TITLE PAGE

Protocol Title:		IMVT-1401-2501: A Proof-of-Concept, Open-label Study to Assess the Safety and Efficacy of Batoclimab in Participants with Graves' Disease (GD)	
Protocol Number:		IMVT-1401-2501	
Compound:		IMVT-1401 (batoclimab)	
Study Phase:		Phase 2a	
Short Title:		A Proof-of-Concept Study to Assess Batoclimab in Participants with Graves' Disease	
Sponsor	**Sponsor Name:**	Immunovant Sciences GmbH	
	Legal Registered Address:	Viaduktstrasse 8 4051 Basel Switzerland	
Regulatory Agency Identifier Number(s):		EudraCT: 2022-002894-27 EU CTIS: 2024-512647-23-00	
Protocol Date:		**Document Version**	**Date**
		V1.0	31 August 2022
		V2.0	13 March 2023
		V3.0	31 July 2023
		V4.0	10 August 2023
		V5.0 (Not Implemented)	15 December 2023
		V6.0	22 October 2024
		V7.0	12 November 2024
		V8.0	20 November 2024

CONFIDENTIALITY NOTICE

The information contained in this document, particularly unpublished data, is the property or under control of Sponsor, and is provided to you in confidence as an Investigator, potential Investigator or consultant, for review by you, your staff, and an applicable Institutional Review Board or Independent Ethics Committee. The information is only to be used by you in connection with authorized clinical studies of the investigational drug described in the protocol. You will not disclose any of the information to others without written authorization from Sponsor, except to the extent necessary to obtain informed consent from those persons to whom the drug may be administered.

INVESTIGATOR AGREEMENT

IMVT-1401-2501: A proof-of-concept, open-label study to assess the safety and efficacy of batoclimab in participants with Graves' disease (GD)

I have read the protocol, including all appendices, and I agree that it contains all the necessary information for me and my staff to conduct this study as described. I will conduct this study as outlined herein, in compliance with the Declaration of Helsinki, current Good Clinical Practice (GCP) standards as defined by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guideline for GCP, all applicable national, state, and local laws and regulations, and the applicable Institutional Review Board/Independent Ethics Committee (IRB/IEC) and other institutional requirements.

I also understand that this material contains confidential information belonging to Immunovant. Except as may be otherwise agreed to in writing, I agree to hold such information in confidence and not to disclose it to others (except where applicable by law) nor use it for unauthorized purposes. In the event of an actual or suspected breach of this obligation, Immunovant is to be promptly notified.

_____ _____

Principal Investigator Name (printed) Signature

_____ _____

Institution Address

_____

Date

CONTACT DETAILS OF KEY PERSONNEL

24-Hour contact for Serious Adverse Events (SAEs) See Section 6.4.5	PrimeVigilance Email: immunovant@primevigilance.com
Medical Monitor	[redacted] Office: [redacted] Mobile: [redacted] Email: [redacted]
Contract Research Organization Contact(s)	EastHORN Clinical Services in CEE Obilicev venac 15 11000 Belgrade, Serbia [redacted]
Sponsor Clinical Research Contact(s)	[redacted] [redacted] Mobile: [redacted] Email: [redacted] [redacted] [redacted] Mobile: [redacted] Email: [redacted]

1. PROTOCOL SUMMARY

1.1. Synopsis

Study Title	A Proof-of-Concept, Open-label Study to Assess the Safety and Efficacy of Batoclimab in Participants with Graves' Disease (GD)
Protocol Number	IMVT-1401-2501
EU CTIS	2024-512647-23-00
Phase of Development	Phase 2a
Investigational Product	Batoclimab: fully human anti-neonatal fragment crystallizable receptor (FcRn) monoclonal antibody
Auxiliary Medicinal Product(s)	Antithyroid drugs (ATD)
Objectives	**Primary Objective:** • To investigate the effects of batoclimab on thyroid hormone levels in participants with GD as assessed by reduction of free triiodothyronine (FT3) and free thyroxine (FT4) at Week 24 **Secondary Objectives:** • To investigate the effects of batoclimab on thyroid hormone levels in participants with GD as assessed by reduction of FT3 and FT4 and changes in ATD at Week 24 • To investigate the effects of batoclimab on thyroid hormone levels in participants with GD as assessed by reduction of FT3 and FT4 at Week 24 and ATD treatment [redacted]

