RSLV-132
PROTOCOL 132-03

A PHASE 2A, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF RSLV-132 IN SUBJECTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

RESOLVE THERAPEUTICS, LLC
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Protocol Title:	A Phase 2a, Double-Blind, Placebo-Controlled Study of RSLV-132 in Subjects With Systemic Lupus Erythematosus
Protocol Number:	132-03
Investigational Product:	RSLV-132
IND Number:	117593
Current Version:	5.0
Prior Version:	4.0
Date of Publication:	27 April 2017
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1 PROTOCOL SYNOPSIS

Name of Sponsor:
Resolve Therapeutics, LLC

Name of Investigational Product:
RSLV-132

Name of Active Ingredient:
RNase-IgG Fc

Number and Title of Study:
Protocol 132-03: A Phase 2a, Double-Blind, Placebo-Controlled Study of RSLV-132 in subjects with Systemic Lupus Erythematosus (SLE)

Phase of development:
2a

Study period:
Patient participation duration: 28 days of screening followed by 22 weeks of treatment and 8 weeks of follow up (approximately 34 weeks total).

Planned study conduct duration: approximately 24 months total (from enrollment of first subject to completion of follow-up for last patient).

Objectives:

- assess the impact of 13 IV infusions of RSLV-132 on cutaneous lupus disease activity using the CLASI activity score.
- assess improvement in disease activity using SLEDAI-2K, BILAG-2004 and PGA;
- evaluate the immunogenicity of RSLV-132 in subjects with SLE;
- assess improvement in tender or swollen joint count;
- assess improvement in patient reported outcomes using the FACIT-Fatigue scale;
- assess the ability of subjects to reduce oral steroids at Day 169;
- evaluate the safety and tolerability of 22 weeks of RSLV-132 exposure;
- assess the proportion of subjects achieving a 50% improvement in CLASI activity score
- assess the following exploratory endpoints
    - evaluate the impact of RSLV-132 treatment on gene expression profile;
    - evaluate the impact of RSLV-132 treatment on autoantibody and complement profiles;
    - evaluate the impact of RSLV-132 on serum protein levels;
    - assess the impact of RSLV-132 on the CLASI damage score

Study design:

This is a multi-center, double-blind, placebo-controlled study to evaluate the impact of 13 intravenous infusions of RSLV-132 in approximately 50 patients with SLE. Each of the approximately 50 subjects will be randomized 2:1 (active:placebo) and will receive 13 infusions of 10 mg/kg of RSLV-132 or placebo as follows on days:

- **1, 8, 15, 29, 43, 57, 71, 85, 99, 113, 127, 141, and 155**

Potential subjects will be screened to assess their eligibility to enter the study within 28 days prior to study entry (i.e., prior to Baseline visit). Following Baseline evaluations on Day 1, subjects will receive their first infusion of RSLV-132 or placebo. Subjects will return to the research unit for follow-up visits as described in Appendix A.

Dose selection rationale: The dose level was chosen based on safety and tolerability data from Protocol 132-02 (multiple ascending dose study in SLE patients).

RSLV-132 shall be prepared for each subject from individual stock vials provided by Sponsor. Details of dilution, dose preparation, and administration instructions will be provided in the Study Drug Reference Manual. The dose for each individual shall be based on the subject's body weight.

Number of subjects (planned):

It is anticipated that approximately 50 subjects will be enrolled in the study

Number of Study Centers (planned):

Approximately 15-20 study sites in the United States, Canada and Europe will be involved in the study.

Diagnosis and main criteria for inclusion:

Subjects with SLE, including cutaneous manifestations of SLE and a CLASI score ≥ 10, and positive serology (increased levels of one or more of the following: Ro-52/60, La, Sm, SmRNP, U1 RNP A/68) at Screening will be eligible for the study.

Inclusion Criteria:

Subjects who meet the following criteria may be included in the study:

1. diagnosis of SLE meeting four of the eleven criteria in the 1997 Update of the 1982 American College of Rheumatology Revised Criteria and a history of active SLE including cutaneous involvement at Screening;
2. SLE with cutaneous manifestations and a CLASI activity score of ≥10 at Screening;
3. elevated levels of any one of the following autoantibodies:
    - Ro-52/60, La, Sm, SmRNP, U1 RNP A/68 (local or central laboratory);
4. no change in medications for the treatment of SLE for the previous 30 days prior to Baseline;
5. able to communicate and able to provide valid, written informed consent;
6. ages 18 to 70, inclusive;

7. minimum weight of 45 kg;
8. Female participants shall be either of non-child-bearing potential (permanently sterilized by tubal occlusion, hysterectomy, or bilateral salpingectomy), or menopausal (more than one year since last menstrual cycle and confirmed by blood FSH levels ≥ 22 mIU/mL) OR practicing highly effective contraception (e.g., oral, injectable, implantable or transdermal contraceptives, a non-hormonal intrauterine device [IUD] with spermicide; female condom with spermicide; contraceptive sponge with spermicide; an intravaginal system, a diaphragm with spermicide; cervical cap with spermicide; a male sexual partner who agrees to use a male condom with spermicide; a sterile sexual partner) for at least 2 months prior to dosing and until 110 days following the End of Study.
9. Male participants must agree to use a male condom with spermicide from the first dose until 90 days after the last dose. Male participants must also agree not to donate sperm from the first dose until 90 days after the last dose.

Exclusion Criteria:

The following will exclude potential subjects from the study:

1. severe, active CNS involvement at Screening;
2. severe renal involvement at Screening (urine protein/creatinine ratio of >200 mg/mmol, or an estimated creatinine clearance of <30 mL/min);
3. use of cyclophosphamide within 3 months of the Baseline visit;
4. use of rituximab within 6 months of the Baseline visit;
5. use of belimumab within 3 months of the Baseline visit;
6. use of background medications within 1 month of Baseline in excess of:
    i. mycophenolate mofetil > 3 g/day;
    ii. azathioprine > 200 mg/day;
    iii. methotrexate > 25 mg/week;
    iv. hydroxychloroquine > 400 mg/day;
    v. prednisone (or equivalent) > 15 mg/day;
7. use of an intravenous steroid “pulse” within 2 months of Baseline;
8. use of an intramuscular steroid injection within 1 month of Baseline;
9. change in SLE medications within 1 month of Baseline;
10. the presence of a clinically significant infection in the judgement of the Investigator within seven days prior to the receipt of the first dose of study drug;
11. positive viral load test for hepatitis B, C, or HIV at Screening;
12. participation in another clinical trial with receipt of an investigational product within 3 months or 5 half- lives, of last administration (whichever is longer) from Baseline;
13. positive pregnancy test at Screening or at Baseline;
14. female subjects currently breast feeding at Baseline;
15. inability or unwillingness to comply with protocol-specified procedures which, in the opinion of the Investigator, would make the subject unsuitable for study participation.

CRITERIA FOR EVALUATION:

Clinical measures:

- CLASI (both activity and damage scores)
- SLEDAI-2K
- BILAG-2004
- PGA
- Tender and swollen joint count

Pharmacodynamics:

- Gene expression profiling of peripheral blood mononuclear cells (PBMCs)
- Analysis of serum proteins
- Autoantibody profiling

Patient reported outcomes:

- FACIT-Fatigue patient reported fatigue index

Evaluations by Day:

Screening Procedures

- informed consent;
- evaluation of inclusion/exclusion criteria;
- complete medical and medication history;
- demographic data;
- weight and height;
- physical examinations;
- vital signs;
- clinical laboratory evaluations (Chem-20, CBC, and UA);
- viral load tests for hepatitis B, C, and HIV;
- serum pregnancy test;
- measurement of cutaneous disease activity (CLASI);
- Photographs of cutaneous disease activity;
- autoantibody profile (Ro-52/60, La, Sm, SmRNP, U1 RNP A/68) (local or central laboratory);
- FSH (when required to confirm menopause in female subjects)

Baseline Procedures

- confirmation of inclusion/exclusion criteria;
- interim medical and medication history;
- physical examination;
- vital signs;
- adverse event baseline assessment;

- measurement of cutaneous disease activity (CLASI);
- photographs of cutaneous manifestations of lupus;
- measurement of SLE activity (SLEDAI-2K, BILAG-2004, PGA);
- tender and swollen joint count;
- patient reported outcome, FACIT fatigue index;
- serum for study drug concentration;
- clinical laboratory evaluations (Chem-20, CBC, and UA);
- whole blood for measurement of gene expression;
- serum for protein analysis;
- serum for measurement of RNase activity;
- evaluation of autoantibody profile (dsDNA, Ro-52/60, La, Sm, SmRNP, U1 RNP A/68) from local or central laboratory;
- serum for complement analysis, C3 and C4;
- assessment of antibodies to RSLV-132;
- urine pregnancy test;
- study drug administration.

