritin. The trial was conducted in accordance with the principles of the Declaration of Helsinki and the International Council for Harmonization Guidelines for Good Clinical Practice. Institutional review board approval was obtained, and all participants provided written informed consent.

Statistical Analyses

A mixed model for repeated measures (MMRM) was used to analyze the primary endpoint. The analysis was conducted on observed data without imputation. The analysis tested a 1-sided hypothesis that mean change from baseline to day 71 in PROMIS Fatigue SF 7a T-score was the same for both treatment groups versus the alternative that RSLV-132 treatment is superior to placebo at the significance level of 5%. The MMRM included fixed effects of randomized treatment group, visit, treatment by visit interaction, baseline PROMIS Fatigue SF 7a T-score, vaccination status (yes/no), COVID duration (days from COVID diagnosis to the first treatment dose), relevant medical history (yes/no), age, and sex with intercept and visit as random effects. The analysis was performed on the modified intent-to-treat (mITT) population consisting of all

participants with at least 1 post-baseline visit and whose COVID-19 duration was at least 168 days prior to the baseline visit. Two participants were eliminated from the mITT population and not included in the efficacy analysis as a result of a protocol deviation resulting in these 2 participants being enrolled with 167 days of COVID-19 duration rather than the required 168 days. Additionally, the following subgroups were analyzed: males, females, and participants who were ANA positive at trial entry. The same statistical approach was utilized for the secondary efficacy endpoints. Data were also analyzed descriptively.

RESULTS

Demographics and Baseline Variables

Baseline demographic and clinical characteristics were similar between the 2 treatment groups. The RSLV-132 group was slightly older than the placebo group (47.1 ± 13.64 vs 40.4 ± 12.53 years) and had a higher proportion of females (56.8% vs 45.6%). Approximately two-thirds of participants were White (RSLV-132: 69.1%; placebo: 64.9%) with a higher proportion of Black participants in the placebo group (35.1%) than in the RSLV-132 group (26.5%). The trial population reported similar degrees of severe fatigue, as indicated by the PROMIS Fatigue SF 7a and FACIT-Fatigue instruments. No participants were positive for SARS-CoV-2 RNA or anti-phospholipid antibodies at baseline or day 71. Anti-nuclear antibody positivity was higher in the placebo group (86.5%) than in the RSLV-132 group (69.1%) (Table 1). The mean duration of symptoms for participants included in the mITT population was 355 days (range, 177–722 days) for the RSLV-132 group and 332 days (range, 169–817 days) for the placebo group. The average duration of PASC symptoms prior to baseline was similar between the placebo and RSLV-132 arms as well as the male and female subgroups (Supplementary Figures 19 and 20).

Table 1. Demographic and Baseline Clinical Characteristics for All Participants Treated

	RSLV-132 (n = 68)	Placebo (n = 37)
Age (mean ± SD), y	47.1 ± 13.64	40.4 ± 12.53
Sex (number, %)		
Male	31 (45.6%)	21 (56.8%)
Female	37 (54.4%)	16 (43.2%)
Race, n (%)		
White	47 (69.1%)	24 (64.9%)
Black or African American	18 (26.5%)	13 (35.1%)
Other	2 (2.9%)	0
Asian	1 (1.5%)	0
Weight (mean ± SD), kg	83.4 ± 21.90	88.6 ± 23.23
BMI (mean ± SD), kg/m^2	29.0 ± 6.49	29.7 ± 7.00
PROMIS Fatigue SF 7a (mean ± SD), raw score	25.9 ± 3.45	26.3 ± 3.36
PROMIS Fatigue SF 7a (mean ± SD), T-score	64.8 ± 5.31	65.4 ± 5.47
FACIT-F (mean ± SD)	17.9 ± 8.92	17.1 ± 6.99
PGA (mean ± SD)	76.7 ± 12.55	77.4 ± 8.99
Positive SARS-CoV-2 (nasal swab/PCR) at baseline	0	0
C-reactive protein (mean ± SD), mg/L	4.6 ± 7.68	4.3 ± 6.44
Serum ferritin, µg/L	81.1 ± 75.22	66·3 ± 47.22
Positive ANA, n (%)	47 (69.1%)	32 (86.5%)

Abbreviations: ANA, antinuclear antibody; BMI, body mass index; FACIT-F, Functional Assessment of Chronic Illness Therapy–Fatigue; PCR, polymerase chain reaction; PGA, Physicians Global Assessment; PROMIS Fatigue SF 7a, Patient-Reported Outcomes Measurement Information System Fatigue Short Form 7a; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SD, standard deviation.