Methodology/Study Design	Study IMVT-1401-2501 is a Phase 2a, proof-of-concept, open-label study designed to assess the safety and efficacy of batoclimab in adult participants with biochemically documented hyperthyroidism due to GD who have failed to achieve euthyroidism on ATD. **Screening Period** Only participants meeting all inclusion criteria and no exclusion criteria will be enrolled in the study. [redacted] **Twenty-four-Week Treatment Period** Approximately 35 participants who meet eligibility criteria will receive open-label batoclimab 680 mg subcutaneously (SC) weekly (QW) for 12 weeks ([redacted] followed by open-label batoclimab 340 mg SC QW for 12 weeks ([redacted] [redacted] **Four-Week Safety Follow-up Period** Participants who discontinue prematurely during the 24-Week Treatment Period, [redacted] will undergo a safety follow-up visit 4 weeks after the last dose of batoclimab.
Number of Subjects	Approximately 35 participants
Study Sites	Single site with the option to open additional sites during the study enrollment period
Randomization	Not applicable
Duration of Treatment	The study includes up to a 4-week screening period, an open-label treatment period of [redacted]
Population	The study population will consist of participants 18 years and older who have GD.
Criteria for Eligibility	**Inclusion Criteria:** Participants must meet all the following criteria to be eligible for inclusion in the study: 1. Have a serologically confirmed GD as documented by presence of elevated stimulatory TSH-R-Ab level (i.e., > SRR 140 %) at the Screening Visit. 2. Have active hyperthyroidism due to GD with the following laboratory values at the Screening Visit: • TSH < lower limit of normal (LLN) • FT3 > upper limit of normal (ULN) and ≤5× ULN • FT4 > ULN and ≤5 × ULN

Note: Participants who have T3 thyrotoxicosis (i.e., TSH <ULN, FT3 > ULN and ≤5× ULN, but FT4 within normal range) at the Screening Visit may be enrolled, if they have serologically confirmed GD as per Inclusion Criterion 1.

3. Meet all of the following ATD requirements at the Screening Visit:
   - Have been on an ATD for ≥12 weeks before the Screening Visit.
   - Had starting total daily ATD dose of ≥20 mg of methimazole or carbimazole, or ≥200 mg of propylthiouracil.
   - Are currently treated with a total daily dose of ≥10 mg of methimazole or carbimazole, or ≥100 mg of propylthiouracil.
4. Are willing and capable of giving written informed consent, which includes being able to comply with all aspects of the study treatment and testing schedule.
5. Are willing to not participate in another interventional study while in this study.
6. Are ≥18 years of age at the Screening Visit.

[redacted]

Exclusion Criteria:

Participants are excluded from the study if any of the following criteria apply:

10. Have a history of hyperthyroidism not caused by GD (e.g., toxic adenoma or toxic multinodular goiter), and/or history or presence of thyroid storm.
11. Have a history of treatment with radioactive iodine or thyroid surgery.

    Note: Participants may be enrolled if they meet Inclusion Criteria 2 and 3.
12. Have a total immunoglobulin G level <6 g/L at the Screening Visit.
13. Have an albumin level <3.5 g/dL (<35 g/L) at the Screening Visit.

[redacted]

[redacted]

15. Have an absolute neutrophil count <1000 cells/mm^3 at the Screening Visit.

[redacted]

