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Evaluation of RNase therapy in systemic lupus erythematosus: a randomised phase 2a clinical trial of RSLV-132

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ABSTRACT

Background Circulating, extracellular RNA is the primary trigger of type I interferon in systemic lupus erythematosus (SLE), and interferon is known to play a central pathogenic role in the disease. RSLV-132 is a catalytically active human RNase molecule fused to human IgG1 Fc designed to digest RNA and thereby decrease the chronic inflammation associated with SLE. The drug was evaluated in a cohort of patients with SLE with moderate-severe cutaneous disease activity and the presence of RNA immune complexes. The primary objective of the study was the assessment of the impact of 13 doses of 10 mg/kg RSLV-132 over 6 months on the mean Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) score.

Methods Sixty-five patients meeting the entry criteria of a baseline CLASI score of 10 or greater and positivity of at least one of five autoantibodies to RNA-binding proteins (SM/RNP, SSA/Ro, SSB/La, Sm, RNP) were randomly assigned (2:1) to receive 13 doses of RSLV-132 10 mg/kg or placebo, respectively. Participants received study drug for 24 weeks on days 1, 8, 15, 29, 43, 57, 71, 85, 99, 113, 127, 141 and 155 with an end-of-treatment visit on day 169 and a follow-up visit at the end of the study on day 215. The primary objective was assessed on days 85 and 169. Secondary objectives included assessment of systemic disease activity using the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K), the British Isles Lupus Assessment Group 2004 Index and the Physician's Global Assessment. Data from these instruments were used to calculate the SLE Responder Index 4 (SRI-4) and the British Isles Lupus Assessment Group-based Composite Lupus Assessment (BICLA) scores.

Results The mean CLASI score change from baseline at day 169 was −5.7 (±7.0) in the placebo group and −6.2 (±8.5) in the RSLV-132 group. A subgroup of participants with moderate-severe systemic disease activity and high baseline SLEDAI scores (≥9) were analysed with respect to BICLA and SRI-4 responses. The RSLV-132 treated participants in the high SLEDAI subgroup had a greater percentage of BICLA responses (62% vs 44%) and SRI-4 responses (23% vs 11%) as compared with placebo. A second subgroup of participants with high baseline CLASI scores (≥21) were analysed with respect to BICLA and SRI-4 responses. The RSLV-132 treated participants in the high CLASI subgroup had a greater percentage of BICLA responses (28% vs 8%) and SRI-4 responses (39% vs 8%) as compared with placebo.

Conclusions Six months of RSLV-132 therapy consisting of a weekly loading dose of RSLV-132 for 1 month, followed by 5 months of biweekly administrations did not significantly improve the mean CLASI score relative to placebo in this cohort of patients with SLE. The study entry criteria selected patients with moderate-severe cutaneous disease activity and no minimum SLEDAI score, which resulted in a wide range of systemic disease activity from inactive to severe as measured by SLEDAI. When the participants with higher SLEDAI and CLASI scores were analysed, a trend towards clinical improvement favouring RSLV-132 was observed. The results warrant further evaluation of RSLV-132 in SLE and suggest that patients with more active systemic disease are most likely to benefit from RNase therapy.

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

⇒ Systemic lupus erythematosus (SLE) is a heterogeneous disease complicating drug development.
⇒ Circulating, extracellular RNA is a potent activator of type I interferons in SLE.
⇒ Interferon plays a central pathogenic role in SLE.

WHAT DOES THIS STUDY ADD

⇒ Extracellular RNA is a novel, potentially important therapeutic target in SLE.
⇒ Increasing extracellular RNase catalytic activity in patients with SLE with moderate-severe disease activity resulted in a suggestion of potential efficacy.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Continued development of RSLV-132 may provide a new therapeutic that can be added to the standard of care in SLE.