Disposition

A total of 120 participants were screened for trial entry, and 8 participants not meeting the eligibility criteria were excluded. Of the remaining 112 participants, 108 were randomized at 4 clinical research sites in the United States. Three randomized participants in the RSLV-132 treatment group withdrew consent before receiving treatment. The safety analysis set therefore consisted of the 105 participants (68 in the RSLV-132 group and 37 in the placebo group) who received at least 1 infusion of trial treatment. An additional 9 (8.6%) participants withdrew from the trial after receiving at least 1 dose of trial treatment: 6 (8.8%) participants in the RSLV-132 group and 3 (8.1%) participants in the placebo group. The timing and reasons for early termination are summarized in Supplementary Table 2. A total of 62 (91.2%) participants in the RSLV-132 group and 34 (91.9%) participants in the placebo group completed the trial (Figure 1).

The first 8 participants who were enrolled in the trial (6 in the RSLV-132 group and 2 in the placebo group) were enrolled under an early version of the protocol with FACIT-Fatigue as the primary endpoint and PASC duration of 12 to 24 weeks. After the eighth participant was enrolled and following additional regulatory agency input, the primary endpoint was changed from FACIT-Fatigue to PROMIS Fatigue SF 7a and participants were required to have been diagnosed with COVID-19 at least 24 weeks prior to baseline. Therefore, these 8 participants were included in the safety analysis but not the efficacy analysis. Efficacy data from a total of 95 participants in the mITT population (61 RSLV-132 and 34 placebo) were analyzed with respect to the primary and secondary endpoints since a further 2 participants (1 participant in each treatment group) did not have a COVID-19 duration of at least 168 days prior to baseline and were therefore not eligible for mITT population.

Efficacy

There was no statistically significant difference in the primary or secondary endpoints between the RSLV-132 and placebo groups at day 71. The change from baseline in the mean PROMIS Fatigue SF 7a T-score at day 71 for the RSLV-132 group was −13.30 ± 9.94 compared with the placebo group, which was −11.24 ± 8.43 ($P = .089$). The mean change in the FACIT-Fatigue secondary endpoint at day 71 in the