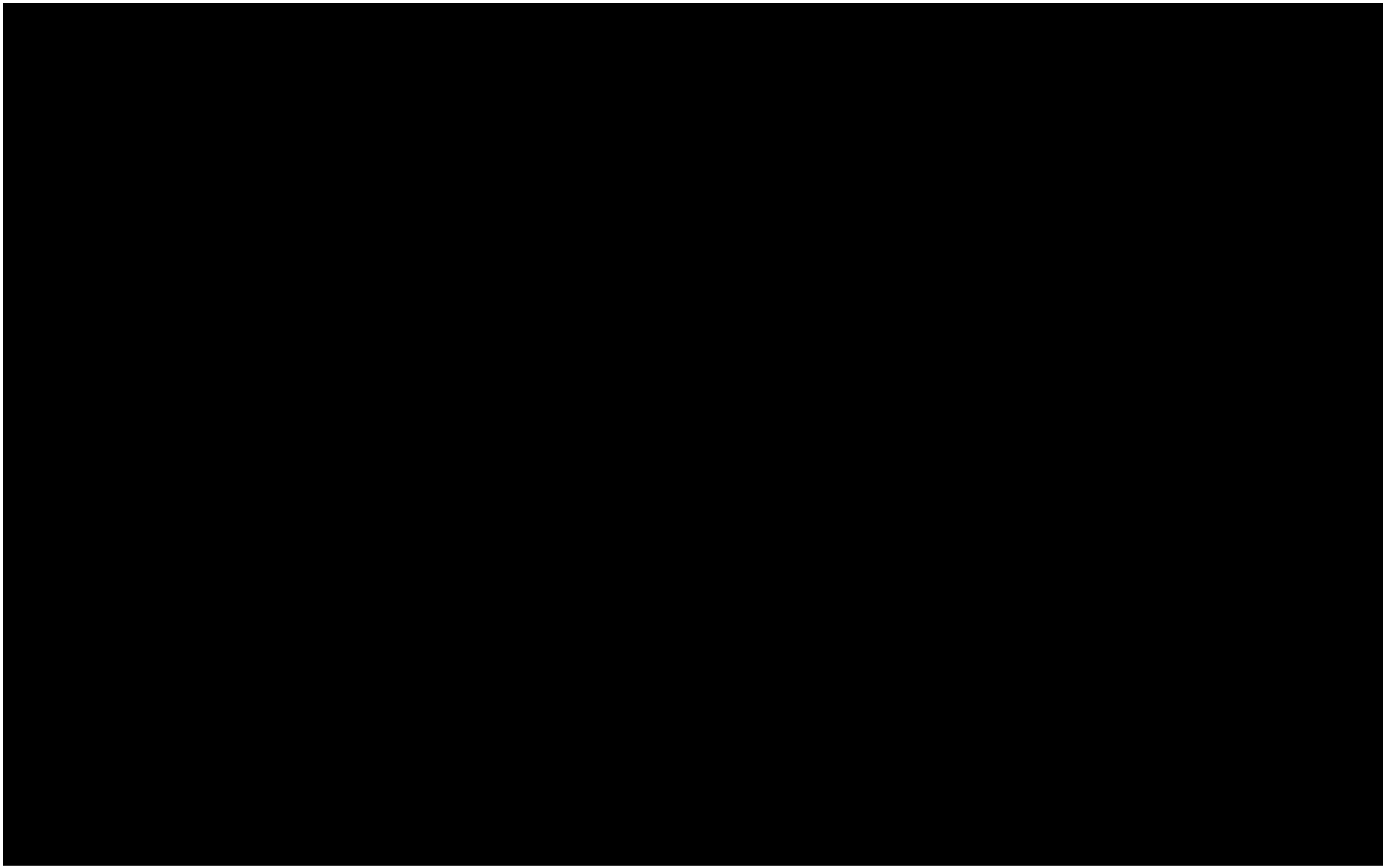
	[redacted]
	40. Have been enrolled in a previous RVT-1401 or IMVT-1401 clinical trial. Note: Participants previously enrolled in an IMVT-1401 clinical trial, with documented assignment to placebo treatment only, may be enrolled in this study.