Additional Procedures

The following procedures will be performed at various visits during the study. A total of twelve post-baseline visits will occur; once weekly for two weeks, then every two weeks for 20 weeks, plus an end of study visit 8 weeks after visit 13:

- physical exam;
- vital signs;
- adverse event assessment;
- medication history;
- measurement of cutaneous disease activity (CLASI);
- measurement of SLE activity (SLEDAI-2K, BILAG-2004, PGA);
- tender and swollen joint count;
- FACIT-fatigue index patient reported outcome;
- photographs of cutaneous manifestations of lupus;
- serum sample for study drug concentration;
- serum sample for measurement of RNase activity;
- serum for protein analysis;
- whole blood for gene expression profile;
- serum sample for autoantibody profile (dsDNA, Sm, Ro-52/60, La, SmRNP, U1 RNP A/68) from local or central laboratory;
- serum for complement analysis, C3 and C4;
- clinical laboratory evaluations (Chem-20, CBC, and UA);

- serum sample for assessment of antibodies to RSLV-132;
- pregnancy test;
- study drug administration.

2 TABLE OF CONTENTS

2.1 List of Tables

2.2 List of Abbreviations and Definitions of Terms

The following abbreviations and specialist terms are used in this study protocol.

Table 1: Abbreviations and specialist terms

Abbreviation or specialist term	Explanation
ACR	American College of Rheumatology
ADA	anti-drug antibodies
AE	adverse event/experience
ALT	alanine aminotransferase (alanine transaminase)
ANA	anti-nuclear antibody
AST	aspartate aminotransferase (aspartate transaminase)
BILAG	British isles lupus activity group
cSFI	classic (SELENA)-SLEDAI flare index
CBC	complete blood count (hematology clinical laboratory evaluations)
CFR	code of federal regulations
Chem-20	chemistry panel of 20 analytes
CLASI	cutaneous lupus erythematosus disease area and severity index
CNS	central nervous system
CRA	clinical research associate
CRF	case report form
CRO	clinical research organization
DNase	deoxyribonuclease
ELISA	enzyme-linked immunosorbent assay
ESR	erythrocyte sedimentation rate

Abbreviation or specialist term	Explanation
FDA	food and drug administration
FSH	Follicle-stimulating Hormone
GCP	good clinical practice
HBs Ag	hepatitis B surface antigen
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IC	Immune complex
ICF	informed consent form
ICH	international committee on harmonization
IFN	interferon
IgG	immunoglobulin G
IgM	immunoglobulin M
IL-1 RA	Interleukin-1 receptor antagonist
IRB	institutional review board
ISM	interferon signature metric (score)
IUD	intrauterine device
IV	intravenous
MTD	maximum tolerated dose
OCS	Oral Corticosteroids
PCR	polymerase chain reaction
pDC	plasmacytoid dendritic cells
PGA	physician's global assessment
PK	pharmacokinetic
PMN	polymorphonuclear (cells)
RNA	ribonucleic Acid
SAE	serious adverse event/experience
SELENA	safety of estrogens in lupus erythematosus national assessment
SLE	systemic lupus erythematosus
SLEDAI	Systemic Lupus Erythematosus Disease Activity Index SELENA Modification
TLR	toll-like receptor
UA	urinalysis
ULN	upper limit of normal

3 INTRODUCTION

3.1 Systemic Lupus Erythematosus, Immune Complexes, Human Safety Data with RSLV-132

Systemic Lupus Erythematosus (SLE) is a heterogeneous autoimmune disorder affecting many tissues and organs including skin, kidney and brain [22]. Despite wide inter-patient diversity with respect to clinical manifestations, a common characteristic of SLE patients is the presence of circulating autoantibodies directed against nuclear antigens [24, 19]. The presence of these autoantibodies signifies that host immune tolerance has been compromised. The physiological cause underlying the loss of tolerance is unclear, but current theories include that SLE patients' cells are predisposed to undergo capricious apoptosis or that host mechanisms involved in clearance of apoptotic cells/debris are impaired [27, 16]. In either scenario, the extracellular accumulation of nuclear-associated antigens, including nucleic acid-containing complexes, elicits B-cells to produce antibodies that recognize these normally sequestered components as foreign antigens. As a result, immune tolerance is broken

When complexed with their respective antigens, SLE patient autoantibodies form immune complexes (ICs) which can promote activation of immune cells in vitro. For example, ICs formed following incubation of SLE patient sera with necrotic and/or apoptotic cell extracts (a source of nuclear antigens), are effective agonists for activating plasmacytoid dendritic cells (pDCs) to produce type 1 interferon (IFN) [5]. Circulating ICs recovered from SLE patients are also capable of eliciting IFN-α output from pDCs in culture, though lower abundance of the endogenous complexes relative to the quantities formed following addition of exogenous antigens promotes smaller quantities of cytokine production [1, 8]. ICs also are capable of stimulating B-cells resulting in NF-κB activation and proliferation [15, 6]. Moreover, SLE patient ICs have been reported to activate human polymorphonuclear (PMN) cell activities including chemotaxis, the oxidative burst response, and netosis [17, 7]. In addition to effects on immune cells, ICs can deposit within tissues (e.g. kidney, blood vessels) where their physical accumulation and associated inflammation appear to disrupt normal homeostatic function [21, 3]. Overall, ICs are positioned at the apex of an effector cascade which instigates and drives SLE disease pathology.

Many common SLE patient autoantibodies are directed against nucleic acids or to proteins that bind to non-coding RNAs. Importantly, recent studies have established that nucleic acids associated with SLE patient ICs are capable of activating Toll-like receptors (TLRs) [12, 18, 14, 4, 13]. Although TLRs are thought to operate as key elements of the innate immune system by recognizing pathogen-associated molecular components, it is now clear that host nucleic acids also can activate specific family members including TLR7, TLR8, and TLR9 [26]. Cells expressing these receptors do so without distributing them to the cell surface; rather, TLRs 7/8/9 are sequestered within endosomes [26]. This positioning is postulated to minimize interaction with host nucleic acids. However, when present within an IC, nucleic acid antigens are actively internalized into cells via receptor-mediated endocytosis. Effector Fc, complement, and B-cell receptors all may facilitate entry of nucleic acid containing ICs into endosomes [18, 14]. Once internalized, the nucleic acid cargo is positioned to bind to and activate resident endosomal TLRs. Activated TLRs, in turn, promote type 1 IFN from pDCs, activate PMNs, and promote B-

cell proliferation and autoantibody production. Thus, the nucleic acid-containing antigens are envisioned to contribute to multiple aspects of SLE disease pathophysiology.

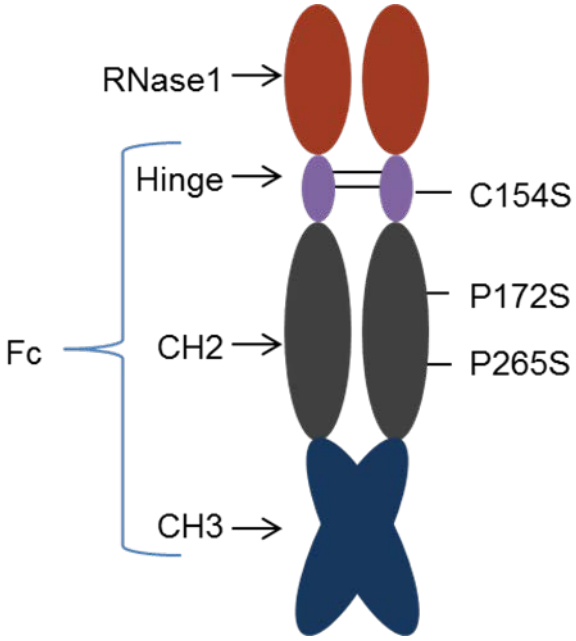
Evidence of the importance of TLR-induced signaling to autoimmunity is further suggested by a mouse transgenic line engineered to overexpresses TLR7 [9]. Overexpression of this receptor is associated with development of spontaneous autoimmunity. A substantial increase in TLR7 expression is associated with enhanced mortality, an increase in circulating anti-DNA antibodies, and dendritic cell dysregulation [9]. Given that the transgenic mice do not require an exogenous agonist to promote the autoimmune phenotype, these findings suggest that elevation of the receptor's steady state expression is sufficient to tilt the homeostatic balance from a state where immune tolerance is maintained to one where tolerance is broken. Since TLR7 is known to recognize RNA-containing ligands [11], the spontaneous development of autoimmunity in the TLR7 transgenic animals suggests that endogenous RNAs are contributing to the pathophysiological response. Importantly, when the TLR7 receptor transgenic mice are crossed with a mouse line over expressing bovine RNase under control of a serum albumin promoter, the double transgenic descendants demonstrate increased survival, reduced activation of T and B lymphocytes, and reduced hepatic inflammation [25]. Thus, the addition of a secreted ribonuclease to the system appears to attenuate the heightened state of autoimmunity, presumably by degradation of the endogenous TLR7 ligands.