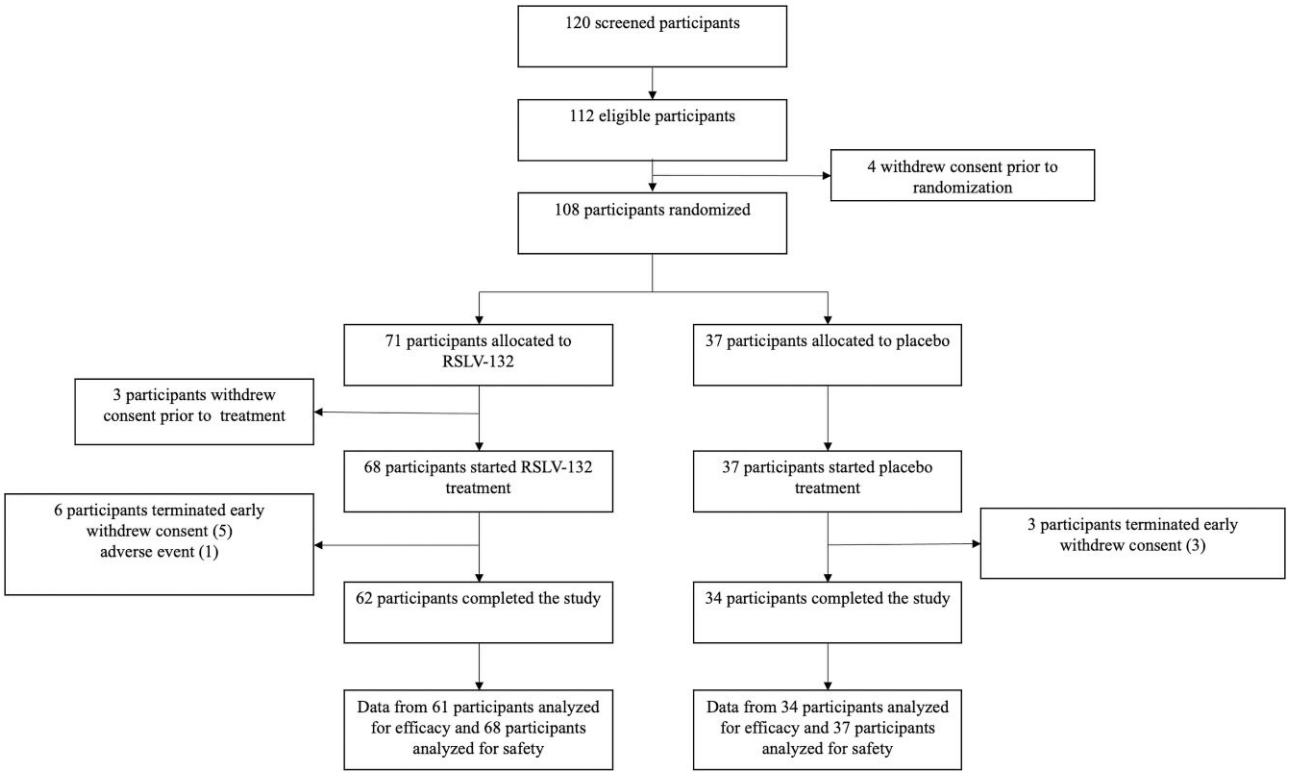

Figure 1. Trial participant disposition. Eligible participants were randomized 2:1 (RSLV-132:placebo) to receive a total of 6 intravenous infusions of placebo or 10 mg/kg RSLV-132 at baseline then weekly for 3 weeks followed by 2 biweekly infusions over the second month.

Table 2. Efficacy Evaluations, Mean (±SD) Change From Baseline (mITT Population)

	Day 29			Day 71		
	RSLV-132	Placebo	*P*	RSLV-132	Placebo	*P*
All participants, N	54	34		55	31	
PROMIS Fatigue SF 7a	−9.22 ± 8.53	−5.98 ± 6.20	.016	−13.30 ± 9.94	−11.24 ± 8.43	.089
FACIT-F	12.00 ± 11.72	8.00 ± 10.83	.023	18.30 ± 12.41	16.13 ± 13.32	.260
PGA	−30.60 ± 24.44	−25.50 ± 23.51	.037	−53.40 ± 25.49	−48.90 ± 23.17	.156
Female subgroup, n	30	15		30	14	
PROMIS Fatigue SF 7a	−10.97 ± 7.80	−5.53 ± 4.93	.041	−14.23 ± 9.66	−11.33 ± 7.70	.299
FACIT-F	15.30 ± 11.55	8.20 ± 9.57	.027	21.10 ± 12.44	20.29 ± 14.00	.618
PGA	−34.60 ± 23.03	−22.30 ± 22.21	.022	−56.80 ± 25.30	−53.80 ± 20.46	.444
Male subgroup, n	24	19		25	17	
PROMIS Fatigue SF 7a	−7.03 ± 9.06	−6.34 ± 7.16	.200	−12.19 ± 10.34	−11.16 ± 9.21	.167
FACIT-F	7.90 ± 10.80	7.80 ± 11.99	.322	14.80 ± 11.70	12.71 ± 12.06	.260
PGA	−25.60 ± 25.70	−28.10 ± 24.79	.381	−49.38 ± 25.63	−44.88 ± 25.05	.129

Abbreviations: FACIT-F, Functional Assessment of Chronic Illness Therapy–Fatigue; mITT, modified intent-to-treat; PGA, Physicians Global Assessment; PROMIS Fatigue SF 7a, Patient-Reported Outcomes Measurement Information System Fatigue Short Form 7a; SD, standard deviation.

RSLV-132 group was 18.30 ± 12.41 and in the placebo group was 16.13 ± 13.32 ($P = .260$). The mean change in the PGA secondary endpoint at day 71 for the RSLV-132 group was −53.40 ± 25.49 and in the placebo group was −48.90 ± 23.16 ($P = .156$) (Table 2). A lack of statistical significance was also observed with the DSST, PGIC, and long COVID–related patient symptom assessment instruments at all time points (data not shown).