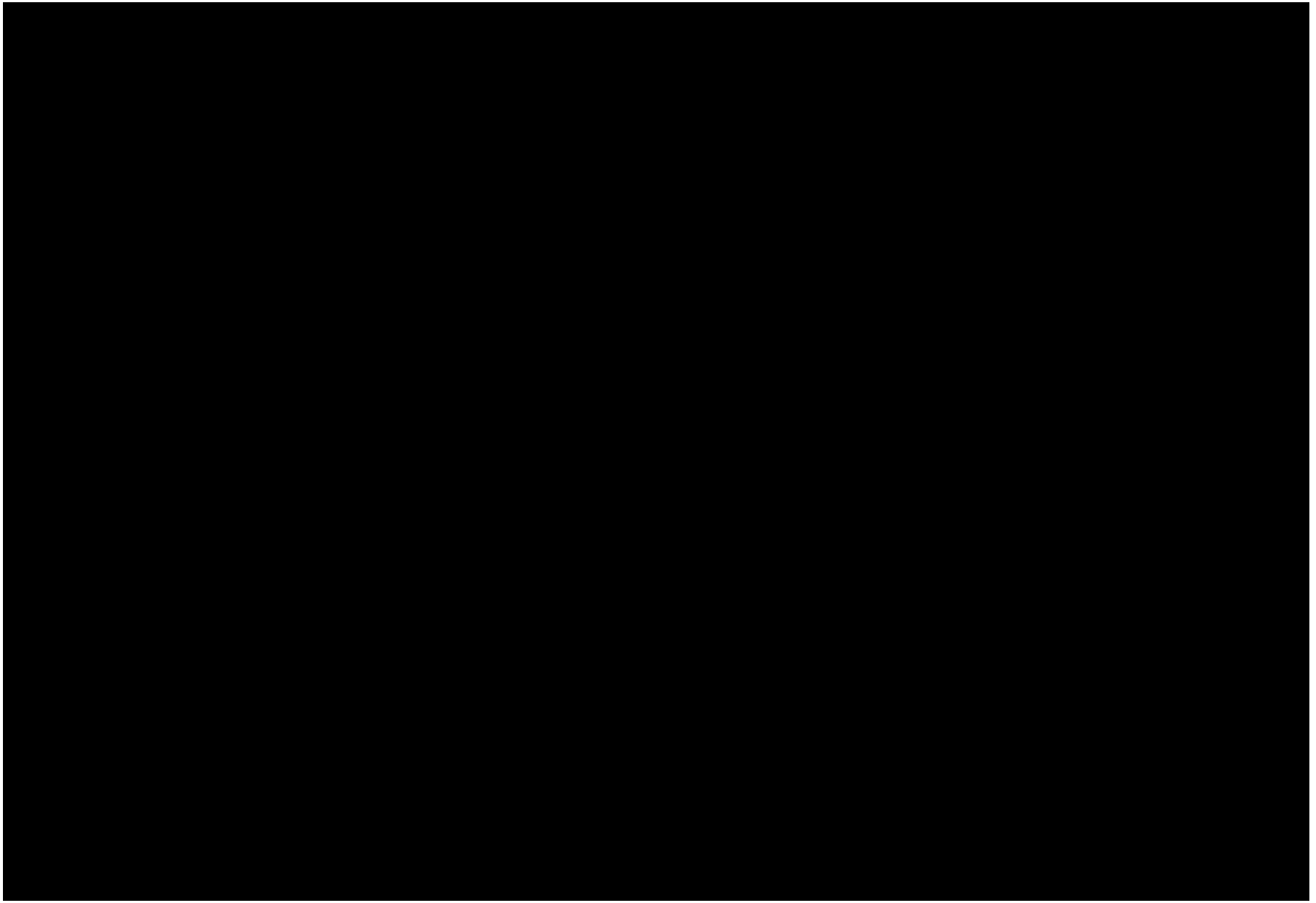
	41. [redacted]
Concomitant Medications	Concomitant medications will be documented for each participant at each scheduled visit from the time of informed consent through the last follow-up visit. [redacted]
[redacted]	
Criteria for Evaluation – Efficacy and Pharmacodynamics	**Primary:** Proportion of participants who at Week 24, without increase in ATD dose compared to baseline, have achieved normalization of FT3 and FT4, or have FT3 and/or FT4 below the LLN. **Secondary:** 1. Proportion of participants who achieve normalization of FT3 and FT4 at Week 24 with ATD dose ≤50% of the baseline ATD dose by Week 24 2. Proportion of participants who are off ATD treatment and achieve normalization of FT3 and FT4, or have FT3 and/or FT4 below the LLN at Week 24
	[redacted]

[redacted]

Statistical Methods	[redacted] The primary efficacy endpoint of the study is the proportion of participants who at Week 24, without increase in ATD dose compared to baseline, have achieved normalization of FT3 and FT4, or have FT3 and/or FT4 below the LLN. [redacted]

[redacted]









