# RSLV-132

# PROTOCOL 132-04

# A PHASE 2, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF RSLV-132 IN SUBJECTS WITH PRIMARY SJOGREN'S SYNDROME


**RESOLVE THERAPEUTICS, LLC**

**721 1st Avenue North**

**St. Petersburg, FL 33701**

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| **Protocol Title:** | A Phase 2, Double-Blind, Placebo-Controlled Study of RSLV-132 in Subjects with Primary Sjogren's Syndrome |
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| **Investigators:** | Multicenter Study: Investigator information on file at Resolve Therapeutics. The Chief Investigator is Prof. Wan Fai Ng of Newcastle University, UK. |
| **Study Monitors:** | The study will be monitored by contract clinical research associates using Resolve Therapeutics operating procedures. |

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| **Clinical Laboratories:** | Laboratories involved in this study are listed on the delegation of responsibilities documentation. |

**Sponsor Approval:**

| | |
|---|---|
| **James Posada, PhD**<br>**Chief Executive Officer** | 10May2017<br>**Date** |

# 1 PROTOCOL SYNOPSIS

## 1.1 Name of Sponsor

Resolve Therapeutics, LLC

## 1.2 Name of Investigational Product

RSLV-132

## 1.3 Number and Title of Study

Protocol 132-04: A Phase 2, Double-Blind, Placebo-Controlled Study of RSLV-132 in Subjects with Primary Sjogren's Syndrome

## 1.4 Phase of Development

Phase 2

## 1.5 Study Period

Patient participation period: 60 days of screening followed by 12 weeks of treatment and 18 weeks of follow-up (approximately 38 weeks total).

Planned study conduct duration: approximately 21 months total (from enrollment of first subject to completion of follow-up for last patient).

## 1.6 Study Objectives

The present study will examine the role of circulating RNA complexed with autoantibodies and immune complexes and its role in activation of inflammatory pathways in patients with primary Sjogren's syndrome. The study will be conducted in a subset of Sjogren's patients who have elevated levels of SSA/Ro autoantibodies and a pattern of elevated interferon-stimulated gene expression in blood cells. Given the well-established inflammatory properties of RNA, RSLV-132 will be administered to digest the circulating RNA bound to autoantibodies and thereby attenuate the chronic activation of multiple inflammatory pathways. A number of biochemical and clinical parameters will be analyzed to determine the potential therapeutic utility of nuclease therapy in Sjogren's syndrome.

**Primary Study Endpoint:** The primary endpoint of the study is to assess the following biochemical parameters in the active versus control groups comparing Baseline and Day 99:

- changes in blood cell gene expression or serum protein levels indicative of reduced inflammation.

**Secondary Study Endpoint:** The secondary endpoints of the study are to assess the following parameters in the active versus control groups comparing Baseline and Day 99:

- safety and tolerability;
- anti-Ro autoantibody levels;
- total immunoglobulins;
- complement levels (C3 & C4)
- erythrocyte sedimentation rate (ESR)
- minor salivary gland histopathology
- minor salivary gland interferon-stimulated gene expression;
- disease activity (ESSDAI or PGA, Schirmer's test, stimulated and unstimulated salivary flow);
- patient-reported outcomes as measured by the following: ESSPRI, FACIT, VAS, Profile of fatigue, EQ-5D-L, Fatigue VAS, and Neuropsychological analysis scales (Neuropsychological analysis to be performed only at Newcastle University);
- Additional exploratory evaluations may be considered as driven by the evolving understanding of the mechanism of action, technical feasibility, and any other clinical or immunological information that may become available during the course of the clinical study. Note: Additional exploratory endpoints will be specified in a separate laboratory manual and will be reported separately to the main safety, tolerability and efficacy endpoints of the study.

## 1.7 Study Design

This is a multi-center, double-blind, placebo-controlled study to evaluate the impact of 8 intravenous infusions of RSLV-132 in 28 patients with primary Sjogren's syndrome. Each of the subjects will be randomized 3:1 (active:placebo) and will receive 8 infusions of 10 mg/kg of RSLV-132 or placebo as follows on days:

- **1, 8, 15, 29, 43, 57, 71, and 85**

Potential subjects will be screened to assess their eligibility to enter the study within 60 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). Additionally, in a 6-month toxicology study in cynomolgus monkeys, 50 mg/kg of RSLV-132 was administered by IV infusion weekly. No dose-limiting toxicity was noted, therefore the No Observed Adverse Effect Level is at least 50 mg/kg, providing at least a 5-fold safety margin for this study.

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 Guide. The dose for each individual shall be based on the subject's body weight.

## 1.8 Inclusion Criteria

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

1. Meet 4 of the 6 criteria (must include histopathology or autoantibodies) of the 2002 American-European Consensus Group (AECG) criteria for Primary Sjogren's Syndrome.
2. elevated levels of anti Ro-52 or anti Ro-60 antibodies (within laboratory positive range);
3. positive interferon signature (whole blood cell interferon signature metric > -1);
4. stable medications used to treat Sjogren's syndrome for the 30 days prior to the Baseline visit;
5. able to communicate and able to provide valid, written informed consent;
6. ages 18 to 85 inclusive;
7. minimum weight of 45 kg;
8. Female participants shall be either of non-child-bearing potential (permanently sterilized by bilateral tubal occlusion, hysterectomy, or bilateral salpingectomy), or menopausal (more than one year since last menstrual cycle and confirmed by blood FSH levels $\geq$ 22 mIU/mL) OR practicing highly effective contraception (e.g., oral (but not including progestogen-only oral contraceptives), injectable, implantable or transdermal contraceptives, a non-hormonal intrauterine device [IUD] or an intrauterine hormone releasing system [IUS]) for at least 2 months prior to dosing and until 125 days after the last dose. In terms of sexual relations, female participants not practicing highly effective contraception as described above should abstain or only engage with male partners who are sterile or vasectomized. Female participants of child-bearing potential will also be required to have a negative serum pregnancy test [ß-hCG] at Screening and negative pregnancy urine test at Baseline. Female participants must agree not to donate eggs from the first dose until 125 days after the last dose.
9. Male participants, who are not sterile or vasectomized, must agree to abstain or only engage with female partners who use highly effective contraception from the first dose until 125 days after the last dose. Male participants must also agree not to donate sperm from the first dose until 125 days after the last dose.

## 1.9 Exclusion Criteria

Any of the following will exclude potential subjects from the study:

1. previously diagnosed with systemic lupus, systemic sclerosis, or inflammatory myopathy.
2. use of hydroxychloroquine within 30 days of Baseline;
3. use of cyclophosphamide within 180 days of Baseline;
4. use of belimumab, abatacept, or TNF inhibitors within 90 days of Baseline;

5. use of rituximab within 6 months of Baseline (documentation of B-cell counts within the normal range for the reference laboratory is required for subjects within 1 year of rituximab usage).
6. use of oral corticosteroids equivalent to prednisone dose of >10 mg/day within 30 days of Baseline;
7. past head and neck radiation;
8. current untreated lymphoma at Baseline;
9. known IgG4-related disease
10. graft versus host disease
11. 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;
12. positive test for hepatitis B, C, or HIV at Screening;
13. participation in another clinical study with receipt of an investigational product within 3 months or 5 half- lives, of last administration (whichever is longer) from Baseline;
14. positive pregnancy test at Screening or Baseline;
15. female subjects currently pregnant or breast feeding at Baseline;
16. inability or unwillingness to comply with protocol-specified procedures which, in the opinion of the Investigator, would make the subject unsuitable for study participation.