In post hoc analyses of earlier time points, statistically significant differences were observed in the primary and secondary efficacy outcomes in the RSLV-132 compared with placebo groups. These differences did not persist at day 71, likely due to an increase in placebo response. For example, at day 29 there was a statistically significant difference in the PROMIS SF 7a instrument between the RSLV-132 group (−9.22 ± 8.53) and the

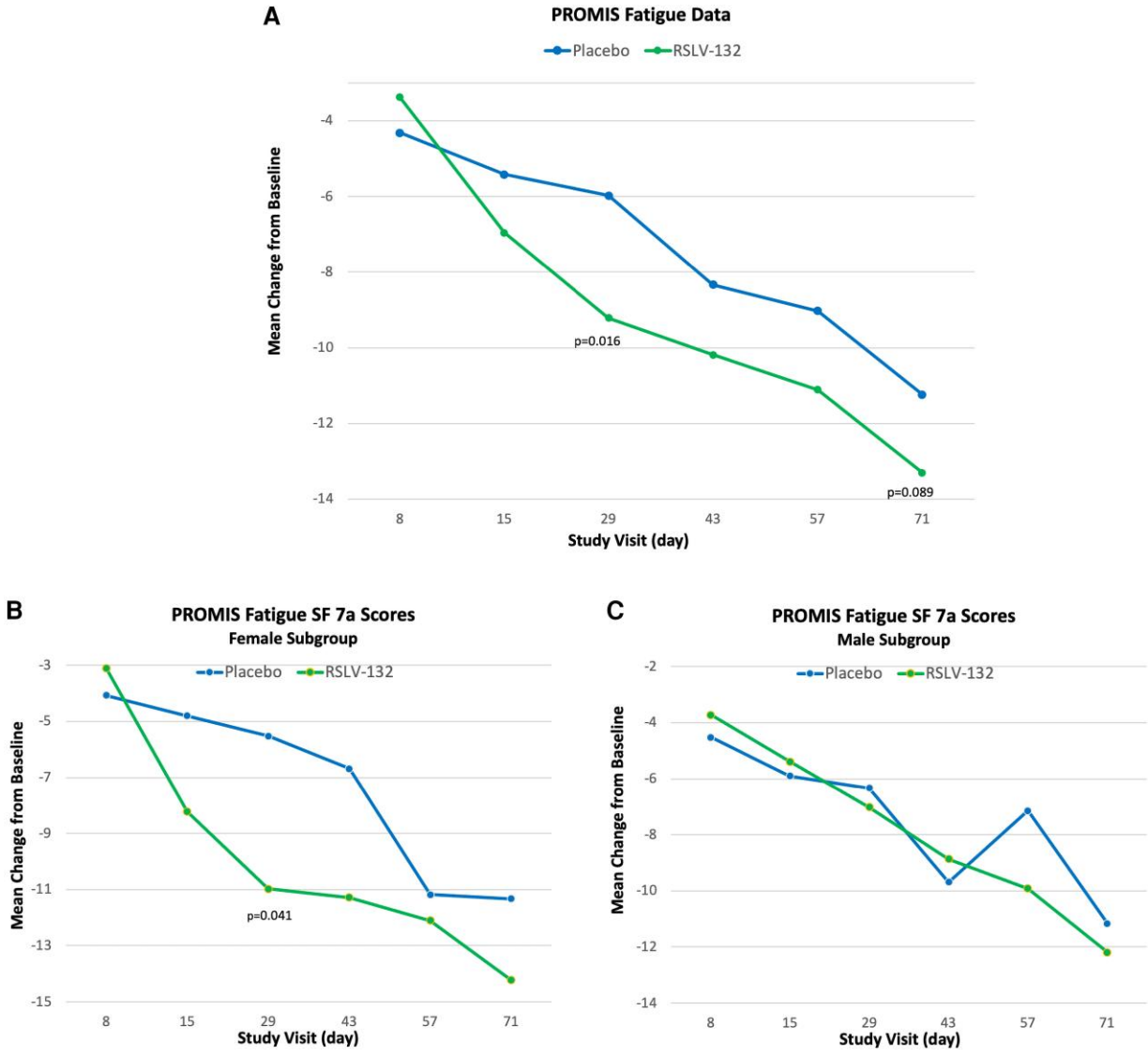

Figure 2. The change from baseline in mean PROMIS Fatigue SF 7a scores are shown for the indicated trial day. *A*, Overall change from baseline in mean PROMIS score for the RSLV-132 and placebo groups (N = 95). *B*, Change from baseline in PROMIS score for the female participants (n = 48). *C*, Change from baseline in PROMIS score for the male participants (n = 47). Abbreviation: PROMIS Fatigue SF 7a, Patient-Reported Outcomes Measurement Information System Fatigue Short Form 7a.

placebo group (−5.98 ± 6.20) ($P = .016$) (Figure 2*A*, Table 2). Similar results were observed with the FACIT-Fatigue instrument, where a mean change from baseline of 12.00 ± 11.72 in the RSLV-132 group compared with 8.00 ± 10.83 in the placebo group achieved statistical significance ($P = .023$) (Supplementary Figure 1, Supplementary Table 1). Statistically significant differences