INTRODUCTION

An estimated 250 000 Americans and 500 000 Europeans suffer from systemic lupus erythematosus (SLE), the vast majority of whom are women. It is a heterogeneous autoimmune disease with varying clinical manifestations including cutaneous involvement with severe skin rash and alopecia, joint pain and renal involvement. Less commonly the central nervous system (CNS) is affected giving rise to neuropsychiatric lupus. In other presentations,

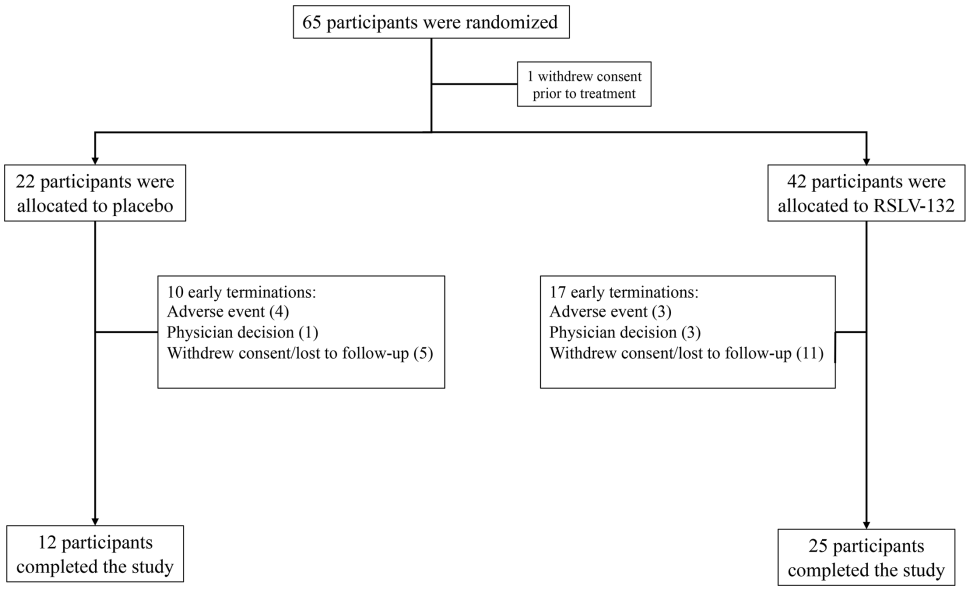

Figure 1 Study participant disposition. Eligible patients were randomised to receive 13 intravenous infusions of placebo or 10 mg/kg RSLV-132 weekly for 4 weeks then twice monthly for 5 months.

the disease targets the lungs. Disease prevalence and severity also have distinct racial and ethnic differences, with African Americans and Asians having a higher prevalence of SLE and more severe organ involvement. Effective clinical management of the disease has proven very challenging due to its heterogeneity. The standard of care has revolved around the use of potent immunosuppressive agents and corticosteroids. While these drugs have resulted in a decrease in mortality from the pre-corticosteroid era, SLE remains a disease with unacceptably high mortality and significant unmet medical need.[1]

At a biochemical level, a decrease in self-tolerance and the presence of autoantibodies in patients with SLE were first reported over six decades ago.[2–4] The majority of characterised autoantibodies recognise self-antigens consisting of nucleic acids or nucleic acid-binding proteins.

The pathogenic role of RNA in SLE has been a focus of increasing attention and investigation given its well-known proinflammatory properties.[5–9] Autoantibodies that bind to RNA-binding proteins have been extensively characterised and their titres carefully measured in clinical practice and clinical studies. Surprisingly, little attention has been paid to the potent inflammatory properties of these antigens.[10] Immune complexes containing Ro, SM/RNP, U1-RNP and Smith maintain RNA in the circulation, in effect acting as delivery vehicles presenting RNA to cells of the immune system.

Two decades ago, investigators discovered that patients with SLE overexpress a group of genes that are regulated by type I interferons. This dysregulation of the interferon pathway, or interferon signature, is now recognised as one of the hallmarks of SLE.[11–13] Since this discovery, a large body of research has elucidated the molecular mechanisms by which the immune system detects and responds to circulating extracellular RNA. Given the importance of rapid detection and robust response to viral RNA, the immune system has evolved numerous, sensitive mechanisms to detect and respond to extracellular RNA, both foreign and self-derived. Key RNA sensors include the retinoic acid-inducible gene I, melanoma differentiation-associated gene 5 and toll-like receptors (TLR) 3, 7 and 8.[14–18] Binding of RNA to these receptors activates downstream transcription factors, most notably Interferon Regulatory Factor 3, with the subsequent production of type I interferon.