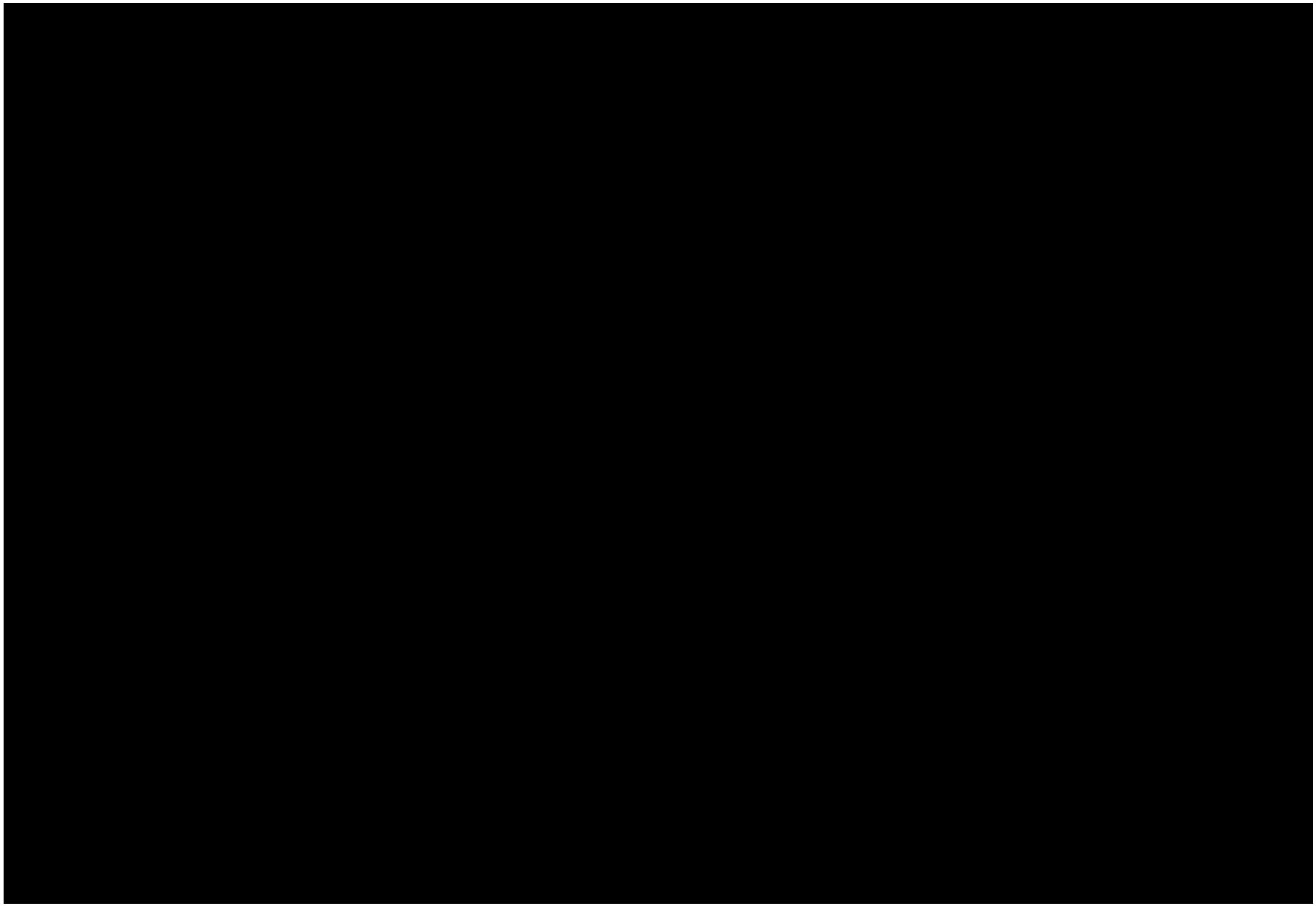




TABLE OF CONTENTS

TITLE PAGE 1
INVESTIGATOR AGREEMENT 2
CONTACT DETAILS OF KEY PERSONNEL 3
1. PROTOCOL SUMMARY 4
1.1. Synopsis 4
[redacted]
TABLE OF CONTENTS 17
LIST OF TABLES 22
LIST OF FIGURES 22
1.4. Abbreviations 23
2. INTRODUCTION 27
2.1. Study Rationale 27
2.2. Background 28
2.2.1. Disease Background 28
2.2.2. Investigational Product Background: Batoclimab 30
[redacted]
2.3. Benefit/Risk Assessment 32
[redacted]
2.3.2. Benefit Assessment 35
2.3.3. Overall Benefit: Risk Conclusion 39
2.4. Study Objectives and Endpoints 40
2.4.1. Primary 40
2.4.2. Secondary 40
[redacted]
2.5. Study Design and Dose Rationale 42
2.5.1. Overall Design 42
2.5.1.1. Screening Period 42
2.5.1.2. Twenty-four-Week Treatment Period 42