## 1.10 Criteria for Evaluation

- Biochemical measures:
    - gene expression profiling of blood cells
    - profiling of serum proteins
    - erythrocyte sedimentation rate (ESR)
    - anti Ro-52/Ro-60, C3, C4, and total immunoglobulins
    - minor salivary gland histopathology
    - minor salivary gland biochemical markers (IFN, B-cell subsets)
    - study drug concentration
    - DNA analysis
    - anti-RSLV-132 antibodies
    - serum RNase activity

- Clinical measures:
    - ESSDAI
    - PGA
    - stimulated and unstimulated salivary flow
    - Schirmer's test

- Patient-Reported Outcomes:
    - ESSPRI
    - FACIT
    - Profile of fatigue
    - EQ-5D-L

- Fatigue VAS (01-100)
- neuropsychological analysis of fatigue

## 1.11 Evaluations by Day

- Screening Procedures:
  - informed consent;
  - assess inclusion/exclusion criteria;
  - demographic data;
  - weight and height;
  - physical examination;
  - complete medical and medication history;
  - vital signs;
  - hepatitis B, C, and HIV antibody tests;
  - serum pregnancy test;
  - chem-21 (see Appendix B), CBC, and UA;
  - interferon-stimulated gene expression analysis (whole blood);
  - anti Ro-52/Ro-60 autoantibodies;
  - FSH (when required to confirm menopause in female subjects)

- Baseline Procedures:
  - confirmation of inclusion/exclusion criteria;
  - physical examination;
  - adverse event baseline assessment;
  - interim medical and medication history;
  - vital signs;
  - measurement of disease activity (ESSDAI, PGA, Schirmer's, stimulated and unstimulated salivary flow);
  - measurement of patient reported outcomes (ESSPRI, FACIT, Profile of fatigue, EQ-5D-L, Fatigue VAS, Neuropsychological analysis);
  - optional minor salivary gland biopsy;
  - urine pregnancy test;
  - chem-21 (see Appendix B), CBC, and UA;
  - serum for study drug concentration and RNase activity;
  - serum for serum protein analysis;
  - whole blood for ESR
  - whole blood for DNA analysis;
  - whole blood for measurement of RNA gene expression;
  - serum for anti Ro-52/Ro-60, total immunoglobulins, C3, and C4;
  - serum for anti-RSLV-132 antibodies;
  - study drug administration.

Additional Procedures:
The following procedures will be performed at various visits during the study. A total of 9 post-baseline visits will occur; once weekly for two weeks, then every two weeks for 14 weeks, plus one further visit 8 weeks after the last study drug administration. There will then be two additional telephone contacts made to subjects at weeks 13 and 18 after the last dose, to monitor any potential late-emerging adverse events. See section 13 and the schedule of events for the specific procedures and collection time points.

- physical exam;
- vital signs;
- adverse event assessment;
- medication history;
- measurement of disease activity (ESSDAI, PGA, Schirmer's test, stimulated and unstimulated salivary flow);
- optional minor salivary gland biopsy;
- measurement of patient reported outcomes (ESSPRI, FACIT, Profile of fatigue, EQ-5D-L, Fatigue VAS, Neuropsychological analysis);
- serum sample for study drug concentration and RNase activity;
- serum for protein analysis;
- whole blood for ESR
- whole blood for DNA analysis;
- whole blood for gene expression profile;
- anti-Ro-52/Ro-60, C3, C4, total immunoglobulins
- chem-21 (see Appendix B), CBC, and UA;
- serum sample for assessment of antibodies to RSLV-132;
- pregnancy test;
- study drug administration.

## 2 TABLE OF CONTENTS

List of Tables

**Table 1: Abbreviations and specialist terms**

| Abbreviation or specialist term | Explanation |
|---|---|
| ADA | anti-drug antibodies |
| AE | adverse event/experience |
| ß-hCG | ß-human chorionic gonadotrophin |
| CBC | complete blood count (hematology clinical laboratory evaluations) |
| CFR | code of federal regulations |
| Chem-21 | chemistry panel of 21 analytes |
| DNase | deoxyribonuclease |
| ELISA | enzyme-linked immunosorbent assay |
| ET | Early Termination |
| ESR | erythrocyte sedimentation rate |
| ESSDAI | EULAR Sjogren's syndrome disease activity index |
| ESSPRI | EULAR Sjogren's syndrome patient reported index |
| Fc | Fragment crystallizable of an antibody |
| FcR | Fc receptor |
| 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 |
| IEC | independent ethics committee |
| IFN | interferon |
| IgG | immunoglobulin G |
| IRB | institutional review board |
| IUD | intrauterine device |
| IV | intravenous |
| MHRA | Medicines and healthcare products regulatory agency |
| MTD | maximum tolerated dose |
| pDC | plasmacytoid dendritic cells |
| PGA | physician's global assessment |
| PK | pharmacokinetic |
| pSS | primary Sjogren's syndrome |
| RNA | ribonucleic acid |
| SAE | serious adverse event/experience |
| TLR | toll-like receptor |
| UA | urinalysis |

# 3 BACKGROUND

## 3.1 Primary Sjogren's Syndrome and Immune Complexes

Primary Sjogren's Syndrome (pSS) is an autoimmune disorder that is estimated to afflict between 0.5% to 1% of the general population, of whom nine out of ten patients are women (Ramos-Casals, 2005; Skopouli, 2000). The disease is characterized by the lymphocytic infiltration of salivary and lacrimal glands with subsequent inflammation, damage and loss of function of the glands causing dry eyes and dry mouth. Involvement of major organ systems including lung, kidney, and liver are common systemic manifestations of pSS (Malladi, 2012). At a biochemical level, pSS is associated with increased immunoglobulin levels and the production of anti-nuclear antibodies against ribonucleoprotein complexes such as SSA/Ro and SSB/La (Bave, 2005; Hall 2015).

Once formed, RNA-containing immune complexes are readily internalized into immune system cells such as dendritic cells, where the RNA bound to the immune complexes is able to interact with Toll-Like Receptors (TLRs), such as the RNA sensor, TLR7. 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 (Theofilopoulos, 2010). Cells expressing these receptors do so without distributing them to the cell surface; rather, TLRs 7/8/9 are sequestered within endosomes (Theofilopoulos, 2010). This positioning is postulated to minimize interaction with host nucleic acids. However, when present within an immune complex, 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 (Means, 2005; Lau, 2005; Brkic 2012). Once internalized, the nucleic acid is positioned to bind to and activate resident endosomal TLRs. Activated TLRs, in turn, promote type 1 IFN production from pDCs, activate PMNs, and promote B-cell proliferation and autoantibody production. Thus, the nucleic acid-containing antigens contribute to multiple aspects of pSS disease pathophysiology.