RNA is the primary trigger of interferon production through binding to TLR7 and is of central importance in SLE.[17–20] Furthermore, a subset of female patients with SLE have been shown to have increased dosage of TLR7 through incomplete X chromosome inactivation. As such, these patients may be more sensitive to circulating extracellular RNA than women with a single dosage of TLR7, or male patients.[21 22] In this case, removal of circulating RNA may be of particular benefit to this subset of patients with SLE.

Given the large body of scientific literature demonstrating the pathogenic role of circulating RNA in SLE, it was hypothesised that digestion of extracellular RNA may be of clinical benefit to patients with SLE. Therefore, a phase 2a clinical trial was designed to test this hypothesis using RSLV-132 an Fc-fusion protein consisting of human IgG1 Fc fused to catalytically active human RNase1.[23]

PATIENTS AND METHODS

Patients

The study enrolled patients aged 18–70 diagnosed with SLE meeting 4 of the 11 criteria of the 1997 update of the 1982 American College of Rheumatology Revised Criteria. Additional key entry criteria included a history of active SLE with moderate-severe cutaneous disease activity and

Table 1 Demographics and baseline characteristics

	Placebo (n=22)	RSLV-132 (n=42)
Age (years), mean (SD)	45.2 (11.6)	45.3 (12.8)
Gender, number (%)		
Female	22 (100)	39 (93)
Male	0 (0)	3[7]
Race		
Caucasian	11 (50)	22 (52)
African American	11 (50)	16 (38)
Other	0 (0)	3[7]
Asian	0 (0)	1[3]
CLASI Activity Score, mean (SD)	22.4 (7.9)	24.1 (9.9)
SLEDAI-2K, mean (SD)	8.6 (3.3)	8.2 (3.7)
<6	14%	21%
6–10	59%	60%
>10	27%	19%
Physician's Global Assessment, mean (SD)	53.7 (14.0)	52.6 (16.2)
BILAG Scores, number (%)		
Mucocutaneous		
BILAG A Score	11 (50)	27 (64)
BILAG B Score	11 (50)	13 (31)
Musculoskeletal		
BILAG A Score	1[5]	3[7]
BILAG B Score	13 (59)	19 (45)
Renal		
BILAG A Score	0 (0)	1[2]
BILAG B Score	3[14]	5[12]
Autoantibodies, % positive		
Anti-dsDNA	33	20
Anti-RNP/Smith	47	40
Anti-Sm	50	53
Anti-SSA/Ro	78	62
Anti-SSB/La	17	7
Anti-Smith	32	32

BILAG, British Isles Lupus Assessment Group; CLASI, Cutaneous Lupus Erythematosus Disease Area and Severity Index; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000.

a baseline Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) score of 10 or greater.[21] Additional biochemical laboratory entry criteria included the presence of at least one of five autoantibodies to RNA-binding proteins (Ro-52/60, La, Sm, SM/RNP and U1 RNP A/68) as measured by a central laboratory. Participants using medications for their SLE were required to maintain a stable dosage for 30 days prior to baseline. The use of cyclophosphamide or belimumab within 3 months of baseline, or rituximab within 6 months of baseline excluded patients from participating in the study. The use of background medications within 1 month of baseline in excess of 3 g/day of mycophenolate mofetil, 200 mg/day of azathioprine, 400 mg/day of hydroxychloroquine or 15 mg/day of prednisone excluded patients from participating in the study. Patients with severe active CNS involvement or severe renal involvement at screening were excluded from the study.

Study design

The present study was a randomised, placebo-controlled, double-blind phase 2a proof-of-concept study in patients with SLE with moderate-severe cutaneous disease activity. A total of 65 participants were randomised without stratification into the study from May 2016 through June 2019. Participants were randomised 2:1 to receive 13 doses of 10 mg/kg RSLV-132 or placebo, respectively, on days 1, 8, 15, 29, 43, 57, 71, 85, 99, 113, 127, 141 and 155 with an end-of-treatment visit on day 169 and a follow-up visit at the end of the study on day 215. Efficacy endpoints were measured on days 85 and 169. Randomization was conducted by computer algorithm, and the codes were transmitted to unblinded pharmacists at 19 clinical study sites in the USA. CLASI scoring was centrally reviewed and adjudicated for entry into the study and each subsequent visit during the study. The study was conducted in accordance with the principles of the Declaration of Helsinki and the International Council for Harmonisation Guidelines for Good Clinical Practice. Institutional review board approval was obtained, and all patients provided written informed consent.