[redacted]

2.5.1.4. Four-Week Safety Follow-up Period....43

[redacted]

2.6. End of Study....44
3. STUDY POPULATION....45
3.1. Inclusion Criteria....45
3.2. Exclusion Criteria....46
3.3. Screen Failures and Rescreening....49
4. STUDY TREATMENT(S)....50
4.1. Study Treatment Administered....50
4.1.1. Investigational Product....50
4.1.1.1. Planned Study Treatments....50
4.1.1.2. Identity of Investigational Product....50
4.1.1.3. Preparation/Handling/Storage/Accountability....50
4.1.2. Comparator Product(s)....51

[redacted]

4.3. Study Treatment Compliance....54
4.4. Concomitant Therapy....54

[redacted]

5. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL....56
5.1. Discontinuation of Study Treatment....56
5.1.1. Individual Stopping Criteria....56
5.1.1.1. Liver Enzyme Stopping Criteria....56

[redacted]

5.2. Discontinuation/Withdrawal from the Study....58
5.3. Lost to Follow-up....59
6. STUDY ASSESSMENTS AND PROCEDURES....60

6.1. Study Periods 60
6.1.1. Screening 60
[redacted]
6.1.4. End of Study Visit 61
[redacted]
6.2.1. Laboratory Assessments 62
[redacted]
6.3. Safety Assessments 63
6.3.1. Concomitant Medications 63
6.3.2. Physical Examinations 64
6.3.3. Vital Signs 64
6.3.4. Electrocardiograms 64
6.3.5. Clinical Safety Laboratory Assessments 64
6.3.6. Adverse Events 65
6.4. Adverse Events and Other Safety Aspects 65
6.4.1. Definition of Adverse Events 65
6.4.2. Criteria for Defining the Severity of an Adverse Event 66
6.4.3. Criteria for Causal Relationship to the Study Treatment 66
6.4.4. Definition of a Serious Adverse Event 67
6.4.5. Reporting of Serious Adverse Events (SAEs) 68
6.4.6. Follow-up of Adverse Events and Serious Adverse Events 69
6.4.7. Pregnancy 69
[redacted]
6.5. Treatment of Overdose 70
6.6. Product Quality Complaints and Medical Device Reporting 70

6.7. Pharmacokinetics 71
[redacted]
7. STATISTICAL CONSIDERATIONS 72
[redacted]
7.3. Study Analysis Populations 73
[redacted]
7.4. Disposition, Demographic, and Baseline Data 73
7.4.1. Participant Disposition 73
7.4.2. Demographic and Baseline Characteristics 73
[redacted]
7.5.3. Subgroup Analyses 74
7.6. Safety Analysis 74
7.6.1. Safety Variables of Analysis 74
7.6.1.1. Adverse Events 74
7.6.1.2. Vital Signs 75
7.6.1.3. Clinical Laboratory 75
7.6.1.4. Electrocardiography 76
7.7. Other Analyses 76
7.7.1. Pharmacokinetic Data 76
[redacted]
7.7.3. Interim Analysis 76
7.7.4. Handling of Missing Data 76
8. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS 77
8.1. Regulatory, Ethical, and Study Oversight Considerations 77

8.1.1. Regulatory and Ethical Considerations 77
8.1.2. Financial Disclosure 78
8.1.3. Informed Consent Process 78
8.1.3.1. Supply of New and Important Information Influencing the Participant's Consent and Revision of the Written Information 78
8.1.4. Data Protection 79
8.1.5. Notification of Serious Breach 80
8.1.6. Data Management 80
8.1.7. Clinical Monitoring 81
8.1.8. Protocol Deviations 81
8.1.9. Source Documents 82
8.1.10. Quality Assurance 82
8.1.11. Study and Site Start and Closure 82
8.1.12. Publication Policy 83
9. REFERENCES 84
Appendix A: Clinical Laboratory Tests 87
[redacted]
Appendix D: Collection of Pregnancy Information 97
Appendix E: Liver Safety Required Actions and Follow up Assessments 98
[redacted]

