CLINICAL STUDY PROTOCOL

Title:	ASCEND-WAIHA A Phase 2, Multicenter, Non-Randomized, Open-Label Study of RVT-1401 for the Treatment of Patients with Warm Autoimmune Hemolytic Anemia
Sponsor	Immunovant Sciences GmbH, a Swiss Limited Liability Company, is the Sponsor of this study. Immunovant, Inc., an affiliate of Immunovant Sciences GmbH, has been engaged by Immunovant Sciences GmbH to manage the day-to-day operations of the study. All references to "Sponsor" contained herein shall refer to Immunovant, Inc., acting pursuant to a services agreement with Immunovant Sciences GmbH.
Compound Name:	RVT-1401
Protocol Number	RVT-1401-2003
Indication	Warm Autoimmune Hemolytic Anemia
Development Phase	2
IND #	145361
Version/ **Effective Date:**	Amendment 2: Version 3.0 23-Dec-2019 Amendment 1: Version 2.0 4-OCT-2019 Original: Version 1.0 23-AUG-2019
Immunovant, Inc. Study Director	[redacted] Telephone: [redacted] Email: [redacted]

Confidentiality Statement

NCT Number: NCT04253236

SPONSOR SIGNATURE PAGE:

Study title: A Phase 2, Multicenter, Non-Randomized, Open-Label Study of RVT-1401 for the Treatment of Patients with Warm Autoimmune Hemolytic Anemia

Protocol Number: RVT-1401-2003

This protocol has been approved by Sponsor's representative. The following signature documents this approval.

[redacted] _____ [redacted] _____

Date

Immunovant, Inc.

MEDICAL MONITOR/SPONSOR INFORMATION PAGE

Medical Monitor/SAE Contact Information:

Role	Contact	Day Time Phone Number and email address	After-hours Phone/Cell/ Pager Number
Primary Medical Monitor	[redacted]	Phone: [redacted] [redacted]	
SAE contact information	[redacted]		

Study Sponsor:

Immunovant Sciences GmbH Registered Address:

Viaduktstrasse 8
4051 Basel
Switzerland

Immunovant, Inc. Address:

320 W. 37th St., 3rd Floor
New York, NY 10018
USA

INVESTIGATOR STATEMENT

- I confirm agreement to conduct the study in compliance with the protocol.
- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.
- I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations and comply with the study protocol. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Principal Investigator Name (Printed)	Signature
Site	Date

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2. PROTOCOL SUMMARY FOR STUDY RVT-1401-2003

Study Title	A Phase 2, Multicenter, Non-Randomized, Open-Label Study of RVT-1401 for the Treatment of Patients with Warm Autoimmune Hemolytic Anemia
Objectives	**Primary** To examine the effect of RVT-1401 on proportion of responders (defined as Hb level ≥10g/dL with at least a ≥2 g/dL increase from baseline without rescue therapy or blood transfusions in the previous two weeks) To assess the safety and tolerability of RVT-1401 in subjects with WAIHA **Secondary** To examine the effect of RVT-1401 on change in Hb levels To examine the effect of RVT-1401 on time to response To examine the effect of RVT-1401 on change in hematocrit levels To examine the effect of RVT-1401 on proportion of participants with Hb levels in the normal range To examine the effect of RVT-1401 on time to achieving Hb levels in the normal range To examine the effect of RVT-1401 on change in fatigue To examine the effect of RVT-1401 on change in dyspnea To examine the effect of RVT-1401 on change in health-related quality of life To assess the change in serum levels of total IgG & IgG subclasses (I-IV) To examine RVT-1401 PK following repeated doses in patients with WAIHA To assess the changes in LDH, bilirubin, haptoglobin To measure anti-RVT-1401 antibodies following repeated doses in patients with WAIHA
Study Phase	Phase 2
Target Population	Warm Autoimmune Hemolytic Anemia

Number of Participants Planned	Approximately 16 participants
Number of Study Centers Planned	Approximately 22 centers
Study Design	Non-randomized, open-label study to investigate the efficacy, safety and tolerability of RVT-1401
Duration of Treatment	12 weeks
Criteria for Evaluation (Endpoints)	**Primary** Proportion of responders at week 13 Assessment of safety and tolerability by analysis of adverse event (AE) data and changes from baseline in vital signs, ECGs, and clinical laboratory values **Secondary** Change from baseline in Hb levels Time to response Change from baseline in hematocrit levels Proportion of participants with Hb levels in the normal range at week 13 Time to achieving Hb levels in the normal range Change from baseline in FACIT-F score Change from baseline in Medical Research Council (MRC) breathlessness scale Change from baseline in EQ-5D-3L score Change from baseline in levels of total IgG & IgG subclasses (I-IV) Concentration of RVT-1401 pre-dose (Ctrough) Change from baseline in LDH, bilirubin, and haptoglobin Immunogenicity determined by change from pre-dose in anti-RVT-1401 antibodies, and characterization of any anti-RVT-1401 to confirm neutralization potential

3. INTRODUCTION

3.1. Background

RVT 1401 is a fully human anti-neonatal Fc receptor (FcRn) monoclonal antibody. FcRn is critical to the regulation of immunoglobulin G (IgG) [Roopenian, 2007]. In addition to its central role in mediating the transport of IgG within and across cells of diverse origin, it also serves to rescue IgG from degradation, thereby prolonging its circulating half-life [Roopenian, 2007]. Targeting the FcRn pathway has been shown to dramatically reduce circulating IgG, including auto-antibodies (Ab) of the IgG subclass, thus supporting its use in the treatment of auto-Ab mediated autoimmune diseases. RVT-1401 functions by inhibiting the binding of IgG to FcRn, resulting in the rapid catabolism of IgG via lysosomal degradation.

3.2. Warm Autoimmune Hemolytic Anemia

Autoimmune hemolytic anemia (AIHA) is caused by increased red blood cell (RBC) destruction triggered by autoantibodies that react against RBC antigens with or without complement. Antibodies in warm autoimmune hemolytic anemia (WAIHA) react optimally at 37 degrees Celsius and is the most common type of AIHA, comprising approximately 70-80% of all adult cases [Sokol, 1981]. The most common antibody isotype involved in WAIHA is IgG, with a greater prevalence of IgG1 and IgG3 [Kalfa, 2016]. Intravascular destruction of RBCs through complement mediated mechanisms contributes in only a minor percentage of WAIHA patients. In most patients, erythrocytes coated by warm reacting IgG are bound by spleen macrophages via FcR, which causes them to be either phagocytosed or have part of their membrane removed in the spleen. In the latter case they form microspherocytes that are then subject to further destruction during their next passage through the spleen [Kalfa, 2016]. $CD8^+$ T cells, and natural killer (NK cells) may also contribute to RBC lysis through antibody dependent cell mediated cytotoxicity (ADCC). RVT-1401, by reducing the levels of anti-RBC IgG, is hypothesized to be effective for the treatment of patients with WAIHA.

The clinical presentation of WAIHA is characterized by fatigue, exertional dyspnea, pallor, and splenomegaly. Common laboratory findings include: decreased hemoglobin (Hb), reticulocytosis, elevated unconjugated bilirubin and lactate dehydrogenase, serum aspartate aminotransferase disproportionately higher than serum alanine aminotransferase, and decreased haptoglobin [Kalfa, 2016].

Based on a paucity of phase 3 trials, the treatment of WAIHA is primarily guided by retrospective reviews, case series, expert opinions and a few small phase 2 trials. Nevertheless, Kalfa, et al, conclude that available evidence demonstrates that WAIHA can be fatal due to an acute presentation or due to refractory disease in spite of multiple lines of therapy. [Kalfa, 2016]. Experts recommend initial treatment with high dose steroids (60-100mg/day) and note that most patients will respond to these doses. Experts also recommend steroid taper after patients respond, due to toxicity of steroids at this high dose. Patients with worsening disease as steroids are tapered are candidates for further lines of therapy with immunosuppressants. Finally, although transfusions are generally reserved for stabilizing patients in the acute phase of WAIHA, some patients

require chronic transfusions due to WAIHA that is refractory to prednisone and or immunosuppressants. [Jaeger, 2019]

3.3. Rationale

3.3.1. Study Rationale

The purpose of the current study is to assess the efficacy and safety of RVT-1401 in the treatment of WAIHA that is worsening or refractory in spite of therapy with steroids and or immunosuppressants or worsening with steroid or immunosuppressant taper. Results from this study will be used to inform dosing and to support progression into a Phase 3 study.

3.3.2. Dose rationale

Two dosing regimens of RVT-1401 will be assessed in this non-randomized open label study. Both will involve once weekly subcutaneous (SC) injections:

- Dosing Regimen A -680 mg weekly for 12 weeks, and
- Dosing Regimen B - 340 mg weekly for 12 weeks

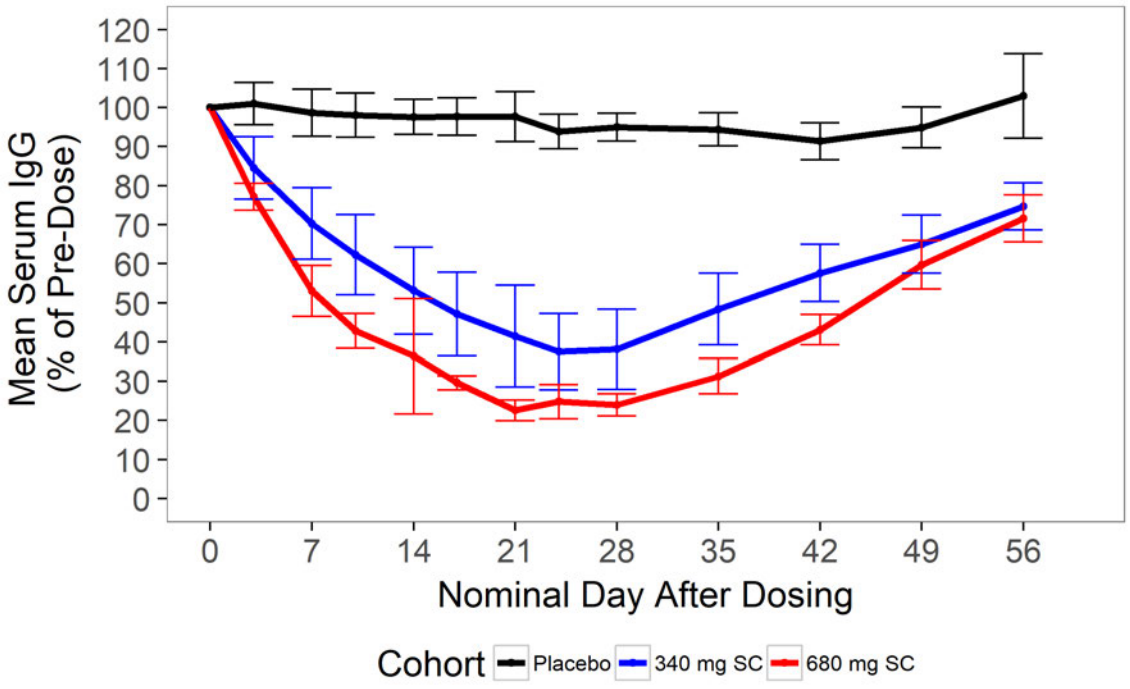
Given that there is a practical limit on the volume that can be administered via SC injection, these two doses represent what can be administered as a single SC injection (340 mg) and two SC injections (680 mg) per week with the current formulation.

Expected Treatment Effect

The proposed dosing regimens are expected to provide a sustained total IgG reduction of approximately 75-80% and 65-70% for Regimen A and B respectively. It is expected that the nadir IgG reduction will be achieved by the 3rd-5th dose (depending on dose studied) and maintained following the remaining doses before rising back to baseline over the next 6 to 8 weeks after stopping treatment.

These assumptions are supported by preliminary pharmacodynamic (PD) results, shown in Figure 1, from the Phase 1 clinical study RVT-1401-1001 (Section 3.3.3). Dosing regimen A (weekly 680 mg) represents the dose that is expected to achieve the maximal effect in IgG reduction. In healthy participants, 4 weekly SC injections of 680 mg of RVT-1401 produced the maximum PD response with an average total IgG percent reduction from baseline of 78%. This effect occurred prior to the 4th dose and no further reduction was observed after dosing, indicating maximal reduction and steady state response had been achieved. In the 340 mg repeat dose cohort, there were some individuals who did not achieve nadir IgG concentration until after the last dose, indicating they may have not reached steady state. Data from this study will be used to support dose selection in future studies.

Figure 1: Mean(+/-SD) Serum IgG Reduction Following Multiple SC Doses of RVT-1401



3.3.3. Clinical Experience

Two Phase 1 clinical studies to assess safety, tolerability, pharmacokinetics (PK), and PD have been conducted in healthy volunteers under the RVT-1401 clinical development program. A total of 99 healthy subjects participated in these two studies, 77 of whom received at least 1 dose of RVT-1401. Table 1 summarizes the doses of RVT-1401administered in healthy subjects. The dosing and recovery phase of these two studies have been completed and the study reports are being finalized. Three additional studies are ongoing, investigating RVT-1401 use in Graves' Ophthalmopathy and myasthenia gravis.

Refer to Investigator's brochure (IB) for additional information on clinical experience with RVT-1401.

Table 1: RVT-1401 Doses in Healthy Subjects

RVT-1401 Dose	Duration	Healthy Subjects
0.1 mg/kg	Single 1 hr IV Infusion	4
0.5 mg/kg	Single SC injection	3
1.5 mg/kg	Single SC injection	6
5.0 mg/kg	Single SC injection	6
340 mg	Single SC injection	6
500 mg	Single SC injection	6
765 mg	Single SC injection	6
100 mg	Single 1 hr IV Infusion	6
340 mg	Single 1 hr IV Infusion	6
765 mg	Single 1 hr IV Infusion	6
1530 mg	Single 1 hr IV Infusion	6
340 mg	4 weeks of once weekly SC injections*	8
680 mg	4 weeks of once weekly SC injections	8
Total for All Studies		**77**

Abbreviations: IV, Intravenous; SC, subcutaneous

* Note: 1 subject received 3 weeks and 1 subject received 2 weeks of once weekly SC injections

3.3.3.1. Safety

See Investigator's Brochure for details.

RVT-1401 has been well tolerated with no Grade 3 or 4 adverse events (AEs), and no withdrawals due to AEs. There have been two serious adverse events (SAEs) (Malpighian carcinoma in left side of the neck and appendicitis) considered unrelated to study drug.

All other AEs in subjects receiving RVT-1401 have been reported as mild or moderate.

The most frequently reported AE was injection site reactions (erythema and/or swelling). The rate of injection site reactions was similar between RVT-1401-treated and placebo-treated subjects and was not dose-related. Injection site reactions have generally resolved within a few hours after dosing; there were two exceptions of mild swelling (one RVT-1401- and one placebo-treated subject) that resolved after 3 and 4 days, respectively. Additionally, injection site reactions were not consistently observed following every injection in the repeat dose cohorts.

Preliminary data suggest no subject who has received RVT-1401 had clinically relevant changes in vital signs or laboratory results, or on electrocardiogram (ECG).

3.3.3.2. Pharmacokinetics

3.3.3.3. Pharmacodynamics

Following the administration of single SC doses of RVT-1401, total IgG reduction increased with increasing dose, with a maximum reduction of 47% observed after a fixed dose of 765 mg. The nadir for IgG reduction following single SC dosing occurred between days 8-15 in most individuals. IgG serum levels on average returned to within 90% of baseline by 43 days after drug administration. Albumin levels were also reduced from baseline when compared to placebo showing a similar dose related trend. The highest albumin reductions occurred following the 765 mg SC dose ( ) but were not considered to be clinically significant reductions as all patients remained within normal limits (3.5 g/dL to 5.5 g/dL) and levels recovered quickly, returning to baseline ~ 2 weeks after nadir.

The amount of IgG reduction has also been assessed following weekly SC administration of 340 and 680 mg of RVT-1401 or placebo for 4 weeks. There were 8 and 7 subjects with data included in the preliminary PD analysis for the 680 mg and 340 mg cohorts respectively. Data from one subject who received 2 doses of 340 mg prior to early study withdrawal due to personal reasons was not included. Across the two cohorts, there were 4 subjects who received placebo with data that contributed to the analysis of PD endpoints. Figure 1 presents the mean IgG concentration-time profiles, as a percent of

pre-dose, for both weekly SC administration of 340 mg and 680 mg doses. While both 340 mg and 680 mg cohorts showed a reduction in serum IgG, the placebo group demonstrated minimal changes in serum IgG. The reduction in serum IgG was more rapid following the 680 mg SC compared with 340 mg SC. The median IgG nadir concentration occurred prior to the last dose in the 680 mg cohort whereas for 340 mg, it occurred approximately 3 days after the last dose. The finding that the 680 mg cohort achieved nadir concentration following the 3rd dose and maintained serum IgG reduction after the 4th dose, indicates a maximum response has likely been achieved, and that higher doses or more frequent dosing would yield little additional benefit. This is consistent with data from other anti-FcRn agents in development that have observed a maximum percent reduction in serum IgG from baseline of ~ 75-80% [Howard, 2019; Kiessling, 2017; Ling, 2018].

Preliminary data following the last dose across both cohorts shows that IgG levels were within normal range and within 30% of the baseline value by 5 weeks after the last dose (average (SD) IgG concentration was 8.64 (2.73) g/L, and 8.95 (2.03) g/L for the 340 mg and 680 mg cohorts, respectively). The return towards baseline indicates the effect of RVT-1401 is reversible.

Additional information is available in the current Investigator's Brochure.

3.4. Benefit: Risk Assessment

Summaries of findings from both clinical and non-clinical studies conducted with RVT-1401 can be found in the current IB.

3.4.1. Risk Assessment

Potential Risk of Clinical Significance	**Mitigation Strategy**	
	Impact on Eligibility	**Monitoring and Stopping Criteria OR Management Criteria**
The potential for allergic reactions exists following administration of any protein to human participants.	Participants with history of anaphylaxis (i.e., serious, life-threatening allergic reactions) are ineligible.	Participants will be closely monitored for reactions for 30 min post-dose.
Changes in circulating complement	None	Serum complement will be monitored throughout the study (Section 8.1). Abnormal values will be discussed with the study medical monitor.
Sustained hypogammaglobulinemia	The following participants will be ineligible: -Participants with a total IgG level of <6g/L at screening -Participant has a past medical history of primary immunodeficiency, T-cell or humoral, including common variable immunodeficiency. -History of or known infection with human immunodeficiency virus (HIV), hepatitis B virus (HBV), or Mycobacterium tuberculosis: - Participants must have negative test results for HBV surface antigen, HBV core antibody, HIV 1 and 2 antibodies, and a negative QuantiFERON-TB Gold test at Screening. - Hepatitis C virus (HCV): - Participants must have a negative test result for HCV antibody or - Participants with a known history of HCV must have documented evidence of sustained virologic response that is consistent with cure of hepatitis C infection that is	Total IgG levels will be monitored throughout the study (Section 8.1).

	confirmed with a negative HCV RNA test at Screening. -Absolute neutrophil count <1000 cells/mm3	
Sustained hypoalbuminemia	Participants with baseline albumin levels <3.5 g/dL will be ineligible. Subjects with advanced liver disease including any diagnosis of cirrhosis of any stage will be ineligible. Non-alcoholic fatty liver disease (NAFLD) including non-alcoholic steatohepatitis (NASH) is allowable if there has been a recent (within 6 months) normal ultrasound, CT, or MRI. If the ultrasound, CT, or MRI demonstrate fatty changes alone, the subject may be enrolled if s/he has a normal range fibroscan for liver fibrosis. AST or ALT ≥1.5x ULN at Screening. The subject may only be enrolled if s/he has a recent (within 6 months) normal ultrasound, CT, or MRI. If the ultrasound, CT, or MRI demonstrate fatty changes alone, the subject may be enrolled if s/he has a normal range fibroscan for liver fibrosis.	Serum albumin levels will be monitored throughout the study (Section 8.1). Criteria that would require dose interruption and/or discontinuation for Grade 2 and Grade 3 albumin levels have been added (Section 6.8.3).

4. OBJECTIVE(S) AND ENDPOINT(S)

Objectives	Endpoints
Primary	
To examine the effect of RVT-1401 on proportion of responders (defined as Hb level ≥10g/dL with at least a ≥2 g/dL increase from baseline without rescue therapy or blood transfusions in the previous two weeks)	Proportion of responders at week 13
To assess the safety and tolerability of RVT-1401 in subjects with WAIHA	Assessment of safety and tolerability by analysis of adverse event (AE) data and changes from baseline in vital signs, ECGs, and clinical laboratory values
Secondary	
To examine the effect of RVT-1401 on change in Hb levels	Change from baseline in Hb levels
To examine the effect of RVT-1401 on time to response	Time to response
To examine the effect of RVT-1401 on change in hematocrit levels	Change from baseline in hematocrit levels
To examine the effect of RVT-1401 on proportion of participants with Hb levels in the normal range	Proportion of participants with Hb levels in the normal range at week 13
To examine the effect of RVT-1401 on time to achieving Hb levels in the normal range	Time to achieving Hb levels in the normal range
To examine the effect of RVT-1401 on change in fatigue	Change from baseline in FACIT-F score
To examine the effect of RVT-1401 on change in dyspnea	Change from baseline in Medical Research Council (MRC) breathlessness scale
To examine the effect of RVT-1401 on change in health-related quality of life	Change from baseline in EQ-5D-3L score
To assess the change in serum levels of total IgG & IgG subclasses (I-IV)	Change from baseline in levels of total IgG & IgG subclasses (I-IV)
To examine RVT-1401 PK following repeated doses in patients with WAIHA	Concentration of RVT-1401 pre-dose (Ctrough)
To assess the changes in LDH, bilirubin,	Change from baseline in LDH, bilirubin, and

haptoglobin To measure anti-RVT-1401 antibodies following repeated doses in patients with WAIHA	haptoglobin Immunogenicity determined by change from pre-dose in anti-RVT-1401 antibodies, and characterization of any anti-RVT-1401 to confirm neutralization potential
Exploratory	
[redacted]	

5. STUDY DESIGN

5.1. Overall Design

This is a Phase 2, non-randomized, sequential, open-label study to investigate the safety, tolerability, PK, PD, and efficacy of RVT-1401 (680 mg/weekly and 340 mg/weekly) in patients with WAIHA. The study design is illustrated in Section 5.2**.**

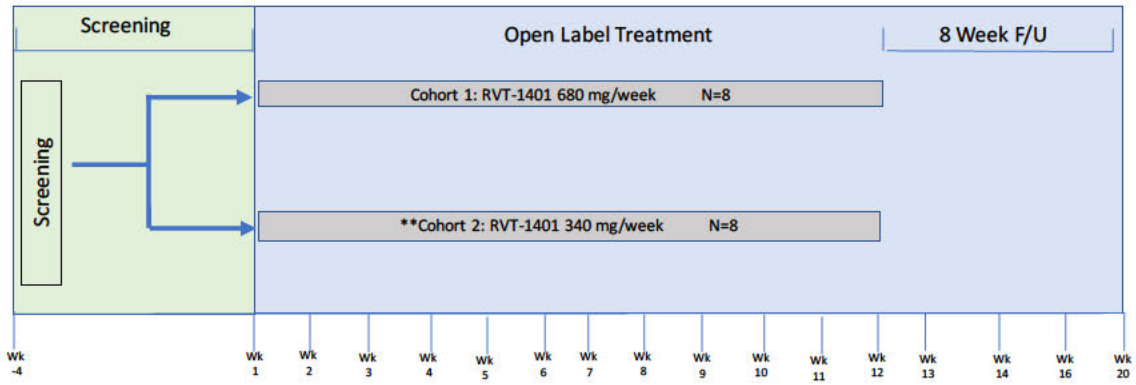
Two cohorts of participants will be enrolled in a non-randomized sequential approach. Participants will be enrolled into Cohort 1 (680 mg/weekly) first followed by Cohort 2 (340 mg/weekly). In the Phase I healthy volunteer study, both dosing regimens were well tolerated (Section 3.3.3). Since 680 mg/weekly has the greater likelihood of demonstrating clinical efficacy, this dosing regimen will be studied in Cohort 1.

Following the initial dose at the Baseline Visit (Week 1, Day 1), study visits will occur weekly throughout the treatment period. Following the final dose at Week 12, visits will occur weekly through Week 14 and then at Week 16 and Week 20. Safety, PK, PD, and clinical assessments will be collected throughout the study. Refer to Section 8.1, Time and Events Table.

Optional home visits will be offered to collect (at a minimum) blood samples, vital signs, and to review adverse events and concomitant medications.

Each participant will participate in the study for up to approximately 24 weeks: up to a 4-week screening period, a 12-week treatment period, and an 8-week follow up period.

5.2. Study Schematic



**Note-Cohort 1 will enroll first followed by Cohort 2

5.3. Treatment Arms and Duration

Participants will receive RVT-1401 for 12 weeks (680 mg/weekly or 340 mg/weekly).

6. PARTICIPANT POPULATION

6.1. Type and Number of Participants

A sufficient number of participants will be enrolled to achieve approximately 16 evaluable participants. Enrollment is competitive.

In order to manage the total study enrollment, the Sponsor may suspend screening and/or enrollment at any site or study-wide at any time.

If participants prematurely discontinue the study, additional replacement participants may be enrolled at the discretion of the Sponsor.

Deviations from inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or participant safety. Therefore, adherence to the criteria as specified in the protocol is essential.

To determine participant eligibility at screening, a single repeat of certain tests such as laboratory values or ECGs is allowed at the discretion of the Principal Investigator.

6.2. Inclusion Criteria

A participant will be eligible for inclusion in this study only if all of the following criteria apply:

1. Male or female ≥ 18 years of age.
2. Diagnosis of primary or secondary WAIHA as documented by a positive direct antiglobulin test (DAT) specific for anti-IgG alone or anti-IgG plus C3d.
3. Secondary WAIHA may only include Stage 0 chronic lymphocytic leukemia (CLL) in which separate treatment is not indicated, nor anticipated to require active management for the duration of the study.
4. Have failed or not tolerated at least one prior WAIHA treatment regimen as per local standards (e.g., steroids, rituximab, azathioprine, cyclophosphamide, cyclosporine, mycophenolate mofetil (MMF), danazol, or vincristine). Failure is defined as worsening or refractory disease despite steroids and or immunosuppressants.
5. Participants with splenectomy ≥3 months from Day 1 who are up to date on vaccinations (based on age and local guidance) are allowed.
6. Haptoglobin < lower limit of normal (LLN) and lactate dehydrogenase (LDH) >upper limit of normal (ULN).
7. At Screening and Baseline, subject's hemoglobin level must be <10 g/dL and the subject must have documented symptoms related to anemia (e.g., weakness, dizziness, fatigue, shortness of breath, chest pain).
8. Karnofsky Performance status ≥ 60.
9. Subject's concurrent treatment for WAIHA may consist only of steroids (stable dose for at least two weeks prior to Day 1), immunosuppressant therapy (azathioprine, MMF, or cyclosporine) that has been at a stable dose for at least four weeks prior to Day 1, or erythropoietin (stable dose for at least 6 weeks prior to Day 1). [Note: starting doses of WAIHA therapy must be maintained throughout the study except in the case of a rescue medication as per local standards for safety. Steroid taper down to 10 mg/day will be allowed for participants who achieve response for at least 2 weeks.]
10. A female participant is eligible to participate if she is of:
    a. Non-childbearing potential defined as pre-menopausal females with a documented bilateral tubal ligation, bilateral oophorectomy (removal of the ovaries) or hysterectomy; hysteroscopic sterilization, or postmenopausal defined as 12 months of spontaneous amenorrhea [in questionable cases a blood sample with simultaneous follicle stimulating hormone (FSH) in the post-menopausal range is confirmatory].
    b. Child-bearing potential and agrees to use one of the contraception methods listed in Section 6.6.1 for an appropriate period of time (as determined by the product label or Principal Investigator) prior to the start of dosing to sufficiently minimize the risk of pregnancy at that point. Female participants must agree to use contraception until 90 days after the last dose of study treatment.

11. Male participants must agree to use one of the contraception methods listed in Section 6.6.1. This criterion must be followed from the time of the first dose of study treatment until 90 days after the last dose of study treatment.
12. Willing and capable of giving written informed consent, which includes compliance with the requirements and restrictions listed in the consent form.

6.3. Exclusion Criteria

A participant will not be eligible for inclusion in this study if any of the following criteria apply:

1. Participants with other types of AIHA (e.g., cold antibody AIHA, cold agglutinin syndrome, mixed type AIHA, or paroxysmal cold hemoglobinuria).
2. Participants requiring more than 2 units of RBC per week in the 2 weeks prior to Screening and Baseline.
3. Use of rituximab, any monoclonal antibody for immunomodulation, or proteasome inhibitor, within the past 3 months prior to Screening.
4. Immunoglobulins given by SC, IV (IVIG), or intramuscular route, or plasmapheresis/plasma exchange (PE) within 60 days before Screening.
5. Total IgG level <6 g/L (at Screening).
6. Absolute neutrophil count <1000 cells/mm^3(at Screening).
7. Albumin level <3.5 g/dL at Screening.
8. Known advanced liver disease including any diagnosis of cirrhosis of any stage.

   Non- alcoholic fatty liver disease (NAFLD) including non-alcoholic steatohepatitis (NASH) is allowable if there has been a recent (within 6 months) normal ultrasound, CT, or MRI. If the ultrasound, CT, or MRI demonstrate fatty changes alone, the participant may be enrolled if s/he has a normal range fibroscan for liver fibrosis.
9. AST or ALT ≥1.5x ULN at Screening.

   The participant may only be enrolled if s/he has a recent (within 6 months) normal ultrasound, CT, or MRI. If the ultrasound, CT, or MRI demonstrate fatty changes alone, the participant may be enrolled if s/he has a normal range fibroscan for liver fibrosis.
10. Participant has any laboratory abnormality (at screening) that, in the opinion of the investigator, is clinically significant, has not resolved at baseline, and could jeopardize or would compromise the participant's ability to participate in this study.
11. Medical history of primary immunodeficiency, T-cell or humoral, including common variable immunodeficiency.
12. Have an active infection, a recent serious infection (i.e., requiring injectable antimicrobial therapy or hospitalization) within the 8 weeks prior to Screening.

13. History of or known infection with human immunodeficiency virus (HIV), hepatitis B virus (HBV), or Mycobacterium tuberculosis:

    - Participants must have negative test results for HBV surface antigen, HBV core antibody, HIV 1 and 2 antibodies, and a negative QuantiFERON-TB Gold test at Screening.

    - Participants with an indeterminate QuantiFERON-TB Gold test result will be allowed one retest; if not negative on retesting, the participant will be excluded.

14. Infection with hepatitis C virus (HCV):

    - Participants must have a negative test result for HCV antibody.

    or

    - Participants with a known history of HCV must have documented evidence of sustained virologic response that is consistent with cure of hepatitis C infection. This is defined as undetectable or unquantifiable HCV RNA at least 12 weeks after stopping HCV treatment (HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C; 2014-2018, AASLD and IDSA). This should be confirmed with a negative HCV RNA test at Screening.

15. Active malignancy or history of malignancy in the 3 years prior to screening (exclusive of non-melanoma skin cancer and cervical cancer in situ).

16. Participant has any medical condition (acute or chronic illness) or psychiatric condition that, in the opinion of the investigator, could jeopardize or would compromise the participant's ability to participate in this study.

17. Body Mass Index (BMI) at Screening $\geq$ 40 kg/m^2.

18. Use of investigational drug within 60 days or 5 half-lives of the drug (whichever is longer) before Screening.

19. Participant has received a live vaccination within 2 weeks prior to the Baseline Visit; or intends to have a live vaccination during the course of the study or within 7 weeks following the final dose of study treatment.

20. History of sensitivity to any of the study treatments, or components thereof or a history of anaphylaxis (i.e., serious, life-threatening allergic reactions) that, in the opinion of the Investigator or Medical Monitor, contraindicates their participation.

21. Pregnant or lactating females as determined by positive serum or urine human chorionic gonadotropin test at screening or baseline.

22. QTcF interval >450 milliseconds for males and >470 milliseconds for females at Screening (a single repeat is allowed for eligibility determination). QTcF >480 msec in participants with Bundle Branch Block.

23. Diagnosis of concomitant idiopathic thrombocytopenia purpura (ITP)/ Evans syndrome with platelet count <100,000.

6.4. Other Eligibility Criteria Considerations

To assess any potential impact on participant eligibility with regard to safety, the Principal Investigator must refer to the following document(s) for detailed information regarding warnings, precautions, contraindications, AEs, and other significant data pertaining to the investigational product(s) being used in this study:

RVT-1401 Investigator's Brochure

6.5. Screening/Baseline Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are never subsequently enrolled. A minimal set of screen failure information is required including date of informed consent, demography, screen failure details, eligibility criteria, and any SAEs. Screen failure data will be recorded within the electronic Case Report Form (eCRF).

6.6. Lifestyle Restrictions

6.6.1. Contraception

Female participants of childbearing potential must not become pregnant and so must be sexually inactive by abstinence or agree to use a highly effective method of contraception (i.e., pregnancy rate of less than 1% per year).

Abstinence

Sexual inactivity by abstinence must be consistent with the preferred and usual lifestyle of the participant. Periodic abstinence (e.g., calendar, ovulation, symptothermal, postovulations methods) and withdrawal are not acceptable methods of contraception.

Contraceptive Methods with a Failure Rate of <1%

Hormonal

- Female participants and female partners of male study participants stable for at least 4 weeks prior to screening on a combined hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal) PLUS a barrier method (i.e., condom or occlusive cap [diaphragm or cervical/vault caps]).

- Female participants and female partners of male study participants stable for at least 4 weeks prior to screening on a Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable) PLUS a barrier method (i.e., condom or occlusive cap [diaphragm or cervical/vault caps]).

- Female participants and female partners of male study participants using a hormonal contraceptive must also use a barrier method (i.e., condom or occlusive

cap [diaphragm or cervical/vault caps]) and should have been stable on their hormonal contraceptive treatment for an appropriate period of time (as determined by the product label or Principal Investigator) prior to the start of dosing to sufficiently minimize the risk of pregnancy at that point.

Long-Acting Reversible

- Female participants and female partners of male study participants with an Intrauterine device (IUD) or intrauterine system (IUS) that meets the <1% failure rate as stated in the product label.

Male Contraception

- Male partner sterilization (vasectomy with documentation of azoospermia) prior to the female participant's entry into the study, and this male is the sole partner for that participant. For this definition, “documented” refers to the outcome of the investigator's/designee’s medical examination of the participant or review of the participant's medical history for study eligibility, as obtained via a verbal interview with the participant or from the participant’s medical records.

- Sterilized male participants who have had vasectomy with documented azoospermia post procedure can be included.

Additional Considerations for Male Participants

- Non-sterilized male participants who are sexually active with a female partner of childbearing potential must use effective method of double barrier contraception. Male participants practicing true sexual abstinence (when this is in line with the preferred and usual lifestyle of the participant) can be included. In addition, male participants must be advised not to donate sperm during this period from signing of Informed Consent Form (ICF), throughout the duration of the study, and for 90 days after the last administration of study drug.

These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring participants understand how to properly use these methods of contraception.

Participants must be completely informed of the unknown risks of pregnancy and agree not to become pregnant during the time they are participating in this study. If there is any question that a participant will not be reliable in the use of appropriate contraceptive methods, they should not be entered into the study.

6.7. Withdrawal Criteria

6.7.1. Reasons for Withdrawal

A Principal Investigator may discontinue/withdraw a participant from the study if any of the following criteria apply:

- Any clinical AE, laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant.
- Participant pregnancy
- Significant protocol violation (e.g., non-compliance with concomitant medications)
- Behavioral or administrative issue
- Participant request to discontinue/withdraw consent for any reason. It is important to document whether the withdrawal of consent is primarily due to an AE, lack of efficacy, or other reason.
- Discontinuation of the study at the request of the Sponsor, regulatory agency or an Institutional Review Board (IRB)/ Independent Ethics Committee (IEC)
- Stopping criteria, as noted in Section 6.8

If a participant meets a withdrawal criterion during treatment, an Early Termination visit will be required (Section 6.7.2).

6.7.2. Participant Withdrawal Procedures

If a participant is prematurely discontinued from the study, the Principal Investigator must make every effort to perform an Early Termination Visit per Section 8.1, Time and Events Table and document the primary reason for withdrawal.

Should a participant fail to attend the clinic for a required study visit, the site should attempt to contact the participant and re-schedule the missed visit as soon as possible. The site should also counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study. In cases where the participant does not return for the rescheduled visit or cannot be reached to reschedule the missed visit, the site should make every effort to regain contact with the participant (3 documented telephone calls and if necessary a certified letter to the participant's last known mailing address) so that they can appropriately be withdrawn from the study with a primary reason of "Lost to Follow-up".

6.8. Safety Management Criteria for Individual Participants

6.8.1. Liver Chemistry Management Criteria

To ensure subject safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of liver events is to be followed.

The following two categories of abnormalities / adverse events are to be considered during the course of the study (irrespective of whether classified/reported as an AE or SAE):

1. Liver laboratory triggers. These require repeated assessments of the abnormal laboratory parameter

2. Liver events. These require close observation and follow-up monitoring. Contributing factors are to be recorded on the appropriate CRF(s).

Please refer to Appendix 2 Table 4 for complete definitions of liver laboratory triggers and liver events. Every liver event defined in Appendix 2 Table 5 to be followed up by the investigator or designated personnel at the trial site, as summarized below. Additionally, required actions in case of liver laboratory triggers and liver events are outlined in Appendix 2, Table 5 (Follow up requirements for liver laboratory triggers and liver events). Repeat liver chemistry tests (i.e. ALT, AST, TBL, PT/INR, ALP and G-GT) regularly to confirm elevation and follow trends.

The following additional follow up should also be considered:

- Obtain a more detailed history of symptoms and prior or concurrent diseases.
- Obtain a history of concomitant drug use (including non-prescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.
- Exclude causes of underlying liver disease, as specified in Section 6.3 Exclusion Criteria
- Perform imaging such as abdominal US, CT or MRI, as appropriate
- Obtain a history of exposure to environmental chemical agents.
- Consider gastroenterology or hepatology consultations.

All follow-up information and procedures performed must be recorded as appropriate in the CRF.

These liver chemistry repeats will be performed using the central laboratory. If results will not be available from the central laboratory, then the repeats can also be performed at a local laboratory to monitor the safety of the subject. If a liver event is subsequently reported, any local liver chemistry tests previously conducted that are associated with this event should have results recorded on the appropriate CRF.

6.8.2. QTc Withdrawal Criteria

- QTc prolongation defined as QTcF >500 ms, or an increase of QTcF >60 ms above baseline on the 12-lead ECG, confirmed (persistent for >5 minutes) on two repeated 12-lead ECGs

6.8.3. Albumin Monitoring Criteria

In addition to lowering IgG, treatment with RVT-1401 is also expected to reduce serum albumin levels (Section 3.3.3.3). The following criteria are to be used to guide study drug administration:

- Grade 2 (albumin levels 2.0 g/dL - 3.0 g/dL): If there are no accompanying clinical signs and/or symptoms, no action will be taken with study drug.
- Grade 3 (albumin levels <2.0 g/dL):
    - Subjects with no signs/symptoms: study drug should be interrupted until albumin reached a level of 2.5 g/dL, at which point it may be restarted
    - Subjects with signs/symptoms limited to peripheral edema managed with diuretics: study drug should be interrupted until albumin reaches a level of 2.5 g/dL, at which point it may be restarted.
    - Subjects with signs/symptoms requiring treatment beyond diuretics: discontinue study drug

Grade 4 albumin levels: permanent discontinuation of study drug

6.8.4. Other Individual Stopping Criteria

- Subject has signs or symptoms of a serious infective episode requiring hospitalization or iv antibiotic therapy.
- Participant has a severe systemic allergic reaction (i.e., anaphylaxis) to study therapy.

6.9. Toxicity Management Criteria

6.9.1. Toxicity Management Criteria (AEs, Cardiovascular, and Injection Site Reactions)

The severity of each AE will be graded and managed according to the criteria in Table 2 (CTCAE version 5.0). Study drug should be permanently discontinued for any grade 4 toxicity other than hemoglobin decrease. Management of hemoglobin < 7.0 g/dL or anemia in the presence of cardiovascular symptoms is described in section 6.9.2. For grade 3 TEAE not considered related to WAIHA signs/symptoms, study drug should be withheld. Study drug may only be restarted following a grade 3 TEAE after discussion with the medical monitor.Table 2 Criteria for Determining the Grade/Severity of Adverse Event Terms

Grade	Criteria
1/Mild	Asymptomatic or mild symptoms, clinical or diagnostic observations only; intervention not indicated
2/Moderate	Limiting age-appropriate instrumental activities of daily living; minimal, local, or noninvasive intervention as indicated
3/Severe or medically significant	Not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living, intervention as indicated
4/Life-threatening	Life threatening consequences; urgent intervention indicated
5/Death	Death related to adverse event

Injection Site Reactions

Injection site evaluations will be made by clinical staff following administration of RVT-1401 as described below. Additional details related to the specific injection site location will be included within a study specific manual. If an injection site reaction is observed, a physician will characterize and document the reaction as an AE. Review of the injection site will continue until the AE is resolved. Symptomatic treatment (e.g., warm compresses, topical steroids, antihistamines if itching is present, or NSAIDs) may be provided for injection site reactions at the discretion of the Investigator.

The injection sites will be monitored for pain, tenderness, erythema and swelling. Each injection site reaction will be categorized using the intensity grading scheme presented in Table 3.

Table 3 Criteria for Determining the Grade/Severity of Injection Site Reactions

Grade	Criteria
1/Mild	Tenderness with or without associated symptoms (e.g., warmth, erythema, itching)
2/Moderate	Pain; lipodystrophy; edema; phlebitis
3/Severe or medically significant	Ulceration or necrosis; severe tissue damage; operative intervention indicated

Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 Published: November 27, 2017.

6.9.2. Management of Rescue Therapy

Rescue therapy during the first 8 weeks of the Treatment Period is permitted for participants with haemoglobin levels <7.0 g/dL or in the presence of signs/symptoms of myocardial ischemia, hypoxia, or TIA/stroke. Participants requiring rescue therapy after the Week 8 visit will be discontinued and an early withdrawal visit scheduled.

Blood Transfusion
The date, time, and number of units transfused should be recorded, along with the results of cross-match testing. Follow-up hemoglobin should be measured with 12 hours of the end of the transfusion. Hemoglobin values will be censored from efficacy analyses for the 2 weeks following a blood transfusion.

Prednisone/Prednisolone
Prednisone/prednisolone rescue (up to a 50% increase from baseline for up to 5 days), is permitted as per the rescue therapy guidelines (Section 6.9.2). The date, time, and dose should be recorded. Hemoglobin values will be censored from efficacy analyses for the 2 weeks following the last dose of prednisone/prednisolone rescue.

Dexamethasone
High dose dexamethasone (up to 40 mg daily for up to 4 days) is permitted as per the rescue therapy guidelines (Section 6.9.2). The date, time, and dose should be recorded. Hemoglobin values will be censored from efficacy analyses for the 2 weeks following the last dose of dexamethasone rescue.

IVIG and Plasma Exchange
Due to the mechanism of action for RVT-1401, the use of IVIG and Plasma exchange are not allowed.

6.9.3. Other Management Criteria

For an individual study participant, medical monitor notification criteria include, but are not limited to:

- Severe signs or symptoms, or significant changes in any of the safety assessments, that put the safety of the individual at risk (e.g. laboratory tests or vital signs, etc.) as judged by the Investigator.
- Initiation of rescue therapy (see Section 6.9.2)

6.10. Participant and Study Completion

A completed participant is one who has completed all phases of the study including the follow-up visits.

The end of the study is defined as the last participant's last visit.

7. STUDY TREATMENT

7.1. Investigational Product and Other Study Treatment

Investigational Product

Study Treatment Name:	**RVT-1401**
Manufacturer:	[redacted]
Dosage formulation:	Sterile solution for injection.
Unit dose strength(s)/Dosage level(s):	680 mg: 2 mL RVT-1401 in two syringes for a total of 4 mL 340 mg: 2 mL RVT-1401 in one syringe for a total of 2 mL
Route of Administration	SC injection
Dosing instructions:	The detailed methods are indicated in the Pharmacy Manual. Participants will be closely monitored for reactions for up to 1 hr post-dose before they leave the clinic.
Dose Preparation	The preparation procedure and expiry details will be included in the Pharmacy manual/product label.

7.2. Treatment Assignment

Participants will receive either open-label RVT-1401 680 mg/weekly or 340 mg/weekly treatment for up to a maximum of 12 weeks.

7.3. Blinding

This is an open-label study.

7.4. Packaging and Labeling

RVT-1401 will be supplied to the study site as a sterile liquid formulation with a nominal fill of at least 1 mL in Nuova Ompi 2R clear glass vials with a flip-off cap. The solution is clear to slightly yellow, essentially free of visible particles, for SC administration. [redacted]

Doses will be prepared by the pharmacist or designee with a label that includes at a minimum the study number, participant number, kit number and vial number. Doses are administered to participants by clinic staff or designee.

See Pharmacy Manual for exact instructions on dose preparation.

All labels will meet all local applicable requirements and Annex 13 of Good Manufacturing Practices: Manufacture of investigational medicinal products (July 2010) and/or other local regulations as applicable.

7.5. Preparation/Handling/Storage/Accountability

A description of the methods and materials required for preparation will be detailed in the pharmacy manual.

- Only participants enrolled in the study may receive study treatment and only authorized site staff may prepare, handle, supply or administer study treatment. All study treatments must be stored in a secure environmentally controlled and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the Investigator and authorized site staff.
- While the Investigator is ultimately responsible, study treatment accountability, reconciliation, and record maintenance (i.e. receipt, reconciliation and final disposition records) can be designated to the Pharmacist or other designee.
- Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff. In the case of unintentional occupational exposure notify the monitor, Medical Monitor and/or the Sponsor study contact.
- A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the Investigator, where this is required by local laws, or is available upon request from the Sponsor.

7.6. Compliance with Study Treatment Administration

The individual dose for a participant is prepared by a Pharmacist, licensed Pharmacy Technician, or designee. The preparation of the dose will be reviewed and confirmed by a second member of the study site staff.

The date and time of each dose administered along with the location of each injection will be recorded in the source documents. The location of each injection and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study drug.

7.7. Treatment of Study Treatment Overdose

An overdose is defined when a participant receives >680 mg in a single visit. The Sponsor does not recommend specific treatment for an overdose.

In the event of an overdose the Investigator or treating physician should:

- contact the Medical Monitor immediately,
- closely monitor the participant for AEs/SAEs and laboratory abnormalities.
- obtain a plasma sample for PK analysis within 2 days from the date of the last dose of study treatment if requested by the Medical Monitor (determined on a case-by-case basis)
- document the quantity of the excess dose as well as the duration of the overdosing in the eCRF

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

7.8. Treatment After the End of the Study

Participants will not receive any additional treatment with the study treatment from the Sponsor after completion of the study because the long-term safety and efficacy of RVT-1401 have not been established.

The Principal Investigator is responsible for ensuring that consideration has been given to the post-study care of the participant's medical condition.

7.9. Concomitant Medications and Non-Drug Therapies

Any concomitant medication should be recorded in the study records, including the doses administered, the dates and times of administration and the reason for administration.

Refer to the study inclusion and exclusion criteria (Section 6.2 and Section 6.3) and the study manual for a list of permitted and prohibited medications.

8. STUDY ASSESSMENTS AND PROCEDURES

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Time and Events Table, are essential and required for study conduct.

This section lists the procedures and parameters of each planned study assessment. All blood draws and rating scale assessments should be completed pre-dose (on dosing days). The timing of each assessment is listed in the Time and Events Table, Section 8.1.

The following points must be noted:

- The IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the Informed Consent Form.
- The total blood volume collected will be specified within the ICF.

8.1. Time and Events Table

	Screening[1]	Treatment Period (Weeks)												Follow-up Period (Weeks)				Early Withdrawal Visit
Study Timepoint (Weeks)	Within 30 days	1 (B/L)	2	3	4	5	6	7	8	9	10	11	12	13	14	16	20	
Time Window (days)			+/-1 day	+/-1 day	+/-1 day	+/-1 day	+/-1 day	+/-1 day	+/-1 day	+/-1 day	+/-1 day	+/-1 day	+/-1 day	+/-2 days	+/-2 days	+/-2 days	+/- 2 days	
Informed consent	X																	
Inclusion/exclusion criteria	X	X																
Demographics and medical history[9]	X																	
Height	X																	
Body weight	X	X																
Complete physical examination	X	X																
Brief physical examination																	X	X
Vital signs[2]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead Electrocardiogram[2]	X	X			X				X				X				X	X
Pregnancy test[3] (females)	X	X	X		X		X		X		X		X	X			X	X
Viral Serology	X																	
Vaccine Titers[2]		X												X			X	X
QuantiFERON® – TB GOLD	X																	
Urinalysis[2, 4]	X	X		X		X		X		X		X		X		X	X	X
Blood chemistry and hematology[2, 8]	X	X	X	X	X	X		X		X		X		X	X	X	X	X
Fasting Lipid Panel[2]		X												X			X	X
Serum complement (CH50, C3)[2]		X		X		X		X		X		X		X		X	X	X
Immunoglobulins (IgM, IgA)[2]		X		X		X		X		X		X		X		X	X	X

	Screening[1]	**Treatment Period (Weeks)**												**Follow-up Period (Weeks)**				**Early Withdrawal Visit**
Study Timepoint (Weeks)	Within 30 days	1 (B/ L)	2	3	4	5	6	7	8	9	10	11	12	13	14	16	20	
Time Window (days)			+/-1 day	+/-1 day	+/-1 day	+/-1 day	+/-1 day	+/-1 day	+/-1 day	+/-1 day	+/-1 day	+/-1 day	+/-1 day	+/-2 days	+/-2 days	+/-2 days	+/- 2 days	
RVT-1401 PK sampling[2]		X	X	X	X	X	X		X		X		X	X				X
Total IgG[2,6]	X	X	X	X	X	X	X		X		X		X	X	X	X	X	X
Immunoglobins (IgG subclasses)[2]		X		X			X		X		X			X		X	X	X
[redacted]																		
Anti- RVT-1401antibody[2, 5]		X		X		X			X					X			X	X
NAb Assessment[2]		X		X		X			X					X			X	X
[redacted]																		
Drug administration		X	X	X	X	X	X	X	X	X	X	X	X					
Injection Site Reaction[7]		X	X	X	X	X	X	X	X	X	X	X	X					
FACIT-F Scale[2]		X		X		X		X		X		X		X		X	X	X
MRC Breathlessness Scale[2]		X		X		X		X		X		X		X		X	X	X
EQ-5D-3L[2]		X				X				X				X		X	X	X
Satisfaction Questionnaire														X				X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

1. Screening can take place over multiple days.
2. Assessments collected on dosing days will be collected pre-dose.
3. Pregnancy tests will be collected pre-dose (via urine dipstick) on dosing days where specified. Serum pregnancy tests should be collected at screening and the final follow up visit.
4. Microalbumin/creatinine ratio at baseline, week 13, and week 20 only.
5. Participants with treatment emergent positive results (change from baseline) for anti- RVT-1401 antibody at Week 20 will be requested to return at approximately 6, 9, and 12 months post-dose for additional samples or until their result is no longer positive. However, for purposes of safety follow-up and database lock participation ends at the Week 20 visit.
6. Two samples for IgG will be collected: one will be sent to the central lab for safety monitoring, while the other sample will be sent to Intertek as the PD endpoint.
7. Local injection site reactions will be assessed at approximately 10 minutes post dose.

8. Hematology, HbA1c and [redacted] will be drawn for site local laboratory analysis, at minimum, and results collected in the instance where central laboratory samples are received hemolyzed. If other central laboratory tests are received hemolyzed, the local result will be captured in the eCRF.
9. History of WAIHA and prior WAIHA treatments will be captured in the eCRF.

8.2. Screening and Critical Baseline Assessments

Screening assessments are outlined in the Time and Events Table, (Section 8.1). The following demographic parameters will be captured: year and month of birth, sex, race and ethnicity.

Medical/medication history will be assessed as related to the inclusion/exclusion criteria listed in Section 6.

Written informed consent must be obtained prior to performance of any study related procedures. Screening can take place over multiple days.

8.3. Study Assessments and Procedures

8.3.1. Physical Exams

A complete physical examination will include, at a minimum, assessment of the Cardiovascular, Respiratory, Gastrointestinal and Neurological systems and skin. Height will also be measured and recorded at screening only and weight at screening and baseline only.

A brief physical examination will include, at a minimum, assessments of the skin, Respiratory, Cardiovascular system, and abdomen (liver and spleen).

8.3.2. Vital Signs

Vital signs will be measured in a supine position and will include temperature, systolic and diastolic blood pressure and pulse oximetry.

8.3.3. Electrocardiogram (ECG)

ECGs will be measured in a supine position.

Twelve-lead ECGs will be obtained during the study using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals. Refer to Section 6.8.2 for QTcF criteria and additional QTcF readings that may be necessary.

8.3.4. Clinical Safety Laboratory Assessments

All protocol required laboratory assessments must be conducted in accordance with a study manual or Laboratory Manual, and Protocol Time and Events Table (Section 8.1). Laboratory requisition/order forms must be completed, and samples must be clearly labelled with the participant number, protocol number, site/center number, and visit date. Details for the preparation and shipment of samples will be provided by the laboratory and are detailed in the study manual or the laboratory manual. Investigators will also

refer to their local institution for samples being analysed by the local laboratory. Reference ranges for all safety parameters will be provided to the site by the laboratory responsible for the assessments.

If additional non-protocol specified laboratory assessments are performed at the institution's local laboratory and result in a change in participant management or are considered clinically significant by the Investigator (e.g., SAE or AE or dose modification) the results must be recorded.

Central laboratory results will be prioritized except where specific test results are not available due to sample hemolysis as specified in the Time and Events (Section 8.1). In these instances, results from site local laboratories will be collected in the eCRF.

Laboratory sample parameters are listed below:

Hematology

Platelet Count	*RBC Indices*:	*Automated WBC Differential:*
Red Blood Cell (RBC)Count	Mean corpuscular volume (MCV)	Neutrophils
White Blood Cell (WBC) Count (absolute)	Mean corpuscular hemoglobin (MCH)	Lymphocytes
Reticulocyte Count	Mean corpuscular hemoglobin concentration (MCHC)	Monocytes
Hemoglobin		Eosinophils
Hematocrit		Basophils
Haptoglobin		

Clinical Chemistry

Blood urea nitrogen (BUN)	Potassium	AST (SGOT)	Total (TBL) and direct bilirubin
Creatinine	Chloride	ALT (SGPT)	Uric Acid
Total Protein	Total carbon dioxide (CO_2)	Gamma glutamyltransferase (GGT)	Albumin
Sodium	Calcium (corrected)	Alkaline phosphatase (ALP)	Lactic acid dehydrogenase (LDH)
Serum complement (CH50, C3)	Immunoglobulin M (IgM)	Immunoglobulin A (IgA)	Immunoglobulin G (IgG)
HbA1c			
Fasted labs			
Glucose (fasted) **Week 1 and Week 13 only**	Insulin (fasted) **Week 1 and Week 13 only**		

Lipid Panel (fasted) **Week 1, Week 13, Final Follow up/Early Withdrawal only**	Total cholesterol Triglycerides HDL cholesterol LDL cholesterol (calculated using Martin-Hopkins equation) Cholesterol/HDL ratio Non-HDL cholesterol (calculated) CRP/ High sensitivity CRP

NOTE: Details of Liver Chemistry Stopping Criteria and Follow-Up Procedures are given in Appendix 2: Liver Safety Required Actions and Follow up Assessments.

Routine Urinalysis

Specific gravity, pH
glucose, protein, blood and ketones by dipstick
Microscopic examination (if blood or protein is abnormal)
Microalbumin/creatinine ratio at baseline, week 13, week 20 (if urine protein is abnormal)

Other tests

QuantiFERON®-TB Gold
Viral Serology [HIV1/HIV2, Hepatitis B (HBsAg), Hepatitis B (Core antibody), Hepatitis C (Hep C antibody]
Vaccine titers for: tetanus, diphtheria, Hepatitis A, Hepatitis B, Pneumococcal
FSH (as needed for confirmation of postmenopausal status)
Pregnancy Tests: serum test at screening, Week 20, and early withdrawal and urine dipstick pre-dose at other timepoints. Positive urine tests should be confirmed with a serum test.

All laboratory tests with values that are considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline. If such values do not return to normal within a period judged reasonable by the Principal Investigator, the etiology should be identified, if possible and the Sponsor notified.

8.3.5. Pharmacokinetics

Blood samples for PK analysis of RVT-1401 will be collected at the time points indicated in Section 8.1, Time and Events Table. The actual date and time of each blood sample collection will be recorded.

Processing, storage and shipping procedures are provided in the study manual or lab manual.

Serum analysis will be performed under the control of the Sponsor. Concentrations of RVT-1401 will be determined in serum samples using the currently approved bioanalytical methodology. Raw data will be archived at the bioanalytical site.

8.3.6. Anti-Drug Antibody (ADA) and Neutralizing Antibody (NAb)

Blood samples for ADA and NAb analysis will be collected at the time points indicated in Section 8.1, Time and Events Table. The actual date and time of each blood sample collection will be recorded.

Processing, storage and shipping procedures are provided in the study manual or lab manual.

ADA analysis will be performed under the control of the Sponsor. Anti-RVT-1401 antibody titers will be determined in serum samples using the currently approved bioanalytical methodology. Raw data will be archived at the bioanalytical site. If anti-RVT-1401 antibody titers are detected, they will be further characterized using a validated NAb assay.

Participants with treatment emergent positive results (change from baseline) for anti-RVT-1401 antibody at Week 20 will be requested to return at approximately 6, 9, and 12 months post-dose for additional samples or until their result is no longer positive. However, for purposes of safety follow-up and database lock participation ends at the Week 20 visit.

8.3.7. Pharmacodynamics

Blood samples for PD analysis will be collected at times indicated in the Time and Events Table (Section 8.1).

Pharmacodynamic Markers

Total IgG, and differentiation by class: IgG subclasses (IgG1, 2, 3, and 4)

The actual date and time of each blood sample collection will be recorded. These samples may be used for the analysis of exploratory biomarkers. Samples will be collected, labelled, stored, and shipped as detailed in the study manual or lab manual.

8.3.8. Exploratory Biomarkers

Blood samples for exploratory biomarker analysis will be collected at times indicated in the Time and Events Table (Section 8.1).

The actual date and time of each blood sample collection will be recorded. The timing of samples may be altered and/or samples may be obtained at additional time points to

ensure thorough biomarker assessment. Samples will be collected, labelled, stored, and shipped as detailed in the study manual or lab manual.

8.4. Rating Scales & Questionnaires

8.4.1. Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) Scale

The FACIT-F scale is a validated scale which measures the physical, emotional and social implications of fatigue, one of the key clinical manifestations of warm autoimmune hemolytic anemia [Acaster, 2015; Webster, 2003]. Scores range from 0-52, with a higher score indicating a higher quality of life. A score of less than 30 would indicate severe fatigue. The scale takes approximately 5-10 minutes to complete.

8.4.2. Medical Research Council (MRC) Breathlessness Scale

The MRC Breathlessness scale is a questionnaire that consists of five statements about perceived breathlessness. The focus of the scale is to quantify the disability associated with breathlessness and not the severity of the breathlessness [Stenton, 2008]. This scale has undergone iterations with the current Modified MRC Subject Version, ranging from Grade 0 (limited to no disability) to Grade 4 (severe disability). This scale has been used in patients with chronic obstructive pulmonary disease (COPD), where the researchers further stratified on patients with low hemoglobin levels. Their data demonstrate that anaemic COPD patients had significantly higher MRC [Ferrari , 2015]. The scale can be self-administered by asking subjects to choose a phrase that best describes their condition. The score is the number that best fits the patient's level of activity. A score can usually be obtained in less than a minute.

8.4.3. EQ-5D-3L Scale

The EQ-5D-3L is a validated measurement of health-related quality of life [Devlin, 2018; Hernandez , 2018]. The scale consists of 2 components, the EQ-5D descriptive system and the EQ visual analogue scale. The descriptive system evaluates mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The scale can be self-administered by subjects who select the most appropriate statement within each category. A lower score corresponds to better quality of life. The EQ VAS records the patient's self-rated health on a vertical visual analogue scale where the endpoints are labelled 'Best imaginable health state' (100) and 'Worst imaginable health state' (0). The patient can select any number from 0-100. Completion of both components of the scale can be performed in under 5 minutes.

8.4.4. Satisfaction Questionnaire

A brief survey asking participants for feedback on their experience with the SC injections during the course of the study will be completed at the end of the treatment period. The survey will take less than 2 min to complete by the participant.

9. DATA MANAGEMENT

For this study, participant data will be entered into a Sponsor-approved electronic database and combined with data provided from other sources (e.g., safety laboratory, PK and PD vendor, etc.) in validated datasets then transmitted electronically to the Sponsor or designee.

Management of clinical data will be performed in accordance with applicable Sponsor approved standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data.

Adverse events and concomitant medications terms will be coded using Medical Dictionary for Regulatory Activities (MedDRA) and the World Health Organization Drug Dictionary Enhanced (WHO-DDE), respectively.

The Principal Investigator will retain original source documents and the Sponsor will receive eCRF-required data as electronic datasets. Participant initials will not be collected or transmitted to the Sponsor.

10. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

10.1. Sample Size Considerations

The sample size for this study was not determined using statistical methods. The sample size was chosen based on clinical and recruitment considerations for this Phase 2 study.

10.2. Statistical Considerations

10.2.1. Analysis Populations

Intention-To-Treat (ITT) Population

All enrolled participants who take at least one dose of study medication will be included in the ITT population. Participants will be summarized by treatment group.

This will be the population for all PD parameters.

Safety Population

All participants who enroll in the study and receive at least one dose of study treatment will be included in the Safety Population. Participants will be summarized by actual treatment group.

This will be the population for the safety analyses, as well as for presentation and summarization of baseline/demographic characteristics.

Pharmacokinetic Population

The PK Population will include all participants who undergo PK sampling and have evaluable concentration-time data for analysis.

Pharmacodynamic Population

The PD population will include all participants who have baseline measure, along with a post baseline measure and receive at least one dose of study treatment.

10.3. Analysis

Final analysis will be performed after the completion of the study and the database is locked.

Data will be listed and summarized. Treatment will be assigned based on the dosing schedule and included in the data listings. Listings will be sorted by participant, day, and time; summaries will be presented by treatment, day, and time.

Unless stated otherwise, descriptive summaries for continuous variables will include n, mean, standard deviation (SD), median, first and third quartiles, minimum, and maximum. The geometric mean with associated 2-sided 95% confidence interval (CI), and the between-participant CV (%CVb) for PK parameters only will also be included. For categorical variables, n and percent will be used as summary statistics. Baseline is the last available assessment prior to time of the first dose unless it is specified otherwise. If there are multiple assessments collected on the same scheduled time, the average of these assessments will be used. For tabulated safety summaries, only the scheduled assessments will be included in the summary tables.

Version 9.4 or higher of the SAS system will be used to analyze the data as well as to generate tables, figures, and listings.

Complete details will be documented in the Statistical Analysis Plan (SAP), which will be signed off prior to the lock of the study database.

10.3.1. Baseline Demographics and Characteristics

Subjects baseline demographics and characteristics will be summarized by the treatment groups, and by overall.

10.3.2. Primary Endpoint for Efficacy

The primary endpoint will be defined as the proportion of responders at Week 13. The Fisher's exact test will be used for the difference between the two treatment groups.

The analysis of the primary endpoint will be performed on ITT based on all available data, without using any imputation method for missing data.

10.3.3. Secondary Endpoints for Efficacy

For each of the continuous secondary endpoints, the actual value, change from baseline and percentage change from baseline for all secondary endpoints will be summarized by visit and treatment group using the n, mean, SD, median, first and third quartiles, minimum, and maximum values. The comparison of the active arms (separately) will be performed using a Mixed Model for Repeated Measures (MMRM)/ Analysis of Covariance model with treatment, Visit, and baseline value in the model. The least square means of the treatment difference, standard errors, 95% CI and p-value for the treatment will be presented at each visit. A 2-sided alpha of 0.05 will be used to determine statistical significance for Treatment. If deemed appropriate, the two active arms may be combined to evaluate any treatment effect for the changes from the baseline.

For categorical secondary endpoints, the number of participants who meet the endpoint and the percentage will be summarized. The percentage will be calculated using those participants who had a value at the time point. Statistical testing may be performed between the two treatments using a Fishers Exact Test. If deemed appropriate, the two active arms may be combined to evaluate any treatment effect for the shift from the baseline.

The analyses of the secondary endpoints will be performed on ITT based on all available data, without using any imputation method for missing data.

10.3.4. Safety Analyses

Safety will be evaluated by assessment of clinical laboratory tests, physical examinations, vital signs measurements, and ECG readings at various time points during the study, and by the documentation of AEs.

AE verbatim text will be coded and classified by body system and preferred (coded) term using the MedDRA. All AEs, both serious and non-serious will be listed. AE summaries by study part and treatment group, of the number and percent of participants reporting each event at least once will be generated.

Clinical chemistry, hematology, and urinalysis values will be listed for each participant and flagged high or low relative to the normal range where appropriate. Descriptive summary statistics will be created by study part, treatment and assessment time.

Other safety data will be summarized descriptively by treatment and time on the Safety Population. Details will be provided in the SAP.

10.3.5. Pharmacokinetic Analyses

Serum compound concentration-time data will be analyzed by non-compartmental methods with Phoenix WinNonlin or other PK software programs. Calculations will be based on the actual sampling times recorded during the study for the PK Population. From the plasma concentration-time data, Ctrough will be determined:

Additional PK parameters may be calculated. PK data will be presented in graphical and tabular form and will be summarized descriptively by Treatment.

10.3.6. Pharmacodynamic Analyses

All participants in the ITT population will be included in the summaries of PD data. The actual value, change from baseline and percentage change from baseline for all PD parameters will be summarized by visit and treatment group using the n, mean, SD, median, first and third quartiles, minimum, and maximum values. Statistical testing may be performed between the two treatment groups using mixed models. Details will be provided in the Statistical Analysis Plan.

Serum IgG and IgG subclass (1-4) levels will be summarized as both raw values as well as percent change from baseline (intra-participant assessment). Additional PK/PD and PD/PD relationships may be evaluated. PD data will be presented in graphical and tabular form and will be summarized descriptively. The correlation coefficients will be generated between PK/PD parameters.

10.3.7. Other Analyses

The analysis of the exploratory endpoints will include all participants in the ITT population.

11. ADVERSE EVENTS (AE) AND SERIOUS ADVERSE EVENTS (SAES)

The Principal Investigator or site staff is responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE. All SAEs must be reported to the Sponsor within 24 hours of awareness of the event (Section 11.3).

Once study participants have completed the study, the Principal Investigator is not obligated to actively seek AEs or SAEs. However, if the Principal Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event reasonably related to the investigational product or study participation, the Principal Investigator must notify the Sponsor at [redacted] within 24 hours of awareness.

11.1. Definition of Adverse Events

An AE is any untoward medical occurrence in a participant or clinical investigation participant, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product.

Events meeting the definition of an AE **include but are not limited to**:

- Any clinically significant, new or worsened, abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements). Clinical significance is determined based on the medical and scientific judgement of the Investigator.
- Signs, symptoms, or the clinical sequelae of a suspected interaction (e.g. with medications or food).
- Signs, symptoms, or the clinical sequelae of an overdose of either investigational product or a concomitant medication (overdose without an AE should be reported as a protocol deviation).

Events that **do not** meet the definition of an AE include:

- Anticipated day-to-day fluctuations of pre-existing condition(s), including the disease under study.
- Abnormal or worsening laboratory, imaging, or other safety findings that are not clinically significant.
- Medical or surgical procedures (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

11.2. Definition and Reporting of Serious Adverse Events

Serious adverse events must be entered within 24 hours of awareness and marked as a SAE within the AE eCRF form, which will send an immediate auto notification **to** [redacted] **and the Medical Monitor.**

If the eCRF is not available, the site must email [redacted] **and the Medical Monitor within 24 hours of the study site personnel's knowledge of the event**.

A SAE is any untoward medical occurrence that, at any dose:

- Results in death
- Is life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at immediate risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

- Requires hospitalization or prolongation of existing hospitalization

Hospitalization planned prior to signing the informed consent is not considered an SAE. Surgeries and other interventions that were under consideration prior to signing the informed consent are not considered an SAE if the underlying condition has not changed from baseline.

"Hospitalization" includes admission to the hospital of any duration. It does not include emergency room visits. Complications that occur during hospitalization are AEs and are SAEs if they prolong hospitalization or fulfill any other serious criteria.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

- Results in disability/incapacity

The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

- Is a congenital anomaly/birth defect
- Is an important medical event that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. Examples of such events are allergic bronchospasm, blood dyscrasias or convulsions where treatment prevents the need for hospitalization.

The following should always be considered serious: invasive or malignant cancers, and development of drug dependency or drug abuse.

- Deaths considered to be the result of progression of WAIHA or failure of treatment should be recorded as SAEs; the most prominent event (e.g. autoimmune hemolytic anemia or thrombosis due to WAIHA) should be recorded as the event term with an outcome of death.
- Hospitalization for urgent transfusion or treatment of symptoms associated with recurrence of WAIHA; the most prominent event should be recorded as the event term.

11.3. Time Period and Frequency for Collecting AE and SAE Information

- AEs will be collected from the time of informed consent through the follow-up period, at the timepoints specified in the Section 8.1, Time and Events Table.
- Medical occurrences that begin prior to any study procedure but after obtaining informed consent may be recorded on the Medical History/Current Medical Conditions section of the eCRF.
- All SAEs will be recorded and reported to the Sponsor within 24 hours of site awareness.
- Any SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to investigational product will be recorded from the time a participant consents to participate in the study up to and including any follow-up contact.

11.4. Method of Detecting and Reporting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence. Appropriate questions include:

- "How are you feeling?"
- "Have you had any (other) medical problems since your last visit/contact?"
- "Have you taken any new medicines, other than those provided in this study, since your last visit/contact?

All AEs and SAEs should be promptly recorded in the eCRF, completing all fields for which data is available. When known, the diagnosis should be entered as the event term in the eCRF, rather than individual symptoms. When the diagnosis is unclear, key symptoms may be entered, and the investigator should obtain appropriate tests to establish a diagnosis, if possible. After the diagnosis is determined, individual symptoms of that diagnosis may be removed from the database. All relevant seriousness criteria should be entered for each SAE. Discharge summaries should be requested for all hospitalizations.

For SAEs, the eCRF will send an auto notification to [redacted] and the Medical Monitor when the form is saved. Each SAE should be assigned a causality at the time of entry, as this is required to determine regulatory reporting. Follow-up information regarding the SAE, including hospital discharge summary, should be emailed to [redacted] after redacting all personally identifying information regarding patient or hospital staff (per European Global Data Protection Regulation).

11.5. Assessing Severity of AEs and SAEs

Severity describes the intensity of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance, such as a severe headache. This is not the same as "serious," which is based on participant/event outcome or action taken.

The Investigator must determine the severity of each AE according to the following criteria:

Criteria for Determining the Grade/Severity of Adverse Event Terms

Grade	Criteria
1/Mild	Asymptomatic or mild symptoms, clinical or diagnostic observations only; intervention not indicated
2/Moderate	Minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living
3/Severe or medically	Not immediately life-threatening; hospitalization or

significant	prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
4/Life-threatening	Life threatening consequences; urgent intervention indicated. (Note that the seriousness criteria "life-threatening" applies only if the event is immediately life-threatening; an event such as cancer or neutropenia may be Grade 4 but not meet seriousness criteria of Life-threatening)
5/Death	Death related to adverse event

Adverse event severity should be recorded in the appropriate section of the AE eCRF and in the participant's source documents.

11.6. Assessing Causality of AEs and SAEs

Regulatory authorities require that both investigator and sponsor assess whether there is a reasonable possibility that the study treatment caused each AE. This assessment requires careful medical consideration of each event in relationship to the timing of drug administration, the presence of other factors which may have caused the event (underlying illness, concomitant medication, complications, exposure to other toxins or allergens, environmental factors, etc.), and the effects of stopping and/or restarting the study treatment. The following definitions are to be used for the relationship of the AE to Study Treatment:

The investigator will assess the causality of each reported AE as follows:

- Probably related: an AE occurring at a reasonable time following administration of a drug, where other causes are unlikely, there is evidence to suggest that the drug caused the event, and/or where the event recurs after reintroduction of the drug (without other explanation for the recurrence).
- Possibly related: an AE occurring at a reasonable time following administration of a drug and for which there is a reasonable possibility that the drug caused the event, e.g. there is some evidence to suggest a causal relationship.
- Not related: an AE with poor or no relationship to the timing of drug administration, or where another cause such as underlying disease, complications, or other medications reasonably explains the event, or where the event does not recur after continued administration or reintroduction of the drug for an adequate period.

11.7. Follow-up of AEs and SAEs

After the initial AE/SAE report, the Principal Investigator is required to proactively follow each event at subsequent visits/contacts until the event resolves. All SAEs and AEs will be followed until resolution, or until the condition stabilizes or until the participant is lost to follow-up. Where necessary, repeated laboratory testing should be

requested to confirm resolution. Ongoing AEs where no further information is likely to be available may be closed after consultation between the Sponsor and Medical Monitor.

11.8. Regulatory Reporting Requirements for SAEs

Prompt notification by the Investigator to the Sponsor of SAEs/adverse event of special interest (AESIs) is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a product under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. The Sponsor will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC and Investigator.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and are forwarded to the Investigators in accordance with local regulations.

The Investigator who receives an Investigator safety report describing a SAE(s)/AESI(s) or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will file it with the IB and will notify the IRB/IEC, as appropriate according to local requirements.

11.9. Overdose

Overdose is less likely in a study where the drug is administered within a clinical unit by a healthcare provider. If there are no symptoms of an overdose, it should be recorded as a protocol deviation. Overdose with symptoms should be recorded as an AE or SAE, as appropriate.

12. PREGNANCY REPORTING

All female participants will be tested for pregnancy prior to study drug dosing. Participants testing positive for pregnancy will be ineligible for study participation.

Any pregnancies in a participant, or the partner of a participant, between the time of informed consent and study termination must be reported to the Sponsor within 24 hours of learning of the pregnancy. Information on the status and health of the mother, the pregnancy and its outcome, and the child will be recorded on the form provided. In case of a partner pregnancy, the partner of the study participant will be asked to sign a partner pregnancy consent form in order to collect pregnancy and outcome information. Information on the status of the mother and child will be forwarded to the Sponsor. Follow-up will be done for the newborn at birth and 12 months of age with parental consent. Any premature termination of the pregnancy will be reported. Complications of the pregnancy affecting either the mother or fetus that meet seriousness criteria (Section 11.2) should be reported as an SAE. A planned abortion is not considered an SAE.

13. RESPONSIBILITIES

13.1. Principal Investigator Responsibilities

13.1.1. Good Clinical Practice (GCP)

The Principal Investigator will ensure that this study is conducted in accordance with the principles of the "Declaration of Helsinki" (as amended in Edinburgh, Tokyo, Venice, Hong Kong, and South Africa), International Conference on Harmonisation (ICH) guidelines, or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the study participant. For studies conducted under a United States IND, the Principal Investigator will ensure that the basic principles of "Good Clinical Practice," as outlined in 21 Code of Federal Regulations (CFR 312), subpart D, "Responsibilities of Sponsors and Investigators," 21 CFR, part 50, 1998, and 21 CFR, part 56, 1998, are adhered to. These standards are consistent with the requirements of the European Community Directive 2001/20/EC.

Since this is a "covered" clinical trial, the Principal Investigator will ensure that 21 CFR, Part 54, 1998, is adhered to; a "covered" clinical trial is any "study of a drug or device in humans submitted in a marketing application or reclassification petition participant to this part that the applicant or FDA relies on to establish that the product is effective (including studies that show equivalence to an effective product) or that make a significant contribution to the demonstration of safety." This requires that Principal Investigators and all sub-investigators must provide documentation of their financial interest or arrangements with the Sponsor, or proprietary interests in the drug being studied. This documentation must be provided before participation of the Principal Investigator and any sub-investigator. The Principal Investigator and sub-investigator agree to notify the Sponsor of any change reportable interests during the study and for one year following completion of the study. Study completion is defined as the date that the last participant has completed the protocol defined activities.

13.1.2. Institutional Review Board (IRB)/Independent Ethics Committee (IEC) Approval

This protocol and any accompanying material to be provided to the participant (such as informed consent form, advertisements, participant information sheets, or descriptions of the study used to obtain informed consent) will be submitted by the Principal Investigator to an IRB or IEC. Approval from the IRB or IEC must be obtained before starting the study and should be documented in a letter to the Principal Investigator specifying the protocol number, protocol version, protocol date, documents reviewed, and date on which the committee met and granted the approval.

Any modifications made to the protocol after receipt of IRB or IEC approval must also be submitted to the IRB or IEC for approval before implementation.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC on an annual basis or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by procedures established by the IRB/IEC.

13.1.3. Informed Consent

The Principal Investigator or designee is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study and before undertaking any study-related procedures. The Principal Investigator must utilize an IRB or IEC-approved consent form for documenting written informed consent. Each informed consent will be appropriately signed and dated by the participant and the person obtaining consent.

Participants must be re-consented to continue their participation in the study if a protocol amendment is made that substantially alters the study design or the potential risks or burden to the participant.

13.1.4. Confidentiality

The Principal Investigator must assure that participants' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only participant number (i.e., not names) and month and year of birth (as allowed) should be recorded on any form or biological sample submitted to the Sponsor, IRB or IEC, or laboratory. The Principal Investigator must keep a screening log showing codes, names, and addresses for all participants screened and for all participants enrolled in the trial.

The Principal Investigator must keep a screening log showing codes, names, and addresses for all participants screened and for all participants enrolled in the trial.

The Principal Investigator agrees that all information received from the Sponsor, including but not limited to the IB, this protocol, eCRFs, the investigational new drug, and any other study information, remain the sole and exclusive property of the Sponsor during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from the Sponsor. The Principal Investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

13.1.5. Study Files and Retention of Records

The Principal Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently

verified. These documents should be classified into at least the following two categories: (1) Investigator's study file, and (2) participant clinical source documents.

The Investigator's study file will contain the IB, protocol/amendments, eCRF and query forms, IRB or IEC and governmental approval with correspondence, informed consent, drug records, staff curriculum vitae and authorization and training forms, and other appropriate documents and correspondence.

The required source data should include the following for each participant:

- participant identification (name, month and year of birth, gender);
- documentation that participant meets eligibility criteria, i.e., history, physical examination, and confirmation of diagnosis (to support inclusion and exclusion criteria);
- participation in trial (including trial number);
- trial discussed and date of informed consent;
- dates of all visits;
- documentation that protocol specific procedures were performed;
- results of efficacy parameters, as required by the protocol;
- start and end date (including dose regimen) of trial medication (preferably drug dispensing and return should be documented as well);
- record of all AEs and other safety parameters (start and end date, and preferably including causality and intensity);
- concomitant medication (including start and end date, dose if relevant; dose changes should be motivated);
- date of trial completion and reason for early discontinuation, if applicable.

All clinical study documents must be retained by the Principal Investigator until at least 2 years after the last approval of a marketing application in an ICH region (i.e., United States, Europe, or Japan) and until there are no pending or contemplated marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and regulatory authorities have been notified. The Principal Investigator may be required to retain documents longer if required by applicable regulatory requirements, by local regulations, or by an agreement with the Sponsor. The Principal Investigator must notify the Sponsor before destroying any clinical study records.

Should the Principal Investigator wish to assign the study records to another party or move them to another location, the Sponsor must be notified in advance.

If the Principal Investigator cannot guarantee this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the Principal Investigator and the Sponsor to store these in sealed containers outside of the site so that they can be returned sealed to the Principal Investigator in case of a regulatory audit. When source documents are required for the continued care of the participant, appropriate copies should be made for storage outside of the site.

Biological samples at the conclusion of this study may be retained in storage by the Sponsor for a period up to 10 years for purposes of this study.

13.1.6. Electronic Case Report Forms (eCRF)

For each participant enrolled, an eCRF must be completed and signed by the Principal Investigator or sub-investigator (as appropriate) within a reasonable time period after data collection. This also applies to records for those participants who fail to complete the study (even during the screening period if an eCRF was initiated). If a participant withdraws from the study, the reason must be noted on the eCRF. If a participant is withdrawn from the study because of a treatment-limiting AE, thorough efforts should be made to clearly document the outcome.

13.1.7. Drug Accountability

The Principal Investigator or designee (i.e., pharmacist) is responsible for ensuring adequate accountability of all used and unused investigational product. This includes acknowledgment of receipt of each shipment of study product (quantity and condition), participant dispensing records, and returned or destroyed study product. Dispensing records will document quantities received from the Sponsor and quantities dispensed to participants, including lot number, date dispensed, participant identifier number, and the initials of the person dispensing the medication.

At study initiation, the monitor will evaluate the site's standard operating procedure for investigational medicinal product disposal/destruction in order to ensure that it complies with the Sponsor requirements. Drug may be returned or destroyed on an ongoing basis during the study as appropriate. At the end of the study, following final drug inventory reconciliation by the monitor, the study site will return all unused investigational medicinal product supplies. If the site cannot meet the Sponsor's requirements for disposal, arrangements will be made between the site and the Sponsor or its representative for destruction or return of unused investigational medicinal product supplies.

All drug supplies and associated documentation will be periodically reviewed and verified by the study monitor over the course of the study.

13.1.8. Inspections

The Principal Investigator should understand that source documents for this trial should be made available to appropriately qualified personnel from the Sponsor or its

representatives, to IRBs or IECs, or to regulatory authority or health authority inspectors.

13.1.9. Protocol Compliance

The Principal Investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

13.2. Sponsor Responsibilities

13.2.1. Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to study participants, may be made only by the Sponsor.

13.2.2. Study Report and Publications

A clinical study report will be prepared and provided to the regulatory agency(ies). The Sponsor will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases.

13.2.3. Posting of Information on Publicly Available Clinical Trial Registers

Study information from this protocol will be posted on publicly available clinical trial registers within 21 days of enrollment of the first participant. Results will be posted as required.

13.3. Joint Investigator/Sponsor Responsibilities

13.3.1. Access to Information for Monitoring

In accordance with ICH Good Clinical Practice guidelines, the study monitor must have direct access to the Principal Investigator's source documentation in order to verify the data recorded in the eCRFs for consistency.

The monitor is responsible for routine review of the eCRFs at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor should have access to any participant records needed to verify the entries on the eCRFs. The Principal Investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

13.3.2. Access to Information for Auditing or Inspections

Representatives of regulatory authorities or of the Sponsor may conduct inspections or audits of the clinical study. If the Principal Investigator is notified of an inspection by a regulatory authority the Principal Investigator agrees to notify the Sponsor medical monitor immediately. The Principal Investigator agrees to provide to representatives of a regulatory agency or the Sponsor access to records, facilities, and personnel for the effective conduct of any inspection or audit.

13.3.3. Study Discontinuation

The Sponsor reserves the right to terminate the study at any time. Should this be necessary, the Sponsor will arrange discontinuation procedures and notify the appropriate regulatory authority (ies), IRBs, and IECs. In terminating the study, the Sponsor and the Principal Investigator will assure that adequate consideration is given to the protection of the participants' interests.

Reasons for stopping the study may include but are not limited to:

- New evidence that, in the opinion of the sponsor, makes continuation of the study unnecessary or unethical
- The sponsor discontinues development of RVT-1401
- Insufficient patient enrollment

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15. APPENDICES

15.1. Appendix 1: Abbreviations and Trademarks

Abbreviations

ADA	Anti-drug antibody
ADCC	Antibody dependent cell mediated cytotoxicity
AE	Adverse event
AESI	Adverse event of special interest
AIHA	Autoimmune hemolytic anemia
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BMI	Body mass index
BUN	Blood urea nitrogen
CI	Confidence intervals
CLL	Chronic lymphocytic leukemia
CO_2	Carbon dioxide
CPK	Serum creatine phosphokinase
CTCAE	Common Terminology Criteria for Adverse Events
DAT	Direct antiglobulin test
ECG	Electrocardiogram
eCRF	Electronic case report form
FcRn	fully human anti-neonatal FC receptor
FDA	U.S. food and drug administration
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GGT	Gamma glutamyltransferase
Hb	Hemoglobin
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
IB	Investigator's brochure
ICF	Informed consent form
ICH	International conference on harmonisation
IEC	Independent ethics committee
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IND	Investigational new drug
INR	International normalized ratio
IP	Investigational product
IRB	Institutional review board
ITP	Idiopathic thrombocytopenia purpura
ITT	Intent to treat
IUD	Intrauterine device

IUS	Intrauterine system
IV	Intravenous
IVIG	Intravenous immunoglobulin
IXRS	Interactive Response System
LDH	Lactate dehydrogenase
LLN	Lower limit of normal
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical dictionary for regulatory activities
MMF	Mycophenolate mofetil
MRC	Medical Research Council
MSDS	Material safety data sheet
NAb	Neutralizing Antibody
NAFLD	Non-alcoholic fatty liver disease
NSAID	Non-steroidal anti-inflammatory agents
PD	Pharmacodynamic
PE	Plasma exchange
PK	Pharmacokinetic
RBC	Red blood cell
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
SD	Standard deviation
SUSAR	Suspected unexpected serious adverse reactions
TB	Tuberculosis
TBL	Total bilirubin
ULN	Upper limit of normal
WAIHA	Warm autoimmune hemolytic anemia
WBC	White blood cell
WHO-DDE	World health organization drug dictionary enhanced

Trademark Information

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15.2. Appendix 2: Liver Laboratory Trigger and Liver Event Definitions and Follow-up Requirements

Table 4: Definitions of liver laboratory triggers and liver events

	Definition/ threshold
LIVER LABORATORY TRIGGERS	• ALT / AST 3x to ≤ 5x ULN • TBL 1.5x to ≤ 2 x ULN
LIVER EVENTS	• ALT or AST > 5 × ULN • ALP > 2 × ULN (in the absence of known bone pathology) • TBL > 2 × ULN (in the absence of known Gilbert syndrome) • ALT or AST > 3 × ULN and INR > 1.5 • Potential Hy's Law cases (defined as ALT or AST > 3 × ULN and TBL > 2 × ULN [mainly conjugated fraction] without notable increase in ALP to > 2 × ULN) • Any clinical event of jaundice (or equivalent term) • ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia • Any adverse event potentially indicative of a liver toxicity*

**These events include: hepatic failure, fibrosis, cirrhosis, and other liver damage-related conditions; non-infectious hepatitis; benign, malignant and unspecified liver neoplasms*
TBL: total bilirubin; ULN: upper limit of normal

Table 5: Follow up requirements for liver laboratory triggers and liver events

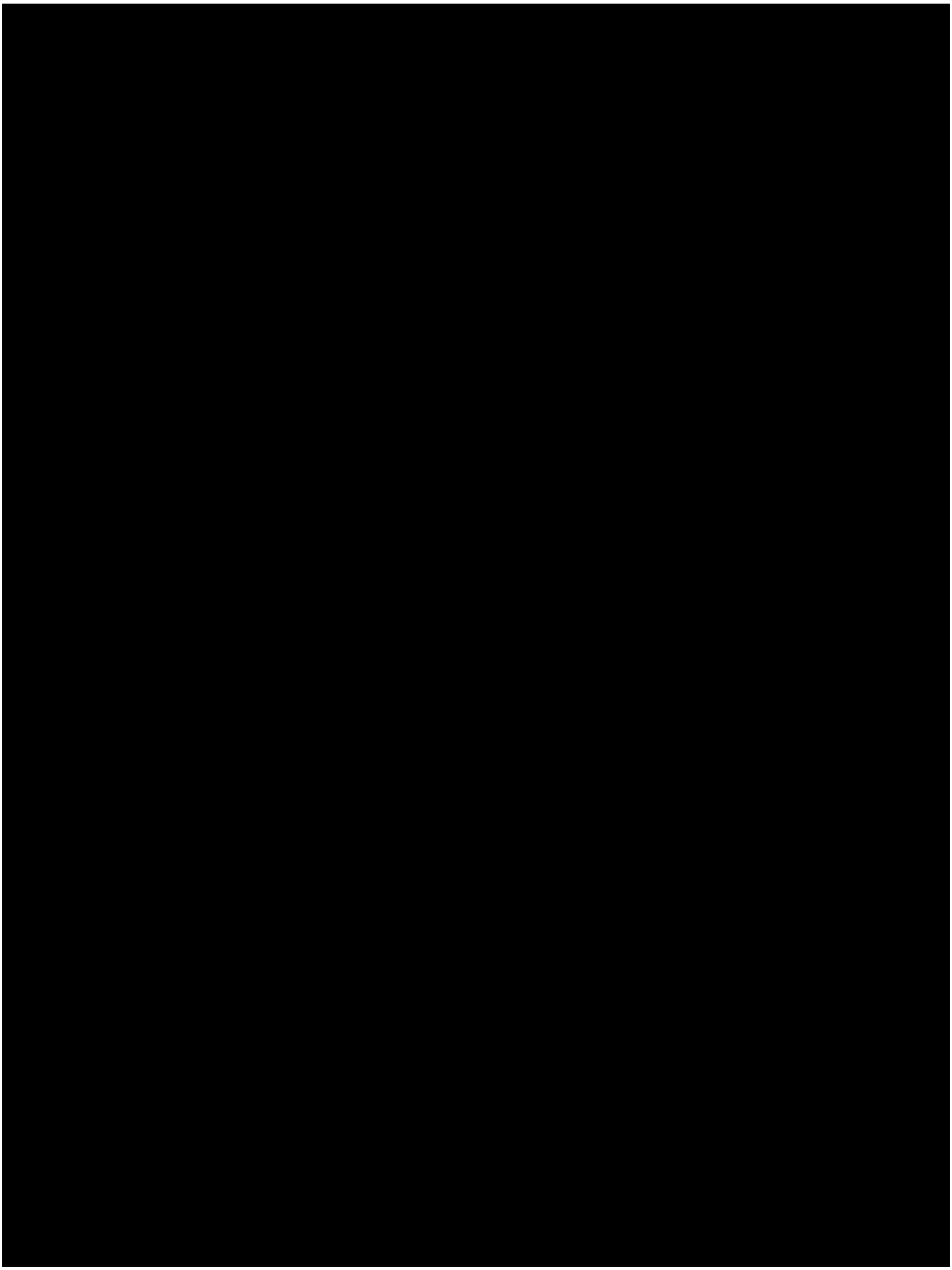
Criterion	***Actions required***	***Follow-up monitoring***
Potential Hy's Law case[a]	• Discontinue the study treatment immediately • Hospitalize, if clinically appropriate • Establish causality • Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate CRF	*ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution*[c] *(frequency at investigator discretion)*
ALT or AST		
> 8 × ULN	• Discontinue the study treatment immediately • Hospitalize if clinically appropriate • Establish causality • Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate CRF	*ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution*[c] *(frequency at investigator discretion)*
> 3 × ULN and INR > 1.5	• Discontinue the study treatment immediately • Hospitalize, if clinically appropriate • Establish causality • Record the AE and contributing factors (e.g., conmeds, med hx, lab)	*ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution*[c] *(frequency at investigator discretion)*

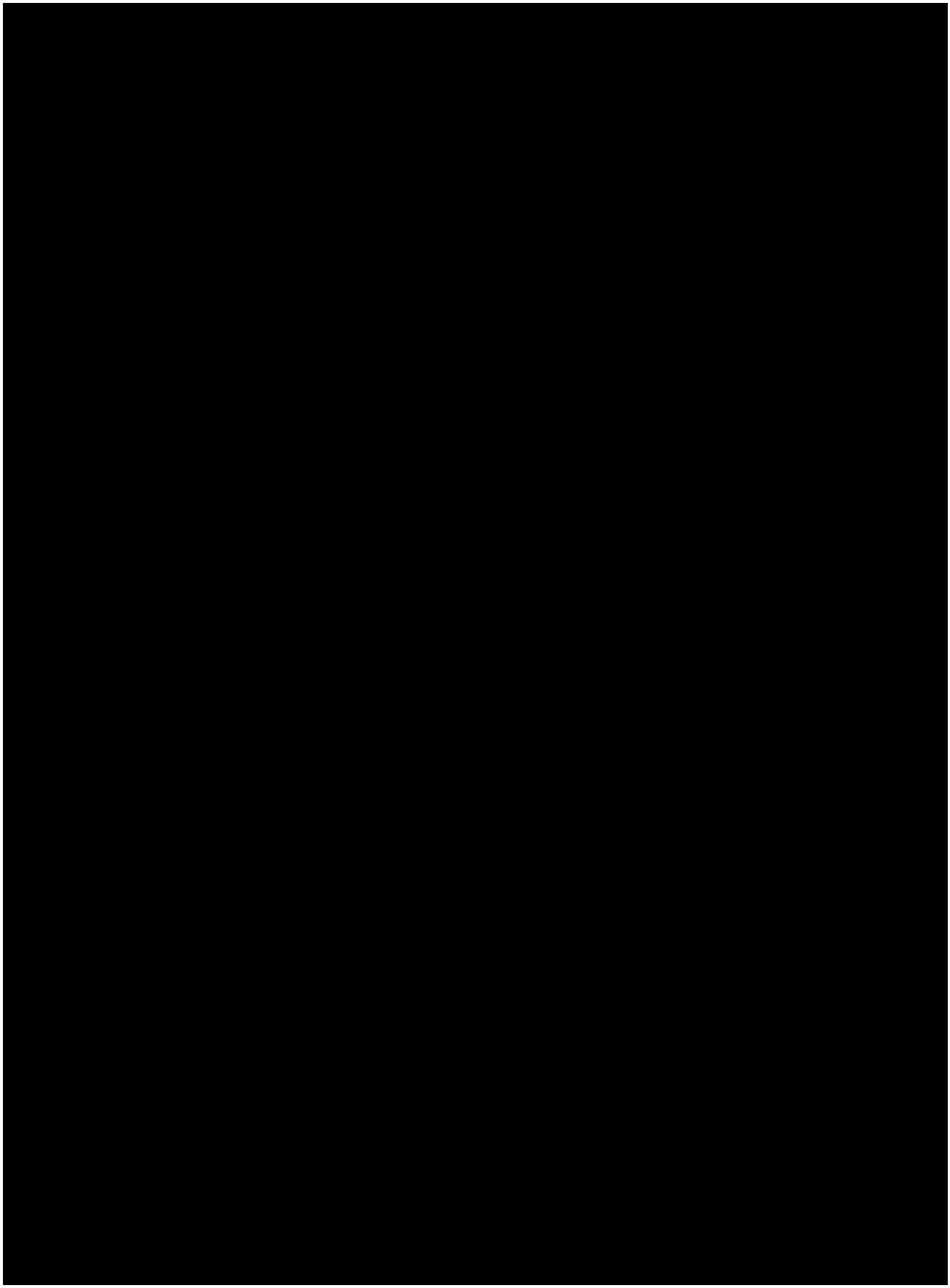
Criterion	***Actions required***	***Follow-up monitoring***
	in the appropriate CRF	
> 5 to ≤ 8 × ULN	• Repeat LFT within 48 hours • If elevation persists, continue follow-up monitoring • If elevation persists for more than 2 weeks, discontinue the study drug • Establish causality • Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate CRF	*ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)*
> 3 × ULN accompanied by symptoms[b]	• Discontinue the study treatment immediately • Hospitalize if clinically appropriate • Establish causality • Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate CRF	*ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)*
> 3 to ≤ 5 × ULN (subject is asymptomatic)	• Repeat LFT within the next week • If elevation is confirmed, initiate close observation of the *subject*	*Investigator discretion* *Monitor LFT within 1 to 4 weeks*
ALP (isolated)		
> 2 × ULN (in the absence of known bone pathology)	• Repeat LFT within 48 hours • If elevation persists, establish causality • Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate CRF	*Investigator discretion* *Monitor LFT within 1 to 4 weeks or at next visit*
TBL (isolated)		
> 2 × ULN (in the absence of known Gilbert syndrome)	• Repeat LFT within 48 hours • If elevation persists, discontinue the study drug immediately • Hospitalize if clinically appropriate • Establish causality • Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate CRF	*ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)* *Test for hemolysis (e.g., reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)*
> 1.5 to ≤ 2 × ULN (subject is asymptomatic)	• Repeat LFT within the next week • If elevation is confirmed, initiate close observation of the subject	*Investigator discretion* *Monitor LFT within 1 to 4 weeks or at next visit*
Jaundice	• Discontinue the study treatment immediately • Hospitalize the subject • Establish causality • Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate CRF	*ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)*
Any AE potentially indicative of a liver	• Consider study treatment interruption or discontinuation • Hospitalization if clinically	*Investigator discretion*

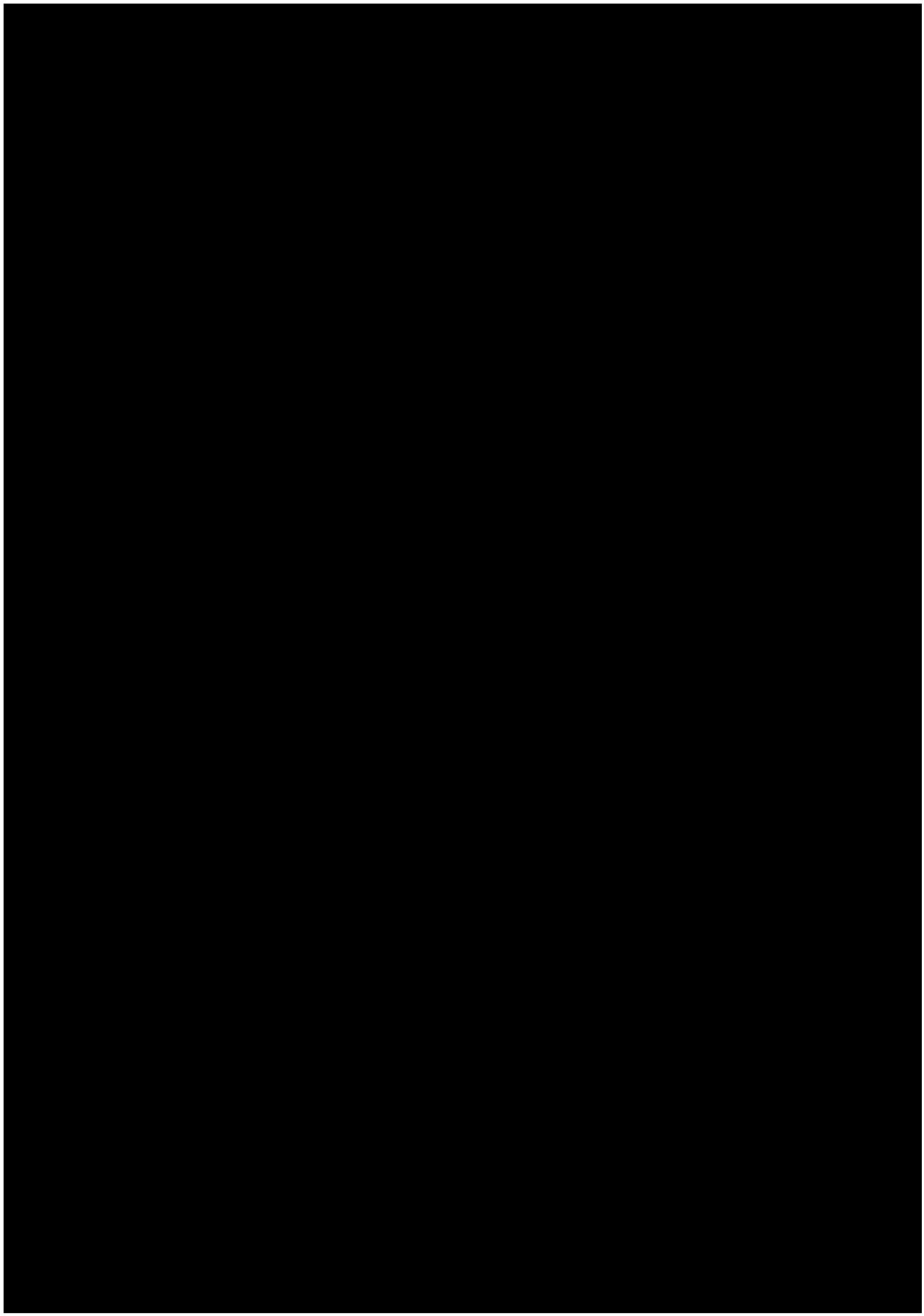
Criterion	***Actions required***	***Follow-up monitoring***
*toxicity**	appropriate • Establish causality • Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate CRF	

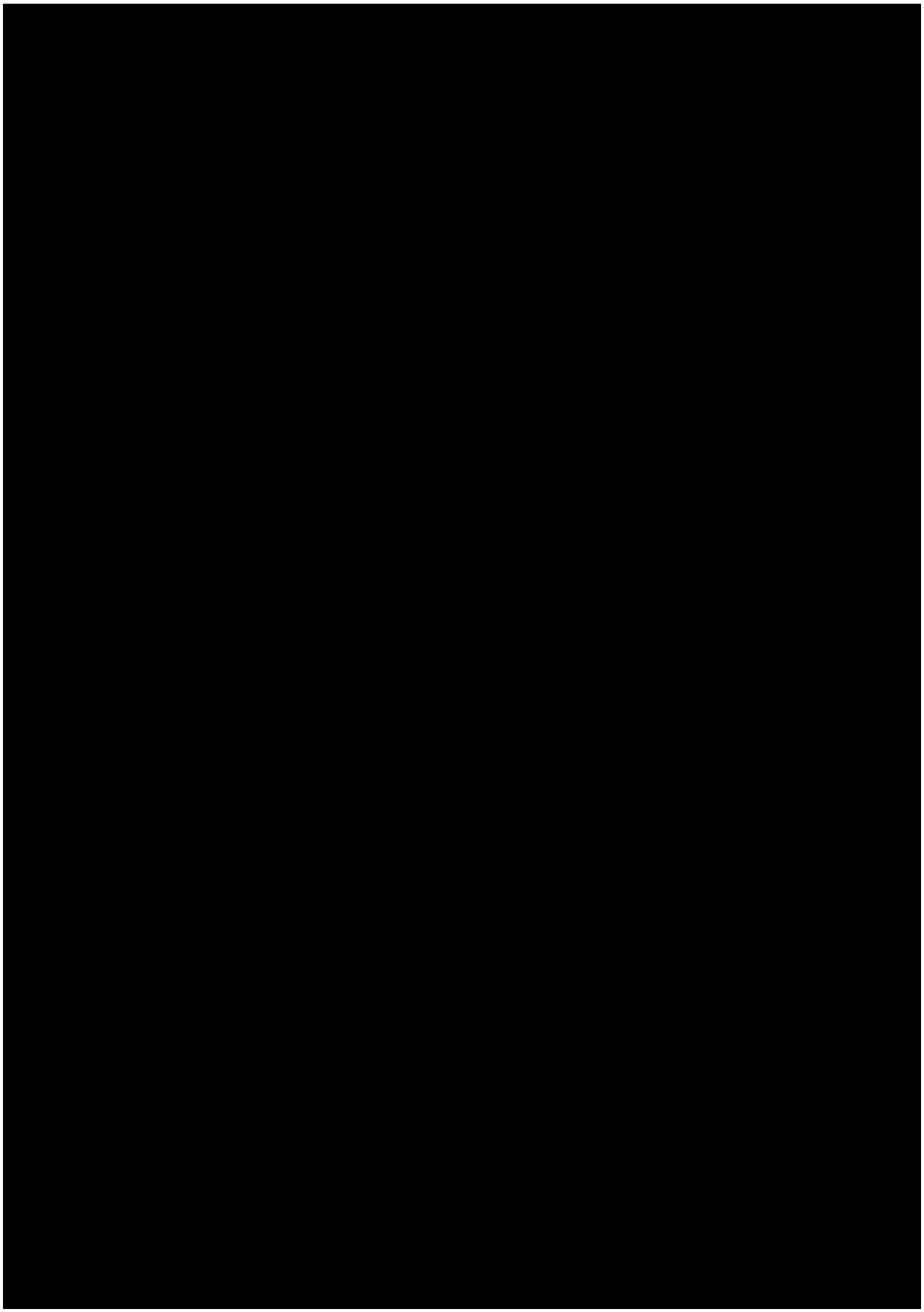
Elevated ALT/AST > 3 × ULN and TBL > 2 × ULN but without notable increase in ALP to > 2 × ULN [b](General) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia [c]Resolution is defined as one of the following: (1) return to baseline values, (2) stable values at three subsequent monitoring visits at least 2 weeks apart, (3) remain at elevated level after a maximum of 6 months, (4) liver transplantation, and (5) death.

At the investigator's discretion, investigation(s) for contributing factors to the liver event may include: serology tests, imaging, pathology assessments, hepatologist consultation; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, and exclusion of underlying liver disease.









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