Efficacy and safety evaluations

The primary objective was to assess the impact of 13 intravenous infusions of RSLV-132 on SLE cutaneous disease activity using the CLASI score, comparing baseline with days 85 and 169 among the drug-treated and placebo groups. Secondary objectives included assessing additional disease parameters using the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K), the British Isles Lupus Assessment Group 2004 Index (BILAG-2004) and the Physician's Global Assessment (PGA). The SLE Responder Index 4 (SRI-4) was calculated, and responders were required to have at least a 4-point improvement in SLEDAI-2K, no new BILAG A or B scores, and PGA not worsening by more than 10%. The British Isles Lupus Assessment Group (BILAG)-based Composite Lupus Assessment (BICLA) was also calculated, and responders were defined as those participants who had an improvement in all A and B BILAG Scores, no worsening in any organ system, no worsening of the SLEDAI-2K score and no worsening of the PGA score greater than 10%. In addition, the proportion of participants achieving a 50% improvement in CLASI score (CLASI-50) at day 169 was evaluated.

Table 2 Treatment-emergent adverse events (TEAEs) overall summary

	Placebo (n=22)	RSLV-132 (n=42)
At least one TEAE	20 (90.9%)	36 (85.7%)
At least one severe TEAE	5 (22.7%)	3 (7.1%)
At least one study treatment-related TEAE	9 (40.9%)	15 (35.7%)
Study treatment discontinuation due to TEAE	4 (18.2%)	7 (16.7%)
Study termination due to TEAE	2 (9.1%)	6 (14.3%)
At least one treatment-emergent SAE	5 (22.7%)	3 (7.1%)
At least one study treatment-related treatment-emergent SAE	1 (4.5%)	1 (2.4%)

SAE, serious adverse event.

A subgroup analysis of SRI-4 and BICLA response rates was conducted among the participants with baseline SLEDAI scores of 9 or greater (which was the top 50% of the SLEDAI scores). This subgroup included 9 participants from the placebo group and 13 from the RSLV-132 group. A second subgroup of participants with baseline CLASI scores of 21 or greater (which was the top 50% of the CLASI scores) was also analysed and included 12 participants from the placebo group and 18 from the RSLV-132 group.

Participants who experienced a flare during the study were treated according to the clinical judgement of the principal investigator. In the event, a participant used an exclusionary dose of corticosteroid or other exclusionary medication for more than 1 day within 60 days of the day 85 or day 169 efficacy endpoints, the data were censored and not used in calculation of the efficacy measures.

The presence of anti-RSLV-132 antibodies was analysed by ICON Laboratory Services (Whitesboro, New Jersey, USA) using a validated electrochemiluminescent immunoassay method using Meso Scale Discovery technology. Samples were analysed at baseline, days 29, 85, 169 and 215 for the presence of anti-RSLV-132 antibodies. Samples were initially screened, and those that were positive in the screening assay were further analysed in a confirmatory assay where the samples were titrated to eliminate false positives. Vital signs, physical exam and laboratory tests were used to monitor safety at each visit. Participants reported all adverse events (AEs) at each visit.

Statistical analysis

Formal hypothesis testing was not conducted. Continuous variables were summarised using descriptive statistics including number of subjects, mean, SD, median, minimum and maximum. Categorical variables were summarised using frequencies and percentages. Percentages were calculated using the total number of subjects in each treatment group for each applicable population and/or subpopulation, unless otherwise noted. In the absence of any predefined hypotheses in this study, the general strategy of the analysis was to examine the data summaries for any trends among the treatment groups. The last observation carried forward method was employed to impute missing data. The following rules were followed when censoring efficacy data based on blinded review before database lock: Subjects who used an exclusionary medication had the data censored for 60 days following the first use of the medication. In the case of steroids, if the dose was increased to an exclusionary level for only 1 day data were not censored. The use of biologics like rituximab resulted in censoring of all data for the rest of the study given the long half-life. Subjects with data censored before day 29 were not included in the efficacy analysis. All data collected in the clinical database were included in the data listings, as appropriate. Subjects who were randomised and never treated were accounted for in the data listings.

RESULTS

A total of 65 participants met all the entry criteria and none of the exclusion criteria, gave written informed consent and were randomised to one of the two treatment groups. Of those participants, 12 (56%) in the placebo group and 25 (56%) in the RSLV-132 group completed the study. The most common reasons for discontinuation included participants withdrawing consent and lost to follow-up (figure 1).