## 3.2 INVESTIGATIONAL AGENT

RSLV-132 is a novel therapeutic being developed for the treatment of systemic lupus erythematosus (SLE) and primary Sjogren's syndrome. This fully human biologic (Figure 1) consists of RNase1 fused to the N-terminus of the Fc region of IgG1. The attachment of the Fc is intended to extend the circulatory half-life of the RNase and by so doing reduce the frequency of administration. RSLV-132 is designed to significantly increase serum RNase activity to enzymatically digest RNA associated with autoantibodies and 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.

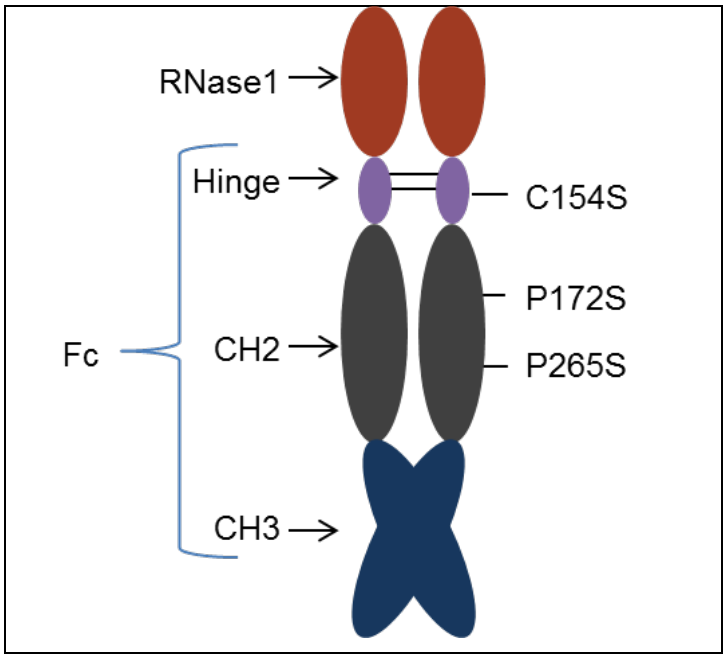


**Figure 1: Structure of RSLV-132**

## 3.3 Study Rationale

There is a preponderance of scientific and clinical evidence that supports the hypothesis that RNA associated with autoantibodies triggers multiple inflammatory pathways following uptake into FcR-bearing cells. RNA-containing autoantibodies and immune complexes circulating in pSS patient blood are specifically delivered to FcR-bearing cells and internalized resulting in the activation of TLRs and the activation of several 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 them biologically inert. Depleting the blood of circulating RNA bound to autoantibodies and immune complexes is hypothesized to decrease the activation of multiple pro-inflammatory cascades and thereby decrease the overall inflammation characteristic of Sjogren's syndrome.

## 3.4 Dose Rationale

RSLV-132 was administered as an IV infusion in a single ascending dose study in healthy volunteers and a multiple ascending dose study in SLE subjects with doses ranging from 0.3 mg/kg – 10.0 mg/kg. No MTD was reached in either of these studies. A study with mild to moderate SLE is currently ongoing where the dose is 10 mg/kg administered bi-weekly over a period of 24 weeks. Additionally, in a 6-month toxicology study in cynomolgus monkeys, 50 mg/kg of RSLV-132 was administered by IV infusion weekly. No dose-limiting toxicity was noted, therefore the No Observed Adverse Effect Level is at least 50 mg/kg, providing at least a 5x safety margin for this study. The duration of treatment is believed to be sufficient to observe changes in biomarkers for this proof-of-concept study.

## 3.5 Pre-Clinical Data

### 3.5.1 Pharmacology

RSLV-132 has been developed to digest RNA bound to immune complexes present in Sjogren's patients. An extensive series of in vitro studies demonstrated that RSLV-132 degrades RNA in a dose-responsive and time-dependent manner and digest immune complex RNA collected from SLE patient serum. The in vitro results support the concept that maintaining RSLV-132 exposure in the blood will result in the degradation of RNA associated with autoantibodies in Sjogren's patients. In vivo experiments involving administration to mice confirmed the ability for RSLV-132 to degrade double stranded RNA and information obtained from intravenous studies in rats and monkeys indicated that the pharmacodynamic properties of RSLV-132 are continually maintained with repeated dosing.

### 3.5.2 Toxicokinetics

Pharmacokinetic studies in rats and monkeys demonstrated that RSLV-132 exposure (Cmax and AUC) was dose proportional and did not change with repeat administration. Adequate exposure and pharmacodynamic responsiveness was demonstrated at all doses employed in the toxicology studies over the entirety of the intended treatment period in both species. Furthermore, RNase catalytic activity correlated well with RSLV-132 protein concentrations, suggesting there was no decrease in drug exposure due to neutralizing anti-drug antibodies in either species.

### 3.5.3 Toxicology

The toxicology of RSLV-132 has been assessed in rats for periods up to 28 days and for up to 26 weeks in monkeys using either every-three-day dosing or weekly dosing schedules, respectively. In animal toxicology studies, RSLV-132 was well tolerated in rats and monkeys when given intravenously at doses up to 50 mg/kg/dose in monkeys, and up to 100 mg/kg/dose in rats for 4 weeks (5-10 doses) and for 26 weeks (26 doses) in the monkey (up to 50 mg/kg).

These dose levels were considered maximum feasible doses based upon dose volume and formulation concentration constraints. Clinical findings were limited to a minor increase in blood fibrinogen seen only in rats. Given the absence of effects upon any other coagulation parameters or any correlating anatomical pathology change, this transient observation was not considered adverse.

In the 4-week monkey study low titer (1:25) ADA responses were observed in several monkeys across all dose groups. In the 26-week monkey study five of the forty animals had high titer ADA responses which impacted exposure. However, in the rat study high titer ADA responses were observed across all dose groups, but the response had no impact on RSLV-132 exposure or pharmacological activity in either the monkey or rat studies. Comprehensive anatomical pathology evaluations in rats and monkeys did not elucidate any target organs aside from lymphoid hyperplasia in the spleen consistent with an immunogenic response to a foreign protein. Safety pharmacology parameters (CNS, respiratory, and cardiovascular systems) were examined in the context of the definitive monkey toxicology study. There were no test article-related clinical signs, or changes in, cardiovascular or respiratory parameters (electrocardiography, blood pressure, heart and respiration rates, and pulse oximetry). In

addition, the brain, lungs, and heart were evaluated microscopically in the rat and monkey studies. There were no microscopic changes in any of these tissues attributable to the test article with the exception of the presence of small numbers of hemosiderin-containing macrophages noted in the choroid plexus of the brains in 13 rats. These findings correlated with a strong ADA response. No further findings were noted in brain tissue.

In the 26-week monkey study, one female given 30 mg/kg was sacrificed in moribund condition on Day 127 of the dosing phase; clinical observations included hunched posture and red periorbital skin while microscopic findings of perivascular/vascular inflammation and/or hemorrhage were present in multiple tissues. Although these changes were test article-related, they likely represented an immunogenic or hypersensitivity reaction to RSLV-132 and not a direct toxic effect. All remaining animals survived to their scheduled sacrifice and no other RSLV-132-related clinical observations were noted.

As RSLV-132 was well tolerated in animals following repeated injections occurring over a one to six-month period, the dosing regimen proposed for the clinical trial is not anticipated to be associated with any significant adverse events. Based upon the results of nonclinical studies, there are no findings which would preclude the continued investigation of RSLV-132 in clinical trials.

## 3.6 RSLV-132 Clinical 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 SLE.

### 3.6.1 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 were 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.

### 3.6.2 Study 132-02 - Multiple Ascending Dose Study Summary

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.

## 3.7 Benefit/Risk Considerations

Potential Risks

RSLV-132 has been studied in 24 healthy volunteers and 24 patients with SLE. The most frequently reported adverse events were headache, nausea, and upper respiratory tract infection, each of which occurred in 5 subjects. Infection of hair follicles was also reported in one subject. Reactions at the site of the injection, such as redness, bleeding and bruising, were reported in several subjects.

In addition to the risks listed above, there may be some unknown or infrequent and unforeseeable risks, including that of unknown drug interactions associated with the use of RSLV-132. The administration of protein drugs like RSLV-132 may result in serious and potentially life-threatening anaphylactic reactions. While none of these reactions have occurred in the previous studies with RSLV-132, it is possible they could occur in the future. Genotoxicity, Carcinogenicity and Reproductive Toxicity studies have not been conducted for RSLV-132 and therefore the risks of these events, while considered low for the class of compound and mechanisms of action, are unknown.

Potential Benefits

Of the evaluable subjects in the 132-02 multi-dose SLE study, 7/16 (44%) had an improvement in SLEDAI score, however given the small size of the study the data are not statistically significant. No studies in pSS have been conducted to date, therefore no data are available to evaluate potential benefits.

Risk minimization

The study population will be carefully chosen using the inclusion and exclusion criteria to minimize the potential for adverse events. Subjects will be informed in a timely manner of any new information about the study drug and allowed to decide if they wish to continue the study. Subjects will be advised to seek medical attention at the appearance of any potential side effects. All subjects will be followed up for 18 weeks following the last infusion of RSLV-132 to allow early detection and management of any delayed significant AE.

The medical monitor will continually review the safety data to identify any trends that may pose significant risk. In addition, processes are in place to communicate serious adverse events to the sponsor and for reporting SUSARs to the relevant regulatory agencies and the Eudra Vigilance Clinical Trial Module.

## 3.8 Population

Subjects aged 18 to 85 years of age diagnosed with Primary Sjogren's Syndrome and meet the inclusion / exclusion criteria will be enrolled in the study.

# 4 STUDY OBJECTIVES AND PURPOSE

The present study will examine the role of circulating RNA complexed with autoantibodies and immune complexes and its role in activation of inflammatory pathways in patients with primary Sjogren's syndrome. The study will be conducted in a subset of Sjogren's patients who have elevated levels of SSA/Ro autoantibodies and a pattern of elevated interferon-stimulated gene expression in blood cells. Given the well-established inflammatory properties of RNA, RSLV-132 will be administered to digest the RNA which is circulating bound to autoantibodies and thereby attenuate chronic activation of multiple inflammatory pathways. A number of biochemical and clinical parameters will be analyzed to determine the potential therapeutic utility of nuclease therapy in Sjogren's syndrome.

# 5 STUDY DESIGN

## 5.1 Primary Study Endpoint

The primary endpoint of the study is to assess the following biochemical parameters in the active versus control groups comparing Baseline with Day 99:

- changes in blood cell gene expression or serum protein levels indicative of reduced inflammation.

## 5.2 Secondary Study Endpoints

The secondary endpoints of the study are to assess the following parameters in the active versus control groups comparing Baseline with Day 99:

- safety and tolerability;
- Ro52/60 autoantibody levels;
- total immunoglobulins;
- erythrocyte sedimentation rate (ESR);
- complement levels (C3 & C4)
- minor salivary gland histopathology
- minor salivary gland interferon-stimulated gene expression;
- disease activity (ESSDAI or PGA, Schirmer's test, stimulated and unstimulated salivary flow) (assessment worksheets provided in study regulatory binder);
- patient-reported outcomes as measured by the following: ESSPRI, FACIT, Profile of fatigue, EQ-5D-L, Fatigue VAS, and Neuropsychological analysis scales (assessment worksheets provided in study regulatory binder);
- Additional exploratory evaluations may be considered as driven by the evolving understanding of the mechanism of action, technical feasibility, and any other clinical or immunological information that may become available during the course of the clinical study. Note: Additional exploratory endpoints will be specified in a separate laboratory manual and will be reported separately to the main safety, tolerability and efficacy endpoints of the study.

## 5.3 Overall Study Design and Plan

This is a double-blind, placebo-controlled study of 28 subjects with primary Sjogren's syndrome. Potential subjects will be screened to assess their eligibility to enter the study within sixty days prior to study entry (i.e., prior to Baseline visit). 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 3:1 (active:placebo) to receive 8 intravenous administrations of 10 mg/kg of study drug or placebo on days: 1, 8, 15, 29, 43, 57, 71, and 85.

## 5.4 Number of Subjects and Centers

Up to 28 subjects will be enrolled at approximately 2-3 clinical centers in the UK.

## 5.5 Estimated Study Duration

The duration of the study from Baseline to the End of Study visit is approximately 30 weeks.

## 5.6 Investigational Product 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. The product accountability will be periodically monitored by an unblinded pharmacy monitor.

# 6 SELECTION AND WITHDRAWAL OF SUBJECTS

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

## 6.1 Subject Inclusion Criteria

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

1. Meet 4 of the 6 criteria (must include histopathology or autoantibodies) of the 2002 American-European Consensus Group (AECG) criteria for Primary Sjogren's Syndrome.
2. elevated levels of anti Ro-52 or anti Ro-60 antibodies (within laboratory positive range);
3. positive interferon signature (whole blood cell interferon signature metric > -1);
4. stable medications used to treat Sjogren's syndrome for the 30 days prior to the Baseline visit;
5. able to communicate and able to provide valid, written informed consent;
6. ages 18 to 85 inclusive;
7. minimum weight of 45 kg;
8. Female participants shall be either of non-child-bearing potential (permanently sterilized by bilateral 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, but not including progestogen-only oral contraceptives), injectable, implantable or transdermal contraceptives, a non-hormonal intrauterine device [IUD], or an intrauterine hormone releasing system [IUS]) for at least 2 months prior to dosing and until 125 days after the last dose. In terms of sexual relations, female participants not practicing highly effective contraception as described above should abstain or engage with male partners who are sterile or vasectomized. Female participants of child-bearing potential will also be required to have a negative serum pregnancy test [ß-hCG] at Screening and negative pregnancy urine test at Baseline. Female participants must agree not to donate eggs from the first dose until 125 days after the last dose.
9. Male participants, who are not sterile or vasectomized, must agree to abstain or only engage with female partners who use highly effective contraception from the first dose until 125 days after the last dose. Male participants must also agree not to donate sperm from the first dose until 125 days after the last dose.

## 6.2 Subject Exclusion Criteria

Any of the following will exclude potential subjects from the study:

1. Previously diagnosed with systemic lupus, systemic sclerosis, or inflammatory myopathy.
2. Use of hydroxychloroquine within 30 days of Baseline;
3. use of cyclophosphamide within 180 days of Baseline;

4. use of belimumab, abatacept, or TNF inhibitors within 90 days of Baseline;
5. use of rituximab within 6 months of Baseline (documentation of B-cell counts within the normal range for the reference laboratory is required for subjects within 1 year of rituximab usage).
6. use of oral corticosteroids equivalent to prednisone dose of >10 mg/day within 30 days of Baseline;
7. past head and neck radiation;
8. current untreated lymphoma at Baseline;
9. known IgG4-related disease
10. graft versus host disease
11. 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;
12. positive test for hepatitis B, C, or HIV at Screening;
13. participation in another clinical study with receipt of an investigational product within 3 months or 5 half- lives, of last administration (whichever is longer) from Baseline;
14. positive pregnancy test at Screening or Baseline;
15. female subjects currently pregnant or breast feeding at Baseline;
16. inability or unwillingness to comply with protocol-specified procedures which, in the opinion of the Investigator, would make the subject unsuitable for study participation.

## 6.3 Subject Withdrawal Criteria

Subjects will be informed that they are free to withdraw from the study at any time and for any reason. A subject should be discontinued from study drug treatment for any of the following reasons: AE which is either intolerable or poses safety concerns, pregnancy or disease worsening. The Investigator may also remove a subject from investigational treatment if, in the Investigator's opinion, it is not in the best interests 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 protocol specified procedures for remaining study visit time points or at a minimum perform early termination assessments specified 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. Subjects that withdraw after receiving study drug will not be replaced.

## 6.4 Women of Child-Bearing Potential

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 bilateral tubal ligation, occlusion);
- the subject is more than one year past her last menstrual cycle and menopause is confirmed by ensuring blood FSH levels ≥ 22 mIU/mL at Screening.

Pregnancy tests will be performed at Screening, prior to dosing at all visits with study drug administration, and at the Day 141 visit (8 weeks after the last dose) for women of childbearing potential. Any subject having a positive pregnancy test will no longer receive study drug and will be followed until birth or end of pregnancy to determine the outcome.

# 7 TREATMENT OF SUBJECTS

## 7.1 Description of Study Drug

RSLV-132 is a novel therapeutic candidate. This fully human molecule consists of the enzyme RNase1 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 as a 9.5 mg/mL sterile liquid concentrate for dilution for intravenous infusion.

## 7.2 Treatment Compliance

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

## 7.3 Concomitant Medications

Subjects entering the study who had no changes to their medications used to treat pSS in the previous 30 days prior to the Baseline visit shall remain on the background medications at the same doses until Day 141 of the study. The use of pilocarpine or cevimeline during the trial is allowed, however subjects shall not use these medications within 12 hours prior to clinical disease activity measurements on days 1, 29, 57, 85, and 99 or use eye drops within 6 hours prior to clinical disease activity measurements on days 1, 29, 57, 85, and 99.

## 7.4 Medications not permitted before and during the trial

No changes in Sjogren's medications shall be permitted during the study with the exception of eye drops and analgesics. Medications prohibited prior to the study are listed in the exclusion criteria. The following medications are prohibited during the trial: hydroxychloroquine cyclophosphamide, belimumab, abatacept, TNF inhibitors, rituximab, and oral corticosteroids >10 mg/day.

## 7.5 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). If unblinding is required, the investigator will contact the unblinded study pharmacist to obtain the study treatment. The investigator must document the date, time and the need for unblinding and promptly inform the Sponsor.

# 8 STUDY DRUG MATERIALS AND MANAGEMENT

## 8.1 Study Drug

RSLV-132 is presented at a concentration of 9.5 mg/mL in a single-use vial containing 5.3 mL of preservative-free sterile solution for dilution for intravenous infusion. 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 drug.

## 8.2 Placebo

The placebo will be sterile, 0.9% sodium chloride solution 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 the drug name, lot number, protocol number, and expiration date. Study drug will be stored at $\leq$ -20°C under secure conditions and protected from light. Prior to administration to the subject, individual dosing solutions will be prepared from vials as detailed in the Study Drug Reference Guide. Details of study drug packaging, labeling, storage, shipping, and preparation, including preparation of matching placebo doses, will also be provided in the Study Drug Reference Guide.

## 8.4 Study Drug Administration

A total of 8 intravenous infusions of RSLV-132 or placebo will be administered at Baseline, weekly for two weeks (three doses), and then once every 2 weeks for the next 10 weeks. The preparation of the study drug and rate of infusion will be provided in the Study Drug Reference Guide. 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 case report forms.

## 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 or returned to the Sponsor after final accountability and reconciliation with the dispensing log.

# 9 ASSESSMENT OF EFFICACY

The study is not powered to demonstrate statistically significant clinical improvement. However, symptoms of primary Sjogren's syndrome will be evaluated and clinical parameters will be compared between the treatment and control arms. The following measurements will be used to assess efficacy; ESSDAI, PGA, stimulated and unstimulated salivary flow, and Schirmer's test.

# 10 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 an 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 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.

## 10.1 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 physical exam, 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).

## 10.2 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 or 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.

AEs which meet the following criteria:

- Serious
- Unexpected (i.e. is not consistent with the applicable product information contained in the Investigator's Brochure)
- There is at least a reasonable possibility that there is a causal relationship between the event and the investigational medicinal product will be classified as Suspected Unexpected Serious Adverse Reactions (SUSARs).

## 10.3 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 Day 211, the final telephone contact with the subject. Any untoward event occurring between screening and baseline and deemed directly related to a study procedure by the investigator will be recorded on the AE CRF.

## 10.4 Serious Adverse Event Reporting Requirements

SAEs will be reported to Resolve at safety@resolvebio.com 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 an 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.

Suspected Unexpected Serious Adverse Reactions (SUSARs) are subjected to expedited reporting and should be unblinded prior to submission to the regulatory authority. Fatal or life-threatening SUSARs must be reported to regulatory agencies and IEC by the sponsor as soon as possible, but no later than 7 days after first awareness of the reaction. Any additional relevant information must be sent within 8 days of the first report. Non-fatal or non-life-threatening SUSARs must be reported as soon as possible but no later than 15 days after first awareness of the reaction.

All UK-relevant SUSARs should be reported to the MHRA. "UK-relevant" includes SUSARs originating in the UK and SUSARs originating outside the UK where the sponsor has an ongoing trial in the UK involving the same medicinal product. For the IEC, only SUSARs occurring within the UK should be reported.

## 10.5 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.

## 10.6 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.

## 10.7 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). The Rheumatology CTC will be provided to sites in the study regulatory binder.

## 10.8 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.

## 10.9 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:

- the test result is associated with accompanying symptoms, and/or;
- the test result requires additional diagnostic testing or medical/surgical intervention, and/or;
- the 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.

## 10.10 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.

# 11 ASSESSMENT OF PHARMACOKINETICS

## 11.1 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 protein levels, and a catalytic activity assay that measures the RNase enzyme activity of RSLV-132.

## 11.2 Pharmacokinetic Analysis

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

# 12 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.

## 12.1 Subject Population for Primary Endpoint Analysis

The effect of RSLV-132 on blood cell gene expression and serum protein levels will be compared between the two arms. Subjects who complete all treatment visits will be included in the primary analysis. Randomized patients who receive the incorrect therapy from that intended will be summarized in the group 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.

## 12.2 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 treatment with either RSLV-132 or placebo. Randomized patients who 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.

## 12.3 Sample Size

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

# 13 STUDY PROCEDURES

## 13.1 Evaluations

Evaluations are summarized in Appendix A. During the course of the study approximately 230 mL of blood will be drawn. Central laboratories will perform all evaluations with the exception of the urine pregnancy test at baseline.

Every attempt will be made to perform evaluations on the scheduled day and time, as appropriate. Evaluations should be performed on the day of the scheduled visit as much as possible. In any case, the visit should occur ± 2 days of the scheduled visit for visit days Day 8 through Day 99 and ±5 days for Day 141. Telephone contacts scheduled for Days 176 and 211 should occur ±10 days of the scheduled contact. All scheduled study visits or calls should occur on the specified number of days after Baseline, even if a preceding visit occurred off-schedule. In the event it should not be possible to adhere to the study schedule, the minimum interval between administrations of RSLV-132 during the 2-week dosing period is 10 calendar days.

## 13.2 Screening Procedures

The following Screening procedures will be performed for all potential subjects at a visit conducted within 60 days of study entry (prior to Baseline):

- informed consent;
- assess inclusion/exclusion criteria
- demographics/weight/height;
- hepatitis-B, C and HIV antibody tests;
- FSH (when required to confirm menopause in female subjects)
- whole blood for interferon signature analysis;
- physical examination;
- pregnancy test (serum);
- complete medical and medication history;
- vital signs (temperature, respiratory rate, blood pressure and pulse);
- chem-21 (see Appendix B), CBC, and UA;
- anti-Ro-52/Ro-60 autoantibodies;

## 13.3 Baseline (Day 1) Procedures

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

- inclusion/exclusion criteria re-evaluated
- directed physical examination;
- pregnancy test (urine);
- interim medical/medication history;
- vital signs (temperature, respiratory rate, blood pressure and pulse);
- chem-21 (see Appendix B), CBC, and UA;
- AE Assessment;
- measure disease activity (ESSDAI, PGA);
- stimulated and unstimulated salivary flow;
- Schirmer's test;
- patient reported outcomes (ESSPRI, FACIT, Profile of fatigue, EQ-5D-L, Fatigue VAS, Neuropsychological analysis (at Newcastle University only));
- optional minor salivary gland biopsy (consented subjects);
- serum for study drug concentration and RNase activity;
- serum protein analysis;
- whole blood for gene expression profile;
- whole blood for ESR;
- whole blood for DNA analysis;
- serum for anti-Ro-52/Ro-60 autoantibodies;
- serum for total immunoglobulins, C3 and C4;
- serum for assessment of anti-RSLV-132 antibodies;

**After completion of above assessments:**

- study drug administration. Subjects will remain under observation in the clinic for at least 2 hours following the first administration of study drug. The clinic shall have resuscitation equipment available in close proximity to the infusion room.

## 13.4 Procedures on Days 8, 15, 43, and 71

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

- directed physical exam;
- pregnancy test (urine);
- interim medical/medication history;
- vital signs (temperature, respiratory rate, blood pressure and pulse);
- adverse event assessment;

**After completion of above assessments:**

- study drug administration

## 13.5 Procedures on Days 29, 57, 85, and 99/Early Termination

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

- directed physical examination;
- urine pregnancy test (except Day 99);
- interim medical/medication history;
- vital signs (temperature, respiratory rate, blood pressure and pulse);
- chem-20 (see Appendix B), CBC, and UA;
- adverse event assessment;
- measure disease activity (ESSDAI, PGA, Schirmer's, stimulated and unstimulated salivary flow);
- patient reported outcomes (ESSPRI, FACIT, Profile of fatigue, EQ-5D-L, Fatigue VAS, Neuropsychological analysis (Day 99 only);
- optional minor salivary gland biopsy (consented subjects) (Day 99 only);
- serum for study drug concentration and RNase activity;
- serum protein analysis;
- whole blood for gene expression profile
- whole blood for ESR;
- serum for anti-Ro-52/Ro-60 autoantibodies
- serum for total immunoglobulins, C3 and C4;
- serum for anti-RSLV-132 antibodies (Day 29 only);

**After completion of above assessments:**

- study drug administration (except Day 99)

## 13.6 Procedures on Day 141

The following procedures will be performed on Day 141:

- directed physical examination;
- pregnancy test (serum);
- interim medical/medication history;
- vital signs (temperature, respiratory rate, blood pressure and pulse);
- adverse event assessment;
- serum for study drug concentration and RNase activity;
- serum for assessment of anti-RSLV-132 antibodies;

## 13.7 Telephone Follow-up on Days 176 and 211 (End of Study)

Subjects will be contacted via telephone at Day 176 and Day 211 to collect follow up information on any adverse events that were ongoing at Day 141, and to determine if there are any new reportable adverse events (e.g. positive relationship to the investigational product). If new reportable adverse events are identified it will be requested that the subject return to the clinic for an unscheduled visit and assessment by the Principal Investigator.

## 13.8 Vital Signs

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

## 13.9 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 if any changes to the subject's symptoms and medications have taken place since the last visit.

## 13.10 Minor Salivary Gland Biopsy

Consented subjects will undergo an optional biopsy of the minor labial salivary glands. The tissue will be examined microscopically to determine the degree of lymphocytic infiltration (Focus score). RNA will be extracted from a portion of the salivary gland tissue and the level of interferon gene expression will be analyzed. Additionally, the properties of cellular subtypes associated with the tissue, such as B-lymphocytes shall be analyzed by Newcastle University (Newcastle, UK).

## 13.11 Study Drug Concentration

Serum samples will be analyzed by ICON central laboratory (Farmingdale, NY) using a validated ELISA assay to determine the serum concentration of study drug at selected visits during the study.

## 13.12 Gene Expression Analysis

Blood will be collected into PAXgene RNA collection tubes, RNA will be extracted and analyzed by Resolve Therapeutics (Seattle, WA) to measure the expression level of genes that are related to inflammatory pathways thought to be involved in primary Sjogren's syndrome and to analyze the presence of various micro RNAs.

## 13.13 DNA Analysis

Blood will be collected into PAXgene DNA collection tubes at Baseline, DNA will be prepared by Resolve Therapeutics (Seattle, WA) and stored for future pharmacogenomic analysis.

## 13.14 Serum Protein Analysis

Serum samples will be obtained at various visits during the study and the level of circulating serum cytokines and other proteins that are thought to be related to the inflammation and autoimmunity process shall be measured by MyriadBRM (Austin, TX).

## 13.15 Anti-Drug Antibodies

Serum will be analyzed for the presence of anti-RSLV-132 antibodies by ICON central laboratory (Farmingdale, NY) 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 samples will be tittered by serial dilution and a numerical titer will be assigned.

## 13.16 RNase Activity Assessments

RSLV-132 RNase enzymatic activity in the serum of subjects will be determined by Resolve Therapeutics (Seattle, WA) using a qualified analytical procedure.

## 13.17 Autoantibody Profile

Serum samples will be analyzed by ICON central laboratory (Farmingdale, NY) to measure complement components C3 and C4 and anti-Ro-52/60 autoantibodies will be analyzed by the University of Washington Medical Center, Clinical Immunology Lab (Seattle, WA).

# 14 STUDY ADMINISTRATION

## 14.1 Protocol Amendments

Protocol amendments that impact subject safety, change the scope of the investigation, or affect the scientific quality of the study must be approved by the IRB/IEC and submitted to the appropriate regulatory authorities before implementation of such study modification.

## 14.2 Direct access to source data/documents

The Investigators and clinical sites will permit trial related monitoring, audits, IRB/IEC review and regulatory inspections as requested by governmental authorities, Resolve Therapeutics or designee, including direct access to source data/documents (i.e., original paper or electronic medical records, laboratory reports, hospital documents, progress reports, signed informed consent forms, etc.) in addition to CRFs. Source documents should be available to support all the data recorded in the eCRF, unless otherwise specified in the eCRF and data queries.

## 14.3 Data Handling and Recordkeeping

CRFs are the sole property of Resolve Therapeutics and should not be made available in any form to third parties, except for authorized representatives of Resolve Therapeutics or appropriate regulatory authorities, without written permission from Resolve Therapeutics.

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 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.

## 14.4 Quality Control and Quality Assurance

During the study, Resolve Therapeutics or its designee will conduct periodic monitoring visits to ensure that the protocol and current Good Clinical Practices (cGCPs) as defined by local regulations are being followed and to resolve data queries. The monitors may review source documents to confirm that the data recorded on CRFs is accurate. The investigator and institution will allow Resolve monitors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification. Additionally, 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.

The study site may be subject to review by the institutional review board (IRB) / independent ethics committee (IEC), and/or to quality assurance audits performed by Resolve Therapeutics, and/or to inspection by appropriate regulatory authorities.

It is important that the investigator(s) and their relevant personnel agree to cooperate and are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process. The Investigator is required to make all study documentation promptly available for inspection during these events and, in the event of an audit by a regulatory agency, to notify Resolve Therapeutics immediately.

Findings and corrective actions of frequent findings will be distributed to all sites to ensure that mistakes are not repeated.

## 14.5 Record Retention

To enable evaluations and/or audits from regulatory authorities or Resolve Therapeutics, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, e.g., CRFs and hospital records), all original signed informed consent forms, copies of all CRFs, SAE forms, source documents, and detailed records of treatment disposition. The records should be retained by the investigator according to local requirements which may include International Conference on Harmonization regulations, or other local requirements, whichever is longer.

If the investigator relocates, retires, or for any reason withdraws from the study, Resolve Therapeutics should be prospectively notified. The study records must be transferred to an acceptable designee, such as another investigator, another institution, or to Resolve Therapeutics. The investigator must obtain Resolve's written permission before disposing of any records, even if retention requirements have been met.

## 14.6 End of Study

The end of the study is defined as the last study visit or telephone contact (whichever is later) for the last subject on study.

## 14.7 Study Discontinuation or Suspension Criteria

Premature discontinuation or suspension of this clinical study may occur because of a regulatory authority decision, change in opinion of the IRB/IEC, safety data, drug availability issues or at the discretion of Resolve Therapeutics.

If this study is prematurely discontinued or suspended, Resolve Therapeutics will promptly notify all investigators. In the event of discontinuation, each investigator must contact all subjects within 15 days. As directed by Resolve Therapeutics, all study materials must be collected and all CRFs completed to the greatest extent possible. The sponsor is committed to scientific integrity and proper dissemination of research results.

## 14.8 Publication of Study Results

Publication of study results is addressed in the Clinical Study Agreement with participating investigators.

# 15 ETHICS

## 15.1 Ethical Conduct of the Study

The study will be performed in accordance with the protocol, International Conference on Harmonization Good Clinical Practice guidelines, and applicable local regulatory requirements and laws.

## 15.2 Institutional Review Board/Independent Ethics Committee

It is the responsibility of the investigator to obtain prospective approval of the study protocol, protocol amendments, informed consent forms, and other relevant documents, e.g., advertisements, if applicable, from the IRB/IEC. All correspondence with the IRB/IEC should be retained in the Investigator File. Copies of IRB/IEC approvals should be forwarded to Resolve Therapeutics or designee.

The only circumstance in which an amendment may be initiated prior to IRB/IEC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the investigator must notify the IRB/IEC and Resolve Therapeutics in writing within 5 working days after the implementation.

## 15.3 Subject Information and Informed Consent

The informed consent form must be agreed to by Resolve Therapeutics and the IRB/IEC and must be in compliance with International Conference on Harmonization, cGCP, local regulatory requirements, and legal requirements.

The investigator must ensure that each study subject is fully informed about the nature and objectives of the study and possible risks associated with participation. The investigator, or a person designated by the investigator, will obtain written informed consent from each subject in accordance with all local and national regulations.

The informed consent form used in this study, and any changes made during the course of the study, must be prospectively approved by both the IRB/IEC and Resolve Therapeutics before use.

## 15.4 Sponsor Responsibilities

Before subject enrollment, the Sponsor or designee is responsible for reviewing with study site staff the definitions, recording and reporting of AEs/SAEs, as well as monitoring instructions.

The Sponsor or designee will notify all appropriate regulatory authorities of SAEs, as necessary, within the required time frames. The Sponsor's Medical Monitor or designee will complete written safety reports with the information provided by the Investigator and study site staff, as needed, for submission to regulatory authorities. Expedited reporting requirements for Suspected Unexpected Serious Adverse Reactions (SUSARS) are detailed in section 10.4.

The Sponsor or designee is responsible for forwarding copies of documents that are submitted to regulatory authorities to the Investigator for submission to the local IRB/IEC, if applicable, and for inclusion in the study site files.

## 15.5 Financing and Insurance

Financing and insurance will be provided per the regulations of individual countries and are addressed in separate documents.

## 15.6 Confidentiality

The investigator must assure that subjects' anonymity will be maintained and that their identities are protected from unauthorized parties. Subjects should not be identified by their names, but by an identification code on e-CRFs or other documents submitted to the Sponsor. The investigator should keep a subject enrolment log showing codes, names and addresses. The investigator should maintain documents not for submission to Resolve Therapeutics, e.g., subjects' written consent forms, in strict confidence.

Every attempt will be made to keep subject participation in this research study confidential; however, absolute confidentiality cannot be guaranteed. The Sponsor, representatives of the Sponsor, the medical institution, and regulatory health authorities may review subject research records. Additionally, the respective IRBs or IECs that oversee the conduct of this study may review medical records of subjects enrolled by the respective institution.

## 15.7 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.

# 16 REFERENCES


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# 17 APPENDICES

## 17.1 Appendix A: Study Procedures

| **Study Procedures** | **Screen (-60 to -1)** | **Baseline Day 1** | **Day 8** | **Day 15** | **Day 29** | **Day 43** | **Day 57** | **Day 71** | **Day 85** | **Day 99/ET** | **Day 141** | **Day 176 Tel. FU** | **Day 211 Tel. FU EOS** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Acceptable visit window (days)[f] | | | ± 2 | ± 2 | ± 2 | ± 2 | ± 2 | ± 2 | ± 2 | ± 2 | ± 5 | ±10 | ±10 |
| Informed consent | X | | | | | | | | | | | | |
| Inclusion/exclusion | X | X | | | | | | | | | | | |
| Demographics/weight/height | X | | | | | | | | | | | | |
| Hepatitis, HIV tests | X | | | | | | | | | | | | |
| FSH (female subjects only) [g] | X | | | | | | | | | | | | |
| Whole blood for interferon signature | X | | | | | | | | | | | | |
| Physical exam | X | X[a] | X[a] | X[a] | X[a] | X[a] | X[a] | X[a] | X[a] | X[a] | X[a] | | |
| Pregnancy test | X[b] | X[c] | X[c] | X[c] | X[c] | X[c] | X[c] | X[c] | X[c] | | X[b] | | |
| Medical/medication history | X | X[d] | X[d] | X[d] | X[d] | X[d] | X[d] | X[d] | X[d] | X[d] | X[d] | | |
| Vital signs | X | X | X | X | X | X | X | X | X | X | X | | |
| Chem-20, CBC, UA | X | X | | | X | | X | | X | X | | | |
| AE assessment | | X | X | X | X | X | X | X | X | X | X | X | X |
| ESSDAI, PGA, salivary flow, Schirmer's test | | X | | | X | | X | | X | X | | | |
| Patient reported outcomes | | X | | | X | | X | | X | X | | | |
| Minor salivary gland biopsy (consented subjects) | | X[i] | | | | | | | | X | | | |
| Serum for study drug concentration and RNase activity | | X | | | X | | X | | X | X | X | | |
| Serum for protein analysis | | X | | | X | | X | | X | X | | | |
| Whole blood for gene expression | | X | | | X | | X | | X | X | | | |
| Whole blood for ESR (performed by local laboratory) | | X | | | X | | X | | X | X | | | |
| Whole blood for DNA analysis | | X | | | | | | | | | | | |
| | | | | | | | | | | | | | |
| Serum for anti-Ro-52 and anti-Ro-60 autoantibodies | X | X | | | X | | X | | X | X | | | |
| Serum for total immunoglobulins, C3 and C4 | | X | | | X | | X | | X | X | | | |
| Serum for anti-RSLV-132 antibodies | | X | | | X | | | | | | X | | |
| Study Drug administration | | X[e] | X[e] | X[e] | X[e] | X[e] | X[e] | X[e] | X[e] | | | | |

Abbreviations: ET = Early Termination, EOS = End of Study

[a] directed physical exam.
[b] serum pregnancy test
[c] urine pregnancy test
[d] interim medication/medical history only.
[e] intravenous infusion of RSLV-132 (10 mg/kg) or placebo according to infusion rate in the Study Drug Reference Manual.
[f] minimum interval between administrations of RSLV-132 during the 2 week dosing period is 10 calendar days.
[g] to be collected when confirmation of menopause is required in female subjects
[h] assessments to be performed for any subjects that terminate early
[i] biopsies may be performed up to 14 days prior to the baseline visit and at or within 7 days prior to or after Day 99

## 17.2 Appendix B: Clinical Laboratory Evaluations

**Chemistry (Chem-21):**
Albumin
Alkaline Phosphatase
ALT
AST
Bicarbonate
Urea BUN
Calcium
Chloride
Cholesterol
Creatinine
Creatine Kinase
GGT
Glucose
LDH
Phosphate
Potassium
Sodium
Total Bilirubin
Total Protein
Triglycerides
Uric acid

**Hematology (CBC):**
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

**Other Tests:**
hepatitis B and C
HIV
serum pregnancy test
urine pregnancy test
FSH
DNA analysis
ESR
study drug concentration
study drug RNase activity
serum protein analysis
anti-RSLV-132 antibodies
anti-Ro-52
anti-Ro-60
C3, C4
total immunoglobulins
gene expression analysis

**Minor Salivary Gland Biopsy**
microscopy: Focus score
RNA extraction for IFN gene expression
cellular sub-type analysis

**Complete Urinalysis (UA):**
pH and Specific Gravity
Bilirubin
Glucose
Ketones
Leukocytes
Nitrite
Occult blood
Protein
Urobilinogen
Microscopic (RBC, WBC) if necessary

## 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 or MHRA 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 – Summary of Changes

| | **From Version 3.0 to Version 4.0** |
|---|---|
| **Overall** | **1.** Clarified that the strips used for the Schirmer's test will not be retained.<br>**2.** Removed plasma collection for the RNA analysis<br>**3.** Clarified the neuropsychological tests will only be performed by the Newcastle site at Baseline and Day 99<br>**4.** Corrected interferon signature inclusion criteria to > - 1<br>**5.** Clarified any untoward event deemed directly related to a study procedure by the principal investigator will be recorded as an AE<br>**6.** Added creatine kinase to chemistry panel and changed Chem-20 to Chem-21<br>**7.** Clarified biopsies may be performed up to 14 days prior to the baseline visit and at or within 7 days prior to or after Day 99 |
| **Section** | **Detail of Changes** |
| Title Page | Updated Version, Prior Version, Date of Publication |
| Synopsis | **Secondary Study Endpoints** : Clarified that neuropsychological analysis will only be performed at Newcastle University<br><br>**Section 1.8 #3:** Corrected interferon signature metric to read > - 1<br>**Section 1.10:**<br>- Removed circulating RNA Analysis<br>- Removed retention of Schirmer's strips<br>**Section 1.11**:<br>- Screening and Baseline: Changed Chem-20 to Chem-21<br>- Baseline and additional procedures: Removed plasma collection for circulating RNA analysis |
| 2 | Updated sections and page numbers based removal of RNA Analysis originally in section13.14 |
| Table 1 | Updated Chem-20 to Chem-21 |
| 6.1 | Corrected interferon signature metric to read > - 1 |
| 10.3 | Clarified any untoward event deemed directly related to a study procedure by the principal investigator will be recorded as an AE |
| 13.2 | Changed Chem-20 to Chem-21 |
| 13.3 | - Changed Chem-20 to Chem-21<br>- Removed retention of **Schirmer's** strips<br>- Clarified that neuropsychological analysis will only be performed at Newcastle University<br>-Removed plasma collection for the RNA analysis |
| 13.5 | - Clarified neuropsychological analysis will only be performed on Day 99<br>- Removed plasma collection for the RNA analysis |
| 13.14 | Removed plasma collection and RNA analysis |
| 17.1 Appendix A | - Clarified telephone contact is + or - 10 days<br>- Removed RNA Analysis |

| | |
|---|---|
| | - Added footnote "i" clarifying biopsies may be performed up to 14 days prior to the baseline visit and at or within 7 days prior to or after Day 99 |
| 17.2 Appendix B | Added Creatine Kinase and changed Chem-20 to Chem-21 |
| 17.4 Appendix D | Updated Appendix D with Protocol changes. |