were also observed with the PGA at day 15 (RSLV-132, −21.70 ± 20.53 vs −13.00 ± 14.56 for placebo; $P = .023$), at day 29 (RSLV-132, −30.60 ± 24.44 vs −25.50 ± 23.51 for placebo; $P = .037$), and day 43 (RSLV-132, −41.20 ± 25.85 vs −32.70 ± 24.20 for placebo; $P = .017$) (Figure 3*A*, Table 2, Supplementary Table 1).

Additional post hoc analyses examined the ANA-positive subgroup and the male and female subgroups. A large percentage of the participants (75%) had a positive ANA at baseline. At day 29 a statistically significant improvement in PROMIS Fatigue SF 7a ($P = .028$), FACIT-Fatigue ($P = .026$), and PGA (day 15, $P = .032$; day 29, $P = .038$) scores was observed with the ANA-positive subgroup (Supplementary Figures 2, 9, and 14). Female trial participants treated with RSLV-132 experienced a statistically significant improvement in fatigue relative to placebo at earlier time points, although not at day 71. For example, despite the reduced sample size and commensurate loss of statistical power, the female subgroup experienced statistically significant improvements in fatigue as measured by PROMIS Fatigue SF 7a ($P = .041$) (Figure 2*B*), FACIT-Fatigue ($P = .027$) (Supplementary Figure 3), and PGA (day 15, $P = .028$; day 29, $P = .022$; day 43, $P = .021$) (Figure 3*B*). In the male subgroup, the RSLV-132 and