The baseline demographics and disease characteristics were similar between the placebo and RSLV-132 groups; however, several differences were noted (table 1). For example, the RSLV-132 group had 7% male participants, and the placebo group was 100% female. The RSLV-132 group had a higher percentage of participants with inactive systemic disease as measured by SLEDAI-2K, with 21% versus 14% in the placebo group. There was a higher use of prohibited medications in the placebo group with 45% of the participants having data censored, as compared with 24% of the RSLV-132 group. The RSLV-132 group also had a lower frequency of anti-dsDNA (20% vs 33%), anti-Ro (62% vs 78%) and anti-La (7% vs 17%) autoantibody positivity relative to the placebo group. In addition, there was a difference in the racial composition of the two groups with a higher percentage of African Americans in the placebo group. These characteristics were not statistically significantly different. The BILAG mucocutaneous domain was the predominant domain affected, with 100% of the placebo group and 95% of the RSLV-132

Table 3 Change from baseline for indicated disease activity measure

	Day 85		Day 169	
	Placebo (n=22)	**RSLV-132 (n=42)**	**Placebo**	**RSLV-132**
CLASI, mean (SD)	−6.5 (6.2)	−6.2 (6.7)	−5.7 (7.0)	−6.2 (8.5)
	Placebo	RSLV-132	Placebo	RSLV-132
SLEDAI-2K, mean (SD)	−2.1 (3.2)	−0.9 (3.3)	−2.2 (3.3)	−1.5 (2.9)
	Placebo	RSLV-132	Placebo	RSLV-132
Physician's Global Assessment, mean (SD)	−14.7 (16.3)	−12.0 (16.2)	−15.0 (14.6)	−10.5 (20.9)
BILAG				
A improvement	N/D	N/D	7/12 (58%)	15/32 (47%)
B improvement	N/D	N/D	11/29 (38%)	16/37 (43%)
New A/B			0	5

BILAG, British Isles Lupus Assessment Group; CLASI, Cutaneous Lupus Erythematosus Disease Area and Severity Index; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000.

group having A or B scores. The musculoskeletal domain was the second most active with 64% of the placebo group and 52% of the RSLV-132 group having A or B scores. There was slight activity in the renal domain with 14% of both groups having A or B scores. Because the entry criteria did not require a minimum SLEDAI-2K score, the study enrolled a significant number of participants with inactive or low systemic disease activity, as measured by SLEDAI-2K. For example, the mean SLEDAI-2K score in the placebo group was 8.6 with a minimum score of 2 and a maximum of 14. The RSLV-132 group had a similar profile with a mean score of 8.2, a minimum of 3 and a maximum of 18. The percentage of participants with SLEDAI scores below 6 was imbalanced with 14% in the placebo and 21% in the RSLV-132 arm.

The incidence of participants with treatment-emergent adverse events (TEAEs), treatment-related TEAEs, study treatment discontinuation due to TEAEs and study termination due to TEAEs was comparable between the RSLV-132 and placebo groups. The incidence of treatment-emergent serious adverse events (SAEs) was lower in the RSLV-132 group compared with the placebo group (table 2). There were no deaths in the study. One participant in the RSLV-132 group was withdrawn from the study due to a treatment-related SAE of hypoaesthesia requiring hospitalisation on the day of the final dose. A further six participants in the RSLV-132 group had study treatment discontinued due to TEAEs, of which five were also withdrawn from the study. One of these participants was withdrawn from the study due to infusion-related reactions (chest pains, light headedness, shortness of breath and skin irritation) on the day of the second dose of RSLV-132. One participant had study treatment withdrawn due to a treatment-related AE of pruritus generalised. Two participants were withdrawn from the study due to treatment-related events of cutaneous lupus erythematosus and proteinuria, and two further participants due to cutaneous lupus erythematosus and rash which were not assessed to be treatment-related. There were no participants in the study who were positive for anti-RSLV-132 antibodies.

The primary objective of the study was to compare the mean change in CLASI score from baseline to day 169 in the two treatment arms. There was no significant difference in the mean change in CLASI score between the placebo and RSLV-132 groups at either time point (table 3). Similar results were observed in the two key secondary objectives, with no statistically significant difference between the RSLV-132 and placebo groups with respect to the mean change in PGA and SLEDAI-2K or improvement in BILAG scores.