Evidence also exists in humans suggesting that TLRs and nucleases impact SLE. A mutation within the promoter of the TLR7 gene is reported to enhance TLR7 expression and to be a risk factor for development of SLE [23]. In addition, polymorphisms within TLRs 7/8/9 have been linked to SLE patients [10]. Likewise, mutations resulting in loss of DNase1 or DNase1L3 each have been reported as predisposing to the development of SLE [28, 2]. Moreover, genetic association studies have established a link between the 3'-5' exonuclease Trex1 and SLE [20]. Therefore, in both mice and humans the balance between the levels of endogenous nucleic acid-containing ligands and expression of the nucleic acid-sensing TLRs appears key in regulating cellular immune responses and autoimmunity.

3.2 RSLV-132

RSLV-132 is a novel therapeutic being developed for the treatment of SLE. This fully human biologic (Figure 1) consists of RNase1 (also known as pancreatic RNase) fused to the N-terminus of the Fc segment of IgG1. The attachment of the Fc segment is intended to extend the circulatory half-life of the RNase and by so doing reduce the frequency of administration. RSLV-132 is intended to utilize the RNase to break down RNA containing immune complexes, thereby reducing the activation of TLRs, decreasing the production of type 1 IFN and decreasing the proliferation of B-cells and autoantibody production.

Figure 1: Schematic of RSLV-132



3.3 Study Rationale

Chronic systemic inflammation is the hallmark of SLE. There is a preponderance of scientific and clinical evidence that supports the concept that RNA associated with autoantibodies specifically delivered to immune system cells triggers multiple inflammatory pathways.

Many investigative drugs either currently or previously tested in lupus are designed to inhibit key inflammatory cytokines such as Interferon-α, Interferon-γ, or B-cell targets such as CD-20, or CD22. All of these targets lie downstream of the initial triggering event and may be only one of the pathways involved in SLE inflammation.

RNA-containing immune complexes circulating in SLE patient blood are specifically delivered to Fc receptor-bearing cells and internalized resulting in the activation of TLRs and the activation of myriad downstream inflammatory pathways. RSLV-132 is an enzymatically active RNase with a long circulating half-life that is designed to digest the RNA contained in these immune complexes and thereby render the immune complexes biologically inert. The therapeutic hypothesis is that over time depleting the blood of RNA immune complexes will decrease the activation of multiple pro-inflammatory cascades and thereby decrease the overall SLE inflammation.

3.4 RSLV-132 Human Safety Data

Two safety studies in humans have been conducted to date with RSLV-132; a single ascending dose study in 32 healthy volunteers, and a multiple ascending dose study in 32 subjects with systemic lupus erythematosus.

3.4.1 Study 132-01 – Single Ascending Dose Study Summary:

This first-in-man study was a double-blind, placebo-controlled study conducted in healthy volunteers in a phase one unit to assess the safety and tolerability of a single, escalating IV dose of RSLV-132 (0.3 mg/kg – 10.0 mg/kg). There we no SAEs, or drug discontinuations due to an AE. The drug was well tolerated at all doses tested and an MTD was not reached. The serum half-life of the drug was measured to be approximately 16 days. None of the subjects in the study were positive for anti RSLV-132 antibodies.

3.4.2 Study 132-02 Multiple Ascending Dose Study Summary: Safety

This was a multi-center, double-blind, placebo-controlled study with successive escalating cohorts to assess the safety and tolerability of repeated IV doses (0.3 mg/kg – 10.0 mg.kg) of RSLV-132 in SLE subjects with inactive or mild disease. The MTD was not reached at the highest dose of RSLV-132 tested. Repeated administration of RSLV-132 doses was generally well tolerated by the subjects in this study. Across all dose cohorts, AEs were observed at the same overall incidence in RSLV 132 subjects as placebo subjects (6/8 subjects [75%] versus 18/24 subjects [75%]). The incidence of AEs and the average number of events per subject did not increase with increasing dose level. The most frequently reported AEs in the RSLV 132 arm were headache, nausea, and upper respiratory tract infection, each of which occurred in 5 subjects (20.8%). The majority of AEs in this study were Grade 1 in severity; 13 subjects (10 RSLV-132 and 3 placebo subjects) experienced Grade 2 AEs, and one subject in Cohort 1 of the RSLV-132 arm experienced a Grade 3 AE of acute cholecystitis (this event was also reported as the only SAE in the study). No Grade 4 or Grade 5 events occurred. Adverse events judged to be related to blinded study drug were reported for 38% of placebo subjects and 29% of RSLV 132 subjects. No dose related trends were observed for any adverse event. No deaths due to AEs occurred. All subjects had at least one out-of-range chemistry, hematology, or urinalysis value, but no values were considered clinically significant in RSLV-132 subjects. No dose-dependent trends were observed in the incidence of out-of-range values and no concerning patterns of laboratory abnormalities were detected. No notable differences between treatment groups and no trends over the course of the study were observed in vital signs or physical findings. No clinically significant ECG abnormalities were reported during the study. No confirmed positive anti-RSLV-132 antibodies were detected in any of the subjects in this 113-day study.

4 TRIAL OBJECTIVES AND PURPOSE

The present study is designed as a proof-of-concept study to demonstrate clinical activity of RSLV-132 in a cohort of SLE subjects with active cutaneous manifestations of SLE. Evidence of clinical activity is sought in a smaller, more homogeneous subset of lupus subjects prior to embarking on a larger phase 2 dose ranging study.

4.1 Primary Objective

- assess the impact of 13 IV infusions of RSLV-132 on cutaneous lupus disease activity using the CLASI activity score comparing Baseline with Day 85 and Day 169 among the drug-treated and placebo groups.

4.2 Secondary Objectives

At Days 85 and 169:

- assess disease activity using SLEDAI-2K, BILAG-2004 and PGA;
- evaluate the immunogenicity of RSLV-132 in subjects with SLE;
- assess improvement in tender or swollen joint count;
- assess improvement in patient reported outcomes using the FACIT-Fatigue scale;
- assess the proportion of subjects achieving a 50% improvement in CLASI activity score

At Day 169:

- assess the ability of subjects to reduce oral steroids at Day 169 relative to Day 85;
- evaluate the safety and tolerability of 22 weeks of RSLV-132 exposure;

4.3 Exploratory Measures

- evaluate the impact of RSLV-132 treatment on gene expression profile;
- evaluate the impact of RSLV-132 treatment on autoantibody and complement profiles;
- evaluate the impact of RSLV-132 on serum protein levels;
- assess the impact of RSLV-132 on the CLASI damage score

5 INVESTIGATIONAL PLAN

5.1 Overall Study Design and Plan

This is a multi-center, double-blind, placebo-controlled study of approximately fifty subjects with SLE. Potential subjects will be screened to assess their eligibility to enter the study within twenty-eight days prior to study entry (i.e., prior to Baseline visit).

Subjects will be evaluated during screening for evidence of active, evaluable cutaneous manifestations of SLE which will be measured by the investigator using the CLASI score and documented using photography. The photographs will be adjudicated by a dermatologist with expertise in the use of the CLASI tool in SLE clinical trials in order to confirm the subject meets the CLASI entry criteria.

Following Baseline evaluations on Day 1, subjects will receive their first intravenous infusion of RSLV-132. Subjects will return to the research unit for additional visits as described in Appendix A.

The subjects will be randomized 2:1 (active:placebo) to receive IV administrations of 10 mg/kg of study drug or placebo as follows on days:

- 1, 8, 15, 29, 43, 57, 71, 85, 99, 113, 127, 141, and 155

5.2 Number of Subjects and Centers

Approximately 50 subjects will be enrolled at approximately 15-20 clinical centers in the United States, Canada and Europe.