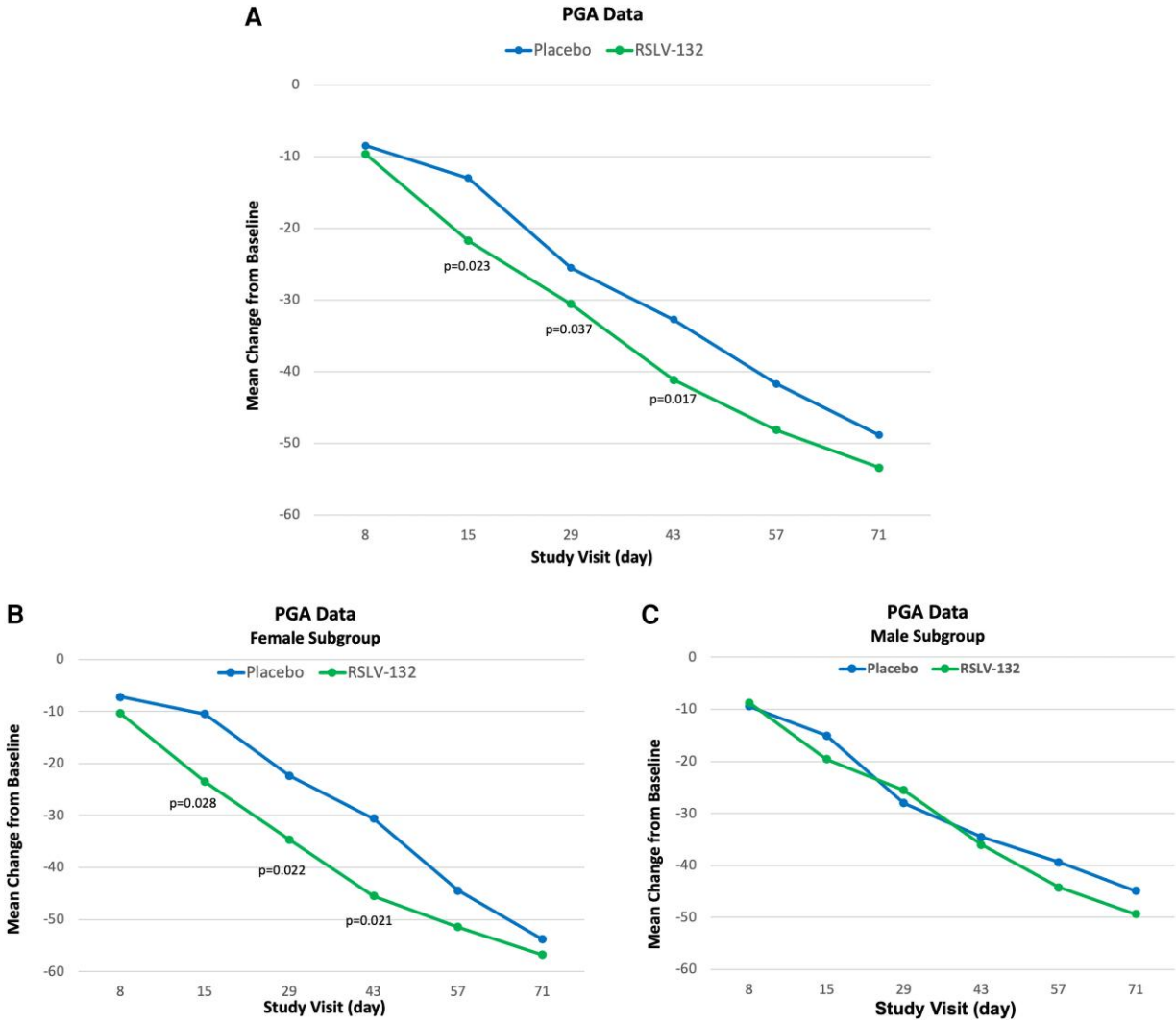

Figure 3. The change from baseline in mean PGA scores are shown for the indicated trial day. *A*, Overall change from baseline in mean PGA score for the RSLV-132 and placebo groups (N = 95). *B*, Change from baseline in PGA score for the female participants (n = 48). *C*, Change from baseline in PGA score for the male participants (n = 47). Abbreviation: PGA, Physicians Global Assessment.

placebo arms were almost indistinguishable (Figures 2*C* and 3*C*, Supplementary Figure 4). The magnitude of this response was larger (but not statistically significant) in the participants diagnosed with SARS-CoV-2 between 168 and 365 days prior to baseline (Supplementary Figures 5, 6, 10, 11, 15, and 16). In the subgroup of patients with a duration of PASC symptoms greater than 365 days, this difference in response among males versus females was less pronounced (Supplementary Figures 7, 8, 12, 13, 17, and 18). These statistically significant differences between ANA-positive compared with ANA-negative and male compared with female participants at earlier time points did not persist at day 71.

Inflammation Markers

Small, but not clinically meaningful, differences in mean change from baseline to day 71 in CRP and ferritin were observed comparing the RSLV-132 and placebo groups; similar results were observed comparing the male and female subgroups (data not shown).

Safety and Tolerability

The incidence of treatment-emergent adverse events and treatment-related adverse events was low and generally comparable between the RSLV-132 and placebo treatment groups (Table 3). No deaths or serious or severe adverse events occurred during the trial. All infections were mild or moderate in severity and assessed as being not related to trial treatment. There were no infusion reactions in either treatment group during the trial. One participant in the RSLV-132 group was withdrawn from the trial due to an adverse event of monkey pox, which was not related to treatment.