Table 4 Composite endpoint analysis

	CLASI-50		SRI-4		BICLA	
	Placebo	**RSLV-132**	**Placebo**	**RSLV-132**	**Placebo**	**RSLV-132**
All participants (N=65)	25%	36%	35%	28%	20%	26%
Baseline CLASI ≥21 (N=30)	25%	39%	8%	39%	8%	28%
Baseline SLEDAI ≥9 (N=22)	11%	31%	44%	62%	11%	23%

BICLA, British Isles Lupus Assessment Group-based Composite Lupus Assessment; CLASI, Cutaneous Lupus Erythematosus Disease Area and Severity Index; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; SRI-4, SLE Responder Index 4.

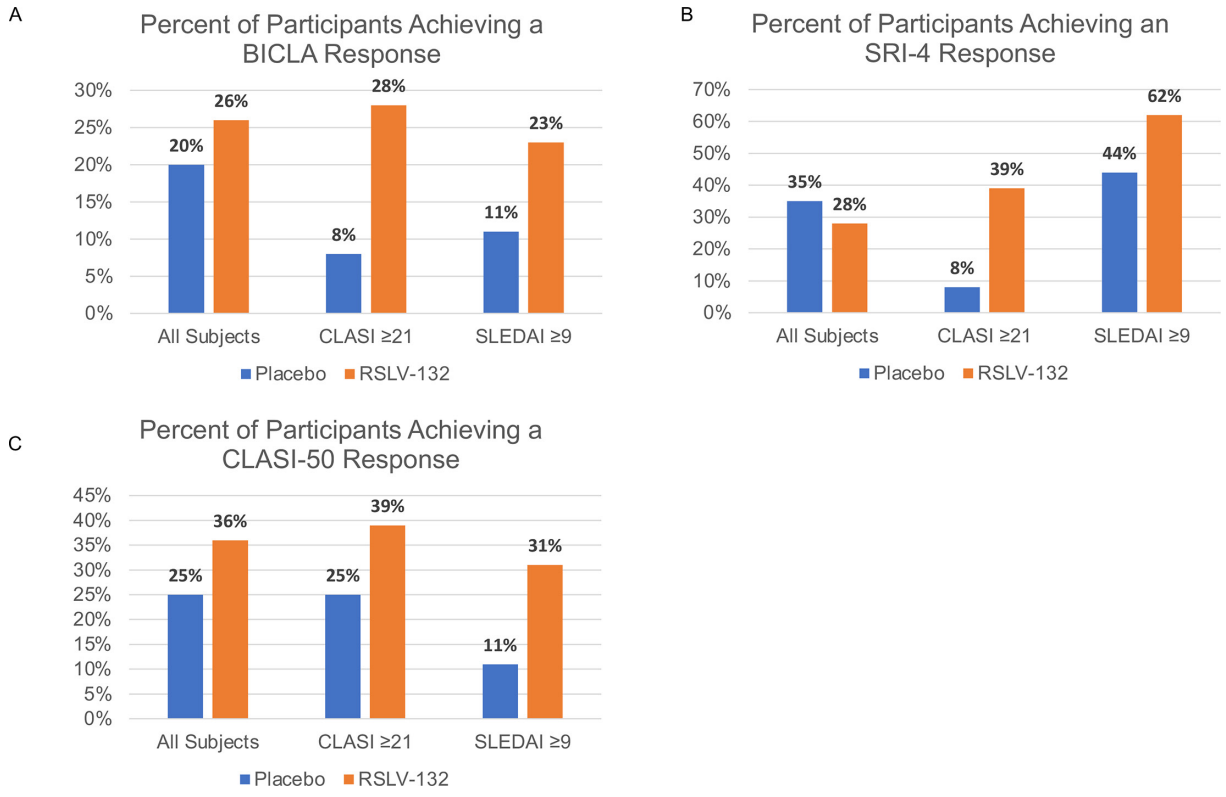

Figure 2 Composite endpoint analysis. BICLA responses were calculated for the mITT population (n=22 placebo, n=42 RSLV-132), the high CLASI subgroup (n=12 placebo, n=18 RSLV-132) and the high SLEDAI group (n=9 placebo, n=13 RSLV-132) (A). SRI-4 responses were calculated for the mITT population, the high CLASI subgroup and the high SLEDAI subgroup (B). CLASI-50 responses were calculated for the mITT population, the high CLASI subgroup and the high SLEDAI subgroup (C). BICLA, British Isles Lupus Assessment Group-based Composite Lupus Assessment; CLASI, Cutaneous Lupus Erythematosus Disease Area and Severity Index; mITT, Modified Intent-to-Treat; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; SRI-4, SLE Responder Index 4.