5.3 Estimated Study Duration

Each subject will be screened within twenty-eight days of admission to the study center (Baseline visit). The duration of the study from Baseline visit to End of Study visit, excluding the screening period is approximately 30 weeks for each subject.

6 SELECTION AND WITHDRAWAL OF SUBJECTS

Subjects who meet all of the inclusion criteria and none of the exclusion criteria will be eligible to be enrolled into the study.

6.1 Subject Inclusion Criteria

Subjects who meet the following criteria may be included in the study:

1. diagnosis of SLE by meeting four of the eleven ACR criteria described in the 1997 update of the 1982 SLE criteria (see Appendix D) including cutaneous involvement at Screening;
2. cutaneous manifestations of SLE and a CLASI activity score of ≥10 at Screening;
3. elevated levels of any one of the following autoantibodies (local or central laboratory):
    - Ro-52/60, La, Sm, SmRNP, U1 RNP A/68;
4. no changes to SLE medications in the 30 days prior to Baseline;
5. able to communicate and able to provide valid, written informed consent;
6. ages 18 to 70 inclusive;
7. minimum weight of 45 kg;
8. Female participants shall be either of non-child-bearing potential (permanently sterilized by tubal occlusion, hysterectomy, or bilateral salpingectomy, or menopausal more than one year since last menstrual cycle and confirmed by ensuring blood FSH levels ≥ 22 mIU/mL); OR practicing highly effective contraception (e.g., oral, implantable, transdermal or injectable contraceptives, a non-hormonal intrauterine device [IUD] with spermicide; female condom with spermicide; contraceptive sponge with spermicide; intravaginal system, diaphragm with spermicide; cervical cap with spermicide; a male sexual partner who agrees to use a male condom with spermicide; a sterile sexual partner) for at least 2 months prior to dosing and until 110 days following the End of Study.
9. Male participants must agree to use a male condom with spermicide from the first dose until 90 days after the last dose. Male participants must agree not to donate sperm from the first dose until 90 days after the last dose.

6.2 CLASI Score Entry Criteria – Adjudication

Prior to being enrolled in the study, each patient's cutaneous SLE disease activity measure and photographs of the cutaneous areas of disease involvement will be submitted to and reviewed by an adjudicator. The adjudicator is a dermatologist with extensive experience in reviewing cutaneous clinical data from SLE subjects in a clinical trial setting. The adjudicator will review the photographs of the cutaneous disease to confirm the subject meets the entry criteria and is eligible for the study.

6.3 Subject Exclusion Criteria

The following will exclude potential subjects from the study:

1. severe, active CNS involvement at Screening;

2. severe renal involvement (urine protein/creatinine ratio of >200 mg/mmol, or an estimated creatinine clearance of <30 mL/min) at Screening;
3. use of cyclophosphamide within 3 months of Baseline;
4. use of background medications within 1 month of Baseline in excess of:
    a. mycophenolate mofetil > 3 g/day;
    b. azathioprine > 200 mg/day;
    c. methotrexate > 25 mg/week;
    d. hydroxychloroquine > 400 mg/day;
    e. prednisone (or equivalent) > 15 mg/day;
5. use of an intravenous corticosteroid "pulse" within 2 months of Baseline;
6. use of an intramuscular steroid injection within 1 month of Baseline;
7. use of rituximab within 6 months of Baseline;
8. use of belimumab within 3 months of Baseline;
9. acute infection or history of acute infection within seven days prior to Baseline;
10. positive viral load test for hepatitis B, C or HIV at Screening;
11. receipt of an investigational product within 3 months of Baseline or five half-lives (whichever is longer);
12. positive pregnancy test at Screening or at Baseline;
13. female subjects currently breast feeding at Baseline;
14. inability or unwillingness to comply with study restrictions, return for follow up appointments, or other considerations, in the opinion of the Investigator, which would make the candidate unsuitable for study participation.

6.4 Subject Withdrawal Criteria

Subjects will be informed that they are free to withdraw from the study at any time and for any reason. The Investigator may remove a subject from investigational treatment if, in the Investigator's opinion, it is not in the best interest of the subject to continue. Notification of discontinuation of investigational treatment will be made immediately to the Sponsor. In case of premature discontinuation of investigational treatment, efforts will be made to perform all End of Treatment (EOT) assessments and an End of Study (EOS) visit outlined in (Appendix A).

If a subject wishes to withdraw from the study, the site staff should confirm whether the subject is agreeable to continue the assessments without the investigational treatment or if they wish no further involvement in the study. In the latter case no further study-related evaluations will be performed and no additional data will be collected.

The date and the reason for discontinuation of investigational treatment or withdrawal from the study will be recorded on the subject's Case Report Form (CRF). Subjects that withdraw after receiving study drug will not be replaced.

6.5 Women of Child-Bearing Potential

As women of ages 18 to 70 years old are eligible to enroll in this study, all women will be considered to be of child-bearing potential unless:

- the subject has undergone a surgical sterilization procedure (e.g. bilateral oophorectomy, hysterectomy, or tubal ligation);
- the subject is greater than 12 months past her last menstrual cycle and menopause is confirmed by ensuring blood FSH levels ≥ 22 mIU/mL

Pregnancy tests will be performed at Screening, Baseline, and End of Study visits for women of childbearing potential.

7 TREATMENT OF SUBJECTS

7.1 Description of Study Drug

RSLV-132 is a novel therapeutic candidate. This fully human biologic consists of RNase1 (also known as pancreatic RNase) fused to the N-terminus of the Fc portion of IgG1. The attachment of the Fc domain is intended to extend the serum half-life of the RNase and reduce the frequency of administration. RSLV-132 is provided in single-use vials for dilution for intravenous infusion. Two lots of drug have been used in the study; lot 1-FIN-1778 which was provided at 9.5 mg/mL, and lot 1-FIN-2899 which was provided at 10.0 mg/mL.

7.2 Treatment Compliance

Study drug will be administered at the clinical site by trained study staff according to the Study Drug Reference Manual provided by the Sponsor.

7.3 Concomitant Medications

Subjects entering the study who had no changes to their SLE medications in the previous 30 days prior to the Baseline visit shall remain on the background medications at the same doses throughout the study. With the exception of decreases in OCS, no changes in lupus medications shall be permitted during the study, including the addition of topical steroids or topical tacrolimus, except for the rescue of a lupus flare.

7.4 Steroid Tapering

One of the objectives of the study is to evaluate the potential steroid sparing effects of RSLV-132. Steroid doses should remain stable through Day 85. Thereafter, Investigators shall decrease the use of oral corticosteroids beginning on Day 85 using the guidance below. No further steroid decreases should occur from Day 141 through Day 169.

- Subjects receiving >7.5 mg of prednisone or equivalent daily AND demonstrating a clinical improvement in the cutaneous manifestations of lupus as measured by a decrease in the CLASI activity by 50% compared with Baseline shall decrease oral corticosteroids as follows:
    - Decrease prednisone (or equivalent) by 2.5 mg/day
    - If the prednisone dose (or equivalent) remains greater than 7.5 mg/day AND cutaneous disease activity remains improved (CLASI activity score decreased by 50% compared with baseline) AND prednisone has been stable for 2 weeks, reduce prednisone by an additional 2.5 mg; repeat after 2 more weeks.
    - If prednisone reduced to 7.5 mg, see below,
    - If after a decrease in prednisone, the CLASI is no longer decreased (compared to baseline) by 50%, the investigator may increase the prednisone to the previous daily dose (not to exceed the baseline dose)
- Subjects receiving ≤7.5 mg/of prednisone or equivalent daily AND demonstrating clinical improvement in the cutaneous manifestations of lupus as measured by a decrease

in the CLASI activity score by 50% compared with baseline, the investigator may, at his/her discretion, decrease prednisone by no greater than 2.5 mg/day every other week.

7.5 Treatment of Flares

Investigators should treat lupus flares as they deem appropriate with the minimum amount of corticosteroid necessary and should return the subject to baseline steroid dose as quickly as medically reasonable. Should a subject require more than steroids for a lupus flare, investigators should treat as necessary and notify the medical monitor.

7.6 Randomization and Blinding

This will be a double-blind, placebo-controlled study. As such, except for the specifically designated unblinded study site pharmacist, the investigator, sponsor, and remaining study site clinical staff will be blinded as to treatment. Ongoing drug accountability will be monitored by an unblinded monitor.