LIST OF TABLES

[redacted]

Table 5. NCI-CTCAE Guidelines (Version 5.0) Criteria 66
Table 6. Criteria for Causal Relationship 66

[redacted]

Table 9. Definition of Liver Enzyme Abnormality Stopping Criteria / Additional Monitoring Criteria 98
Table 10. Follow-up Requirements for Liver Enzyme Abnormalities 99

LIST OF FIGURES

Figure 1. Study Schema 11

[redacted]

1.4. Abbreviations

Abbreviation	Definition
Ab	Antibody
ADA	Antidrug antibody
ADCC	Antibody-dependent cell-mediated cytotoxicity
AE	Adverse event
[redacted]	
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
Anti-TSH-R	Anti-thyrotropin receptor
[redacted]	
AST	Aspartate aminotransferase
ATD	Antithyroid drug
[redacted]	
CAS	Clinical activity score
CDC	Complement-dependent cytotoxicity
CI	Confidence interval
[redacted]	
CRO	Contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
CTR	Clinical Trials Regulation
CV	Coefficient of variation
d/D	Day
DILI	Drug-induced liver injury
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
[redacted]	
ED	Early discontinuation
eGFR	Estimated glomerular filtration rate
EU	European Union
EU CTIS	European Union Clinical Trials Information System
Fc	Crystallizable fragment

Abbreviation	Definition
FcRn	Neonatal fragment crystallizable receptor
FDA	Food and Drug Administration
[redacted]	
FT3	free triiodothyronine
FT4	free thyroxine
GCP	Good Clinical Practice
GD	Graves' disease
GGT	Gamma-glutamyl transferase
[redacted]	
ICF	Informed Consent Form
ICH	International Council for Harmonisation/International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
[redacted]	
IgG	Immunoglobulin G
IgG1/2/3/4	Immunoglobulin G1/2/3/4
IgM	Immunoglobulin M
[redacted]	
INR	International normalized ratio
IRB	Institutional Review Board
[redacted]	
ITT	Intent-to-Treat
IV	Intravenous(ly)
[redacted]	
LFT	Liver function test
LLN	Lower limit of normal
LSM	Least square means

Abbreviation	Definition
mAb	Monoclonal antibody
[redacted]	
MedDRA	Medical Dictionary for Regulatory Activities
MG	Myasthenia gravis
[redacted]	
NCI	National Cancer Institute
OR	Odds ratio
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
[redacted]	
PPD	Purified protein derivative
PT	Prothrombin time
Q1/Q3	First quartile/third quartile
QoL	Quality of life
QTcF	QT correction with Fridericia's formula
QTL	Quality tolerance limit
QW	Once a week (or weekly)
RAI	Radioactive iodine
RBC	Red blood cell
SAE	Serious adverse event
[redacted]	
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SC	Subcutaneous(ly)
SCR	Screening
SD	Standard deviation
SE	Standard error
[redacted]	

Abbreviation	Definition
SOC	System organ class
SOP	Standard operating procedure
SRM	Study reference manual
SRR	Specimen to reference ratio
SUSAR	Suspected unexpected serious adverse reaction
TBL	Total bilirubin
TEAE	Treatment-emergent adverse event
TED	Thyroid eye disease
Tg	Thyroglobulin
Tg-Ab	Thyroglobulin antibody
[redacted]	
TPO	Thyroid peroxidase
TPO-Ab	Thyroid peroxidase antibody
TSH	Thyrotropin
TSH-R	Thyrotropin receptor
TSH-R-Ab	Thyrotropin receptor antibody
ULN	Upper limit of normal
V	Visit
wAIHA	Warm autoimmune hemolytic anemia
WBC	White blood cell
Wk	Week
[redacted]	

2. INTRODUCTION

2.1. Study Rationale

Graves' disease (GD) is an autoimmune disease that represents the most common cause of hyperthyroidism. It is characterized by the infiltration of immune effector cells and thyroid-antigen–specific T cells in the thyroid and tissues expressing the thyrotropin receptor (TSH-R). The production of autoantibodies to well-defined thyroidal antigens, such as thyrotropin receptor antibodies (TSH-R-Abs), subsequently induces the production and release of thyroid hormone, the proliferation of the thyrocytes, and further enlargement of the thyroid gland (Ross 2016). These autoantibodies are characterized for being functionally significant, given that they can either act as agonists that stimulate thyroid growth, antagonists that block the activity of thyrotropin (TSH; blocking TSH-R-Ab), or being functionally inactive (neutral immunoglobulins). TSH-R stimulatory antibodies are the causative agent of GD in patients with hyperthyroidism, constituting a specific biomarker of GD (Ross 2016, Kahaly, et al., 2018, Davies, et al., 2020).