The SRI-4, and BICLA composite endpoint scores and the percentage of participants achieving a 50% reduction in CLASI score (CLASI-50) were calculated for all participants. In addition, subgroups of participants with severe cutaneous disease (CLASI scores ≥21) or moderate-severe systemic disease (SLEDAI-2K score ≥9) were analysed. There were 9 placebo and 13 RSLV-132 treated participants in the high SLEDAI subgroup and 12 placebo and 18 RSLV-132 treated participants in the high CLASI subgroup. The RSLV-132 treated participants in the high SLEDAI subgroup had an increased frequency of SRI-4 responses (62% vs 44%) and an increased frequency of BICLA responses (23% vs 11%) as compared with the placebo group (table 4, figure 2). A similar trend was observed in the high CLASI subgroup, with the frequency of SRI-4 responders in the RSLV-132 group being 39% versus 8% in the placebo group and the frequency of BICLA responders being 28% in the RSLV-132 group versus 8% in the placebo group.

DISCUSSION

This is the first SLE clinical trial to our knowledge targeting the removal of circulating extracellular RNA, the primary trigger of type I interferons. The study evaluated RSLV-132 in a cohort of 64 patients with SLE with moderate-severe cutaneous disease activity. The primary objective was to assess the impact of 13 doses of 10 mg/kg RSLV-132 on the mean CLASI score. The mean change in CLASI score at day 169 was similar between the RSLV-132 and placebo groups. Similar results were observed in the key secondary objectives involving the SLEDAI-2K and BILAG instruments (table 3).

The entry criteria of the study did not require a minimal SLEDAI score which resulted in 20% of the RSLV-132 group and 14% of the placebo group with inactive systemic disease as defined by SLEDAI. Disease activity, as measured by SLEDAI, varied widely from inactive to moderate with a mean SLEDAI of approximately 8. This cohort of patients with SLE had very active cutaneous disease with mean CLASI scores of 22–24. There was no correlation between the CLASI and SLEDAI instruments, participants with very severe cutaneous disease activity in many cases had inactive disease as measured by SLEDAI. The overall correlation between the two instruments was 0.04.

While the mean CLASI scores between the two groups did not show a meaningful difference, when subgroups with higher SLEDAI or CLASI scores were analysed a larger number of responders in the RSLV-132 subgroup as compared with placebo were noted. For example,

study participants with high baseline SLEDAI scores (≥9) or high baseline CLASI scores (≥21) had an increase in BICLA, SRI-4 and CLASI-50 responses in the RSLV-132 treated group as compared with placebo (figure 2).

The safety profile of RSLV-132 was excellent in the study with treatment-emergent AEs and SAEs below the level observed in the placebo group. In addition, no anti-RSLV-132 antibodies were detected in any of the study participants.

Extracellular RNA is a potentially fruitful target in SLE, given the numerous downstream inflammation cascades that are activated by circulating extracellular RNA molecules. The present study was informative as it highlighted the population of patients with SLE for whom RSLV-132 is most likely to be of clinical benefit. RSLV-132 had an excellent safety profile in this study and demonstrated a trend towards efficacy in patients with more active systemic disease. The results warrant further larger studies in patients with active systemic disease as measured by SLEDAI score. The primary weakness of the present study was the small size of the study cohort.

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Contributors JP was responsible for the overall content of the manuscript and is the gaurantor of the work. DJB and JP designed the study with input from VPW and SAB. VPW adjudicated all of the CLASI score data for the study and was involved in writing the manuscript. SAB enrolled patients into the study, provided input on the study design and was involved in writing the manuscript.

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Competing interests JAP owns equity in Resolve Therapeutics, there are no other competing interests.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by Advarra ID: Pro00025784. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Selected data are available upon reasonable request. Please direct any requests to JP.

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