Except in a medical emergency, the investigator or designee and blinded study site clinical staff will remain blinded during the conduct of the study and until such time that all discrepancies in the clinical database are resolved (i.e., at the time of the database lock). The date/initials and reason for the investigator and/or clinical staff removing the study blind will be documented.

8 STUDY DRUG MATERIALS AND MANAGEMENT

8.1 Study Drug

RSLV-132 is presented as a single-use, preservative-free vial of sterile solution concentrate for dilution for intravenous infusion at a strength of either 9.5 mg/mL or 10.0 mg/mL. The formulation buffer contains 10 mM sodium citrate pH 6.0, 220 mM trehalose and 50 mM L-arginine. All excipients meet multiple compendia requirements and are not of animal origin.

The Sponsor, or designee, will provide the investigator with adequate quantities of the study drugs (see Table 2).

Table 2: Study Drug

Study Drug	RSLV-132
Form[a]	Sterile injectable solution for intravenous administration packaged in a single-use vial. RSLV-132 will be diluted in saline for infusion.
Strength	Lot 1-FIN-1778, 9.5 mg/mL
	Lot 1-FIN-2899, 10.0 mg/mL

[a] Specific ingredients/purity will be identified on the Certificate of Analysis (or equivalent) that is supplied with the study drug. The lot numbers for each concentration of the study drugs will be provided to the clinical site by the supplier/manufacturer and will be on vial labels.

8.2 Placebo

Placebo will be sterile saline for infusion and will be provided by each site and prepared by the unblinded pharmacist.

8.3 Study Drug Packaging, Labeling, Storage, Shipping, and Preparation

The study drug will be provided to the sites in single use vials, clearly labeled with drug name and lot number. Study drug will be stored at <-20°C under secure conditions and protected from light. Prior to administration to the subject, individual dosing solutions will be prepared from a vial as detailed in the Study Drug Reference Manual. Details of study drug packaging, labeling, storage, shipping, and preparation, including preparation of matching placebo doses, will likewise be provided in the Study Drug Reference Manual.

8.4 Study Drug Administration

RSLV-132 or placebo will be administered intravenously at 10 mg/kg at baseline, then weekly for two weeks and then once every 2 weeks for the next 20 weeks (13 administrations) to subjects with SLE. The preparation of the study drug and rate of infusion will be provided in the Study Drug Reference Manual. For each dose, the date, actual infusion rate, start and stop time of infusion will be recorded in the source documents and transcribed into the CRFs.

8.5 Study Drug Accountability

The unblinded pharmacist will maintain an accurate record of the receipt of the Investigational Product as shipped by the Sponsor (or designee), including the date received. In addition, an accurate drug disposition record will be kept, specifying the amount dispensed to each subject and the date of dispensation.

8.6 Study Drug Handling and Disposal

At the completion of the study, all unused drug supplies will be destroyed by the sites after final accountability and reconciliation with the dispensing log.

9 ASSESSMENT OF SAFETY

Safety of the treatment will be compared between the two groups by assessing adverse events and laboratory results as well as any physical findings that have changed from baseline.

All patients who have received any infusion with either RSLV-132 or placebo will be included in the overall analysis of safety. All data relating to safety will be listed and summarized by treatment group using descriptive statistics. The change from baseline for each of the vital signs parameters will also be computed and included in individual patient listings and descriptive summaries.

Deaths that occur during the study and the proportion of subjects discontinuing the study due to adverse events will as well be summarized by treatment group.

All adverse events will be coded and tabulated by MedDRA System Organ Class (SOC) and preferred term (PT) and presented in descending frequency. Adverse events will also be tabulated by severity and relationship to the study medication. Serious adverse events will be summarized separately.

9.1 Adverse Event Definition

An adverse event (AE) is any untoward medical occurrence in a subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. Adverse events may be reported by the subject, discovered by Investigator questioning, or detected through PE, a laboratory test requiring further attention, or other means.

Adverse events can therefore be any unfavorable or unintended sign, symptom or disease temporally associated with the use of an investigational medicinal product, whether or not considered related to the investigational medicinal product. Adverse events include:

- Any sign, medical diagnosis or symptom
- Any new undesirable medical experience or unfavorable and unintended worsening of an existing condition that occurs during or after treatment, whether or not considered related to study drug
- Abnormal laboratory results that have associated symptoms or findings, require specific treatment, or require a change in subject management.

Whenever possible, the Investigator should group signs or symptoms that constitute a single diagnosis under a single event term. For example, cough, rhinitis and sneezing might be grouped together as “upper respiratory tract infection”. If possible, abnormal laboratory results that meet the definition of an AE (that warrant management, investigation or treatment) should be reported as a clinical diagnosis rather than the abnormal value itself (e.g., “anemia” rather than “decreased blood count”). Adverse events will be graded according to the Rheumatology CTC (Woodworth et al., J. Rheumatology 2007; 34(6): 1401-1414).

9.2 Serious Adverse Event Definitions

An AE is classified as serious if it meets any of the following criteria:

- Results in death
- Is life-threatening
    - This definition implies that the subject, in the view of the Investigator, was at immediate risk of death at the time of the event. It does not include an event that, had it occurred in a more severe form, might have caused death.
- Requires in-patient hospitalization or prolongs an existing hospitalization
    - Hospitalizations for surgeries planned before study entry, for social reasons, or for normal disease management procedures (including treatment adjustment) are not to be considered SAEs according to this criterion.
- Results in persistent or significant disability and/or incapacity
- Results in an adverse outcome in a child or fetus of a patient exposed to the study treatment regimen before conception of during pregnancy.
- Otherwise considered medically important in the judgment of a health care professional. Medical and scientific judgment should determine whether an AE is classified as an SAE in many situations. Medically important conditions that may not result in death, not be life-threatening, nor require hospitalization, may be considered SAEs when they may jeopardize the subject or may require intervention to prevent one of the outcomes listed above. Examples of such events are allergic bronchospasm requiring intensive treatment in an emergency room, blood dyscrasias or convulsions that do not result in in-patient hospitalization.

9.3 Adverse Event Reporting

All AEs, both serious and non-serious, will be recorded on the AE CRF at each visit from the time the subject receives the first dose of study medication until the End of Study visit.

9.4 Serious Adverse Event Reporting Requirements

SAEs will be reported to Resolve on the SAE report form within 24 hours of awareness of the event by the investigator.

In the event that the investigator does not become aware of the occurrence of a SAE immediately, the investigator is to report the event within 24 hours of his/her first awareness of the SAE.

Any SAE occurring any time after the reporting period must be promptly reported if a causal relationship to investigational product is suspected.

The initial report should include as much relevant information as possible but at a minimum should include subject Number, date of event onset, event term/description of event, investigator’s assessment of relationship to study drug.

For all SAEs, the investigator is obligated to pursue and provide information to Resolve or its designee in accordance with the timeframes for reporting specified above. In addition, an investigator may be requested by Resolve to obtain specific additional follow-up information in an expedited fashion. This information may be more detailed than that captured on the AE case report form. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications and illnesses must be provided. All new information including final outcome should be submitted as soon as possible.

9.5 Non-Serious Adverse Event Reporting Requirements

Non-serious AEs are to be reported on the AE CRFs, which are to be submitted as outlined in the study guidelines.

9.6 Adverse Event Follow Up

For adverse events with a causal relationship to the investigational product, follow-up by the investigator is required until the event or its sequelae resolve, stabilize or are explained.

9.7 Severity Assessment

As required on the AE case report forms, the investigator will assess the severity of an event according to the Rheumatology CTC (Woodworth et al., J. Rheumatology 2007; 34(6): 1401-1414).

9.8 Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and non-serious). Causality is determined as not related, possibly related, or definitely related according to the following definitions:

- Not related: The event can be readily attributed to other factors such as the subject's clinical state, environmental factors, or other concomitant medications or therapies administered.
- Possibly Related: Follows a reasonable temporal sequence from administration and is unlikely to be attributed to the subject's clinical state or environmental factors or other therapies administered.
- Definitely related: Clear-cut temporal association with study drug administration with improvement on cessation of study drug AND cannot be readily attributed to other factors such as the subject's clinical state, environmental factors, or other concomitant medications or therapies administered.

9.9 Abnormal Test Findings

When laboratory results are outside the normal range, a decision regarding whether the result is of clinical significance or not shall be made by the Investigator and shall be based, in part, upon

the nature and degree of the observed abnormality. Abnormal evaluations may be repeated, to rule out lab error.

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- Test result is associated with accompanying symptoms, and/or;
- Test result requires additional diagnostic testing or medical/surgical intervention, and/or;
- Test result is considered to be an AE by the investigator or Sponsor.

An abnormal test result, in the absence of any of the above conditions, does not constitute an AE.

Any abnormal test result that is determined to be an error does not require reporting as an AE.

9.10 Hospitalization

AEs reported from the clinical study associated with subject hospitalization or prolongation of subject hospitalization, are considered serious.

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical AE is not an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (e.g., for work-up of persistent pre-treatment lab abnormality);
- Social admission (e.g., subject has no place to sleep);
- Administrative admission (e.g., for yearly physical exam);
- Protocol-specified admission during a clinical study (e.g., for a procedure required by the study protocol);
- Pre-planned or optional admission not associated with a precipitating clinical AE.

10 ASSESSMENT OF PHARMACOKINETICS

10.1 Measurement of RSLV-132 Drug Levels

RSLV-132 drug levels in subject serum samples will be quantitated by two different assays; a validated ELISA assay that directly measures RSLV-132 (ICON Laboratories), and a catalytic activity assay that measures the RNase enzyme activity of RSLV-132 (Resolve Therapeutics, LLC).

10.2 Pharmacokinetic Analysis

Pharmacokinetic (PK) parameters will be calculated for each subject, whenever possible, based on the serum concentrations of RSLV-132.

11 STATISTICS

A statistical analysis plan will be prepared after completion of the final protocol and will be finalized before database lock. The statistical analysis plan will include more details on the statistical analysis and presentation of the data. The fundamentals of the analysis are listed below. Data will be analyzed and reported by subject's sex and gender.

11.1 Subject Population for Efficacy/Activity Analysis

The efficacy/activity analysis set will include all subjects randomized and that receive at least one dose of study drug.

11.2 Analysis of the Primary Objective

The primary objective is a comparison of the mean improvement (from Baseline to Day 85; or Baseline to Day 169 in CLASI Activity scores of those in the efficacy analysis set receiving RSLV-132 and those receiving placebo.

11.3 Analysis of the Secondary Objectives

The following secondary objectives will be compared between the two treatment arms:

- The immunogenicity of RSLV-132 as measured by the presence of RSLV-132 antibodies
- Improvements (from Baseline to Day 85 and Day 169) in the SLEDAI-2K, PGA, and BILAG-2004 scores
- Improvement (from Baseline to Day 85 and Day 169) in the FACIT-Fatigue scale
- Improvements (from Baseline to Day 85 and Day 169) in tender or swollen joint count
- Reduction in oral steroids at Day 169 relative to Day 85
- The proportion of subjects achieving a 50% improvement in CLASI activity score

11.4 Exploratory Analysis

Differences between the gene expression profiles, autoantibody and complement profiles, and serum protein levels will be compared between the two treatment arms. A comparison will be made of the mean improvement (from Baseline to Day 85; or Baseline to Day 169 in CLASI damage scores of those randomized to be treated with RSLV-132 and those randomized to receive placebo.

11.5 Subject Population for Safety Analysis

The safety of RSLV-132 will be compared between the two arms using the following safety parameters: adverse events, previous and concomitant medications, previous and concomitant diseases and laboratory data. The safety population will include all patients who received any treatment with either RSLV-132 or placebo. Randomized patients that receive the incorrect therapy from that intended will be summarized in the group according to the therapy actually received. Patients who are not randomized but who receive treatment or placebo will also be included in the safety population and summarized according to the therapy actually received. In

the unlikely event of a patient commencing one study therapy and crossing over to the other, the data for that patient will be included in summaries and analyses with the original group.

11.6 Sample Size

The sample size chosen for this study was based upon precedent set by other studies of similar nature and was not based on power calculations.

12 STUDY PROCEDURES

12.1 Evaluations

Evaluations are summarized in Appendix A. During the course of the study approximately 295 mL of blood will be drawn. A central laboratory will perform all evaluations with the following exceptions:

- anti-drug antibody evaluations will be performed by ICON.
- autoantibody assessments will be performed by the University of Washington Clinical Laboratory.
- measurement of drug concentration by will be performed by ICON.
- measurement of RNase enzyme activity will be conducted by Resolve Therapeutics.
- serum protein analysis will be conducted by Myriad RBM.
- blood-cell gene expression analysis will be performed by Q^2 Solutions.
- Each site will perform a urine pregnancy test on females at the baseline visit only

Every attempt will be made to perform evaluations on the scheduled day and time, as appropriate. If evaluations cannot be performed on the day of the scheduled visit a window of ± 3 days may be applied for visit Days 8 through 155 and ±5 days for Day 169 and Day 215. In the event visit windows are utilized the minimum interval between administrations of RSLV-132 should be 10 calendar days.

All scheduled study visits should occur on the specified number of days after Baseline, even if a preceding visit occurred off-schedule.

12.2 Screening Procedures

The following Screening procedures will be performed for all potential subjects at a visit conducted within 28 days of study entry (prior to Baseline):

- informed consent;
- assess inclusion/exclusion criteria;
- demographic data;
- weight, and height;
- viral load for hepatitis-B and C and HIV (Appendix B);
- physical examination;
- pregnancy test (serum);
- medical and medication history;
- vital signs (temperature, respiratory rate, blood pressure and pulse);
- clinical laboratory evaluations (including Chem-20, CBC, and UA), laboratory evaluations may be repeated if abnormal;
- measurement of cutaneous SLE activity (CLASI);
- photographs of cutaneous SLE lesions for adjudication (if CLASI ≥10);
- evaluation of autoantibody profile (Ro-52/60, La, Sm, SmRNP, U1 RNP A/68) local or central laboratory.

12.3 Baseline (Day 1) Procedures

Prior to study drug administration (pre-dose procedures):

- the inclusion/exclusion criteria will be re-evaluated (CLASI score and concomitant medications only);
- directed physical examination;
- pregnancy test (urine);
- AE Assessment;
- interim medical/medication history;
- vital signs (temperature, respiratory rate, blood pressure and pulse);
- clinical laboratory evaluations (Chem-20, CBC, and UA);
- measurement of SLE disease activity (CLASI, SLEDAI-2K, BILAG-2004, PGA);
- tender and swollen joint count
- photographs of cutaneous SLE lesions;
- FACIT Index (subject completes form);
- serum sample for study drug concentration;
- serum for protein analysis;
- serum sample for measurement of RNase activity;
- whole blood for gene expression profile;
- serum sample for autoantibody profile (Ro-52/60, La, Sm, SmRNP, U1 RNP A/68, dsDNA) C3 and C4 (local or central laboratory);
- serum for assessment of antibodies to RSLV-132;
- **after completion of above assessments:**
    - study drug administration

12.4 Procedures on Days 8, 15, 43, 71, 99, 127, and 155

Prior to study drug administration (pre-dose procedures):

- adverse event assessment;
- interim medication history;
- vital signs (temperature, respiratory rate, blood pressure and pulse);
- serum for assessment of anti-RSLV-132 antibodies (Day 15 only)
- measurement of cutaneous disease activity (CLASI) – (Days 99, 127 and 155 only);
- **after completion of above assessments:**
    - study drug administration

12.5 Procedures on Days 29, 57, 85, 113, 141, and 169/End of Treatment (EOT)

Prior to study drug administration (pre-dose procedures):

- directed physical examination;
- adverse event assessment;
- interim medication history;
- vital signs (temperature, respiratory rate, blood pressure and pulse);

- Chem-20, CBC, UA;
- measurement of SLE activity (SLEDAI-2K, BILAG-2004, PGA);
- measurement of cutaneous disease activity (CLASI);
- tender and swollen joint count;
- photographs of cutaneous disease activity (Days 85 and 169 only);
- FACIT fatigue index (subject completes form) (Days 85 and 169 only);
- serum for study drug concentration (Days 29, 85, and 169 only);
- serum for protein analysis (Day 85 and 169 only);
- serum for RNase activity (Days 29, 85, and 169 only);
- whole blood for gene expression profile (Days 29, 85, and 169 only);
- serum for autoantibody profile (Ro-52/60, La, Sm, SmRNP, U1 RNP A/68, dsDNA) C3 and C4 (local or central laboratory);
- serum for assessment of anti-RSLV-132 antibodies (Days 29 and 85 only);
- **after completion of above assessments:**
    - study drug administration (except Day 169)

12.6 End of Study Day 215 Evaluations

The following procedures will be performed on Day 215:

- directed physical examination;
- pregnancy test (serum).
- adverse event assessment;
- interim medication history;
- vital signs (including temperature, respiratory rate, and seated blood pressure and pulse);
- clinical laboratory evaluations (Chem-20, CBC, and UA);
- serum for study drug concentration;
- serum for measurement of RNase activity;
- whole blood for gene expression profile;
- serum for assessment of antibodies to RSLV-132;

12.7 Vital Signs

Vital signs (including temperature, respiratory rate, and seated blood pressure and pulse) will be obtained. Blood pressure and pulse will be measured after the subject has been seated for at least five minutes.

12.8 Medical/Medication History

Subjects arriving at the clinical unit for the Screening visit will have a complete medical history performed including the current and past medications the subject has been using. At subsequent visits to the clinic only an interim medical/medication history shall be performed to determine what changes to the subject's symptoms and medications have taken place since the last visit.

12.9 CLASI Clinical Assessment

A CLASI assessment shall be performed for each subject at scheduled visits to determine the SLE disease activity for each subject at the visit. The assessment will include determination of both the CLASI Activity Score and the CLASI Damage Score. The assessment shall be performed by a qualified, licensed rheumatologist that has completed training provided by the Lupus Foundation of America (LFA) on the use of the instrument.

12.10 SLEDAI-2K, BILAG-2004, PGA, and Tender and Swollen Joint Count Clinical Assessments

SLEDAI-2K, PGA, BILAG-2004, and tender and swollen joint count assessments shall be performed for each subject at scheduled visits to determine the SLE disease activity for each subject at the visit. The above mentioned clinical assessments shall be performed by a qualified, licensed rheumatologist that has experience in performing such assessments and has participated in clinical trials in which such measurements were performed.

12.11 Study Drug Concentration

Serum samples will be analyzed using a validated, competitive ELISA assay to determine the serum concentration of study drug at selected visits during the study.

12.12 Gene Expression Analysis

RNA will be extracted from whole blood to measure the expression level of genes that are related to inflammatory pathways though to be involved in SLE. Samples will be obtained at selected visits during the study from Baseline to the End of Study visit.

12.13 Protein Analysis

Serum samples will be obtained at various visits during the study to analyze the level of circulating serum proteins. The protein analysis will measure protein levels related to the inflammatory process. The analysis will be carried out using a multiplexed immunoassay.

12.14 Anti-Drug Antibodies

Serum will be analyzed by ICON for the presence of anti-RSLV 132 antibodies using a validated immunoassay. Each positive serum sample will be evaluated for ADA specificity by repeating the immunoassay in the presence of an excess of RSLV-132. Confirmed positive, specific serum samples will be titered by serial dilution and a numerical titer will be assigned.

12.15 RNase Activity Assessments

RNase activity will be determined by Resolve Therapeutics using a qualified analytical procedure. Serum samples for RNase activity will be collected, processed, stored and shipped according to instructions provided in a separate study manual. Samples will be obtained periodically during the study from Baseline to the End of Study visit.

12.16 Autoantibody Profile

Serum samples will be analyzed using validated methods. The analysis shall provide values for the following autoantibodies and indicate if the result is positive, equivocal, or negative using the validated assay range for the testing laboratory: Ro-52/60, La, Sm, SmRNP, U1 RNP A/68, and dsDNA.

13 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The Investigator(s) will permit trial-related monitoring, audits, IRB review, and regulatory inspection(s) by providing direct access to source data/documents.

13.1 Study Monitoring

Blinded Study Monitors will be responsible for monitoring this clinical trial. The Study Monitors will monitor the study conduct, proper CRF and source documentation completion. To this end, the Study Monitors will visit the study site at suitable intervals and be in frequent contact through verbal and written communication. It is essential that the Study Monitors have access to all documents (related to the study and the individual participants) at each monitoring visit. In turn, the Study Monitors will adhere to all requirements for subject confidentiality as outlined in the Informed Consent Form (ICF). The investigator and investigator's staff will be expected to cooperate with the Study Monitors, to be available during a portion of the monitoring visit to answer questions, and to provide any missing information.

An unblinded monitor will periodically visit each site to evaluate drug compliance and accountability but will not be involved in the monitoring of any clinical data.

13.2 Audits and Inspections

A Quality Assurance representative from Resolve or a clinical research organization may conduct audits at the study site(s). Audits will include, but are not limited to, drug supply, presence of required documents, the informed consent process, laboratory specimen processing, and comparison of CRFs with source documents. The Investigator agrees to cooperate with audits conducted at a reasonable time and in a reasonable manner.

Regulatory authorities may also audit the Investigator during or after the study. The Investigator should contact Resolve Therapeutics immediately if this occurs, and must fully cooperate with the audits conducted at a reasonable time in a reasonable manner.

The Investigator is required to make all study documentation promptly available for inspection, review or audit at the study site upon request by sponsor, its representatives, or any appropriate regulatory agencies.

13.3 Institutional Review Board

In accordance with 21 CFR 56, the protocol, advertisement, and ICF will be reviewed and approved by the IRB. The Sponsor will supply relevant material for the investigator to submit to the IRB for the protocol's review and approval. Verification of the IRB unconditional approval of the protocol and the written ICF statement will be transmitted to the investigator.

The IRB will be informed by the investigator of subsequent protocol amendments and of serious and unexpected AEs. Approval for protocol amendments will be transmitted in writing to the investigator. If requested, the investigator will permit audits by the IRB and regulatory inspections by providing direct access to source data/documents.

The investigator will provide the IRB with progress reports at appropriate intervals (not to exceed one year) and a Study Progress Report following the completion, termination, or discontinuation of the investigator's participation in the study.

14 ETHICS

14.1 Ethical Conduct of the Study

The study procedures outlined in this protocol will be conducted in accordance with the U.S. Code of Federal Regulations governing Protection of Human Subjects (21 CFR 50), Financial Disclosure by Clinical Investigators (21 CFR 54), Institutional Review Boards (21 CFR 56), Investigational New Drug Application (21 CFR 312), and Applications for FDA Approval to Market a New Drug (21 CFR 314), as appropriate. As such, these sections of U.S. Title 21 CFR, along with the applicable International Conference on Harmonization (ICH) Guidelines, are commonly known as Good Clinical Practices, which are consistent with the Declaration of Helsinki.

14.2 Written Informed Consent

Written informed consent for the study will be obtained from all subjects before protocol specific procedures are carried out. The ICF generated by the IRB will be approved (along with the protocol) by the IRB and will be acceptable to the Sponsor.

The investigator (or designee) will explain the nature of the study and the action of the test product. The subjects will be informed that participation is voluntary and that they can withdraw from the study at any time. In accordance with 21 CFR 50, the informed consent process shall be documented by the use of a written ICF approved by the IRB and will be signed by the subject prior to protocol-specific procedures being performed. The subject will be given a copy of the signed consent, and the original will be maintained with the subject's records.

14.3 Disclosure

All information provided regarding the study, as well as all information collected/documented during the course of the study, will be regarded as confidential. The investigator agrees not to disclose such information in any way without prior written permission from the Sponsor.

Any publication of the results, either in part or in total (articles in journals or newspapers, oral presentations, abstracts, etc.) by the Investigator(s) or their representative(s), shall require prior notification and review, within a reasonable time frame, by the Sponsor, and cannot be made in violation of the Sponsor's confidentiality restrictions or to the detriment of the Sponsor's intellectual property rights.

15 DATA HANDLING AND RECORDKEEPING

There will be no alterations in the protocol without agreement between the Sponsor and the investigator. There will be no alterations in the protocol affecting subject safety without the express written approval of the Sponsor, investigator, and the IRB.

Investigators are required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. The case history for each individual shall document that informed consent was obtained prior to participation in the study

The results from screening and data collected during the study will be recorded in the subject's CRF (either paper or electronic CRF). To maintain confidentiality, the subjects/patients will be identified only by numbers and/or initials. The completed CRFs will be transferred to the Sponsor or designee. Copies of each CRF will be retained by the Investigator. All source documents, records, and reports will be retained by the study site in accordance with 21 CFR 312.62(c). Data handling and record keeping are further described in the Data Management Plan.

15.1 Inspection of Records

All primary data, or copies thereof (e.g., laboratory records, CRFs, data sheets, correspondence, photographs, drug accountability records, and computer records), which are a result of the original observations and activities of the study and are necessary for the reconstruction and evaluation of any study report, will be retained in the study site archives for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified.