Table 3. Treatment-Emergent Adverse Events for All Participants Treated

	RSLV-132 (n = 68)	Placebo (n = 37)
At least 1 TEAE	18 (26.5%)	7 (18.9%)
At least 1 treatment-related TEAE	9 (13.2%)	4 (10.8%)
At least 1 severe TEAE	0	0
At least 1 serious TEAE	0	0
TEAE leading to study discontinuation	1 (1.5%)	0
Deaths	0	0
Infections	6 (8.8%)	2 (5.4%)
Most commonly reported TEAEs		
Headache	7 (10.3%)	1 (2.7%)
Nausea	6 (8.8%)	0
Upper respiratory tract infection	3 (4.4%)	0

Data are presented as n (%).

Abbreviation: TEAE, treatment-emergent adverse event.

DISCUSSION

This is the first clinical trial to our knowledge to evaluate the potential role of nucleic acids in a post-viral illness. The study was designed to evaluate catalytically active RNase in patients with PASC experiencing severe fatigue. Numerous studies have documented the persistence of SARS-CoV-2 RNA and RNA debris many months following infection. Given the known proinflammatory properties of extracellular RNA, this trial sought to determine if clearing RNA from latent extracellular reservoirs may have a positive clinical impact on PASC-related fatigue.

The mean changes from baseline in the PROMIS Fatigue SF 7a, PGA, and FACIT-Fatigue scores at day 71 were not statistically significantly different between the RSLV-132 and placebo groups ($P = .089$). The absence of a statistically significant difference at the end of the trial may, at least in part, be due to an increased placebo response during the later stages of the observation period. Statistically significant differences between RSLV-132 and placebo groups in primary and secondary efficacy outcomes were observed at earlier time points.

The lack of objective molecular entry criteria may have introduced heterogeneity into the study that could have influenced the placebo response. Molecular phenotyping may aide in patient selection in future studies. For example, a recent exhaustive study of patients with post-viral ME/CFS revealed striking differences in gene expression, including statistically significantly decreased expression of RNA- and Rnase-related pathways in the muscle tissue of male participants, which were not observed in females [29].

While the primary efficacy endpoint at day 71 was not met in the overall sample of patients with PASC and severe fatigue, treatment response to Rnase therapy differed between female and male participants at earlier time points in the trial. A post hoc subgroup analysis comparing female and male subgroups revealed statistically significant improvement in fatigue among the female participants relative to male participants. Female participants treated with RSLV-132 experienced statistically significant improvements in their fatigue and overall disease activity relative to placebo as measured by the PROMIS (day 29), FACIT-Fatigue (day 29), and PGA (days 15, 29, 43) scores, despite the study not being powered to detect these differences. Similar trends were not observed in male participants.

The molecular basis for the drug response observed in female participants is unknown at the present time. However, it is plausible that some of the females in the trial may have an increased sensitivity to the inflammatory effects of RNA and therefore derive more benefit from its removal than males. In autoimmune diseases such as SLE some females are known to have increased expression of TLR7 because of incomplete XCI, which is thought to increase activation of the interferon pathway driving the disease symptoms. Studies in PASC have shown that females are at higher risk of certain PASC symptoms such as fatigue relative to males, suggesting that differing molecular mechanisms may be involved in the development of PASC in females versus males. These hypothesized mechanisms will need to be evaluated in future studies.

A limitation of the study is the lack of clear clinical and molecular diagnostic criteria of PASC, which may have resulted in the inclusion of participants with other post-viral illnesses. In addition, the study was not powered to compare RSLV-132 efficacy between ANA-positive and -negative individuals or those with and without abnormal systemic inflammation at baseline. Larger future studies are needed to address these questions.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. J. A. P. designed and oversaw the study, analyzed the data, and participated in writing the manuscript. J. S. A. was one of the principal investigators of the study, helped design the study, analyzed the data, and participated in writing the manuscript. J. B. B. was one of the subinvestigators and helped with enrolment and study procedures and reviewed the manuscript. E. K. is the biostatistician responsible for the design of the statistical analysis plan and the analysis of the efficacy data and participated in writing the manuscript. S. A. is a medical writer who helped analyze the efficacy data, subject disposition, and safety data. She also participated in writing the regulatory submissions and the manuscript.

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Potential conflicts of interest. J. A. P. owns equity in Resolve Therapeutics. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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