Pharmacological treatment options for the treatment of GD are limited to thionamide antithyroid drugs (ATDs), which block thyroid hormone synthesis. Unfortunately, these have remained largely unchanged for several decades despite their limited efficacy, with half of adults either experiencing relapse after stopping ATD or remaining at high risk of relapse while on ATD due to persistence of stimulating TSH-R antibodies. Targeting the direct cause of hyperthyroidism in GD using TSH-R specific modalities provides a targeted approach to the autoimmune etiopathogenesis.

Batoclimab (formerly RVT-1401) is a fully human monoclonal antibody (mAb) in the form of immunoglobin G1 (IgG1) with 2 γ heavy chains and 2 λ light chains, linked by disulfide bonds. [redacted] Batoclimab has high affinity and specificity for the immunoglobulin G (IgG) binding site on the neonatal fragment crystallizable receptor (FcRn). By competitively binding with IgG for this binding site on FcRn, batoclimab blocks the FcRn-mediated recycling of IgG, resulting in increased lysosomal catabolism and decreased levels of circulating IgG, thereby also reducing pathological antibodies responsible for various autoimmune disorders, such as GD. In a 12-week double-blind, placebo-controlled Phase 2b study (Study RVT-1401-2001) in euthyroid participants with active moderate to severe thyroid eye disease (TED), batoclimab administered subcutaneously (SC) at weekly (QW) doses of 255, 340, and 680 mg, led to dose-dependent decreases in both total (binding) anti-TSH-R antibodies and stimulatory anti-TSH-R antibodies, which were greater in all groups compared to placebo.

The purpose of this Phase 2a, proof-of-concept open-label study is to assess the efficacy and safety of [redacted] treatment with batoclimab in participants with hyperthyroidism and at the time of screening have failed treatment with ATD. [redacted]

[redacted]

[redacted]

2.2. Background

2.2.1. Disease Background

Graves' disease is an autoimmune disorder that affects 2% to 3% of the adult population (NORD).

The disease is characterized by hyperthyroidism, diffuse goiter, and often ophthalmopathy (Weetman, 2000). The complications of untreated hyperthyroidism include weight loss, osteoporosis, fragility fractures, atrial fibrillation, embolic events, and cardiovascular dysfunction (Bartalena, 2013, Biondi and Kahaly, 2010).

The underlying pathogenesis of GD is the loss of immunological tolerance to the TSH-R leading to the production of TSH-R-Abs that bind to the receptor located on the surface of the thyrocytes. There are 3 types of TSH-R-Abs: stimulating TSH-R-Ab, blocking TSH-R-Ab, and neutral antibodies. Each of these shows a different degree of affinity for TSH-R, inducing different degrees and types of thyroid dysfunction. In particular, stimulating TSH-R-Ab, which are predominantly of the IgG1 isotype, bind to the receptor and activate the 3′,5′-cyclic adenosine 5′-monophosphate pathway, thus inducing thyroid growth and increasing thyroid hormone production (Morshed and Davies, 2015).

For the treatment of GD, there are 3 options that are effective and have an established safety profile: thyroidectomy, radioactive iodine (RAI) treatment, or ATD. Surgery involves removal of the thyroid, and RAI destroys the thyroid because ionizing radiation causes deoxyribonucleic acid (DNA) damage. Since surgery is anatomically invasive and RAI is accompanied by exposure to radiation, both are considered more aggressive treatments than ATD. Furthermore, in addition to their invasiveness, the requirement for lifelong thyroid hormone replacement therapy after RAI and surgery leads to a preference for ATD as a primary therapy in Asia, Latin America, and Europe (Kahaly, et al., 2018, Ross 2016). In the United States, RAI has been the therapy most preferred by physicians