16 REFERENCES

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17 APPENDICES

17.1 Appendix A: Study Procedures

Study Procedures	Screen (-28 to -1)	Baseline Day 1	Day 8	Day 15	Day 29	Day 43	Day 57	Day 71	Day 85	Day 99	Day 113	Day 127	Day 141	Day 155	Day 169 (EOT)	Day 215 (EOS)
Acceptable Visit Window (days)			± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 5	± 5
Informed Consent	X															
Inclusion/exclusion	X	X[a]														
Demographics	X															
Weight, height	X															
Hepatitis, HIV tests	X															
Physical exam	X	X[b]			X[b]		X[b]		X[b]		X[b]		X[b]		X[b]	X[b]
Pregnancy tests	X[c]	X[d]														X[c]
AE assessment		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Medical/medication history	X	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chem-20, CBC, UA	X	X			X		X		X		X		X		X	X
SLEDAI, BILAG, PGA, joint count		X			X		X		X		X		X		X	
CLASI	X	X			X		X		X	X	X	X	X	X	X	
Photographs of cutaneous disease	X	X							X						X	

Study Procedures	Screen (-28 to -1)	Baseline Day 1	Day 8	Day 15	Day 29	Day 43	Day 57	Day 71	Day 85	Day 99	Day 113	Day 127	Day 141	Day 155	Day 169 (EOT)	Day 215 (EOS)
Acceptable Visit Window (days)			±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±5	±5
FACIT index		X							X						X	
Serum for study drug concentration		X			X				X						X	X
Serum for protein analysis		X							X						X	
Serum for RNase activity		X			X				X						X	X
Whole blood for gene expression		X			X				X						X	X
Serum for autoantibody, C3, C4 profile	X	X			X		X		X		X		X		X	
Serum for ADA		X		X	X				X							X
Study Drug administration		X[f]	X	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]		

a CLASI activity and damage score and confirm no changes in SLE medications only
b directed physical exam
c serum pregnancy test for women of childbearing potential (7.4)
d urine pregnancy test for women of childbearing potential (7.4)
e interim medical/medication history only
f RSLV-132 or placebo shall be administered according to the infusion rate and time set forth in the Study Drug Reference Manual

17.2 Appendix B: Clinical Laboratory Evaluations

Chemistry (Chem-20):	**Hematology (CBC):**	**Other Tests:**
Albumin Alkaline Phosphatase ALT AST Bicarbonate BUN Calcium Chloride Cholesterol Creatinine GGT Glucose Lactate dehydrogenase Phosphate Potassium Sodium Total Bilirubin Total Protein Triglycerides Uric acid	Hematocrit Hemoglobin Mean corpuscular hemoglobin Mean corpuscular hemoglobin concentration Mean corpuscular volume Platelet count Red blood cell count White blood cell count White blood cell differential (Percent and Absolute): Basophils Eosinophils Lymphocytes Monocytes Neutrophils Bands	Hepatitis B, and C HIV Pregnancy Test (serum and urine qualitative) RNase activity Study drug concentration Serum protein analysis Anti-RSLV-132 antibodies Autoantibody profile C3 and C4 Gene expression FSH
Complete Urinalysis (UA):		
pH and Specific Gravity Bilirubin Glucose Ketones Leukocytes Nitrite Occult blood Protein (Albumin/Creatinine) Urobilinogen Microscopic (RBC, WBC)		

17.3 Appendix C: Investigator Protocol Agreement Page

By signing, I confirm that my staff and I have read and understand this protocol, and agree to comply with the conduct and terms of this study. My staff and I have agreed to abide by the following responsibilities:

- To conduct the study in compliance with Sponsor agreements, this protocol, any future amendments, any conditions of the governing reviewing EC/IRB or regulatory agency, and with any other study conduct procedures implemented by Resolve Therapeutics.
- To supervise all testing involving human subjects.
- To abide by FDA regulations, Good Clinical Practices (GCP), and all applicable regional regulations.
- Ensure that the requirements for obtaining informed consent from each study participant or their legal representative are met.
- To report any Serious Adverse Events to Resolve Therapeutics in a timely manner as required by the protocol.
- To report any Serious Adverse Events to the IRB in a timely manner.
- To report Non-Serious Adverse Events as required by the protocol.
- To assure access by Resolve Therapeutics representatives to original source documents.
- To maintain confidentiality and assure security of Resolve Therapeutics confidential documents that include but are not limited to: the protocol, case report forms, Investigator's Brochure, final study documents, manuscript drafts, unpublished data, sponsor correspondence, etc.
- To cooperate fully with any study related GCP audit as performed by the sponsor's quality assurance group.
- To cooperate fully with any regulatory agency audit.

Principal Investigator (printed name): _____

Principal Investigator (signature): _____

Date Signed (mm/dd/yyyy) _____

17.4 Appendix D: ACR SLE Classification Criteria

1997 Update of the 1982 American College of Rheumatology revised criteria for classification of systemic lupus erythematosus

1. Malar Rash	Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
2. Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions
3. Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation
4. Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by physician
5. Nonerosive arthritis	Involving 2 or more peripheral joints, characterized by tenderness, swelling, or effusion
6. Pleuritis or pericarditis	1. Pleuritis--convincing history of pleuritic pain or rubbing heard by a physician or evidence of pleural effusion OR 2. Pericarditis--documented by electrocardigram or rub or evidence of pericardial effusion
7. Renal disorder	1. Persistent proteinuria > 0.5 grams per day or > than 3+ if quantitation not performed OR 2. Cellular casts--may be red cell, hemoglobin, granular, tubular, or mixed
8. Neurologic disorder	3. Seizures--in the absence of offending drugs or known metabolic derangements; e.g., uremia, ketoacidosis, or electrolyte imbalance OR 4. Psychosis--in the absence of offending drugs or known metabolic derangements, e.g., uremia, ketoacidosis, or electrolyte imbalance
9. Hematologic disorder	1. Hemolytic anemia--with reticulocytosis OR 2. Leukopenia--< 4,000/mm3 on ≥ 2 occasions OR 3. Lyphopenia--< 1,500/ mm3 on ≥ 2 occasions OR 4. Thrombocytopenia--<100,000/ mm3 in the absence of offending drugs

10. Immunologic disorder	1. Anti-DNA: antibody to native DNA in abnormal titer OR 2. Anti-Sm: presence of antibody to Sm nuclear antigen OR 3. Positive finding of antiphospholipid antibodies on: 1. an abnormal serum level of IgG or IgM anticardiolipin antibodies, 2. a positive test result for lupus anticoagulant using a standard method, or 3. a false-positive test result for at least 6 months confirmed by Treponema pallidum immobilization or fluorescent treponemal antibody absorption test
11. Positive antinuclear antibody	An abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs

17.5 Appendix E: Summary of Changes

	From Version 4.0 to Version 5.0
Overall	1. Clarified that there are two lot numbers and concentrations of study drug. 2. Clarified which assessments should be performed for subjects that discontinue early from the study. 3. Clarified that all AEs, both serious and non-serious, will be recorded on the AE CRF at each visit from the time the subject receives the first dose of study medication until the End of Study visit.
Section	**Details of Changes**
Title Page	• Updated Version, Prior Version, Date of Publication • Updated version number and date to footer
6.4	Updated section to clarify that efforts will be made to perform all End of Treatment (EOT) assessments and an End of Study (EOS) visit outlined in (Appendix A).
7.1	Clarified RSLV-132 is provided in single-use vials for dilution for intravenous infusion. Two lots of drug have been used in the study; lot 1-FIN-1778 which was provided at 9.5 mg/mL, and lot 1-FIN-2899 which was provided at 10.0 mg/mL.
8.1	Clarified RSLV-132 is presented as a single-use, preservative-free vial of sterile solution concentrate for dilution for intravenous infusion at a strength of either 9.5 mg/mL or 10.0 mg/mL. Table 2: Added Lot 1-FIN-1778, 9.5 mg/mL and Lot 1-FIN-2899, 10.0 mg/mL Footnote: Clarified the lot numbers for each concentration of the study drugs will be provided to the clinical site by the supplier/manufacturer and will be on vial labels.
9.3	Clarified all AEs, both serious and non-serious, will be recorded on the AE CRF at each visit from the time the subject receives the first dose of study medication until the End of Study visit.
17.5 Appendix E	Updated table with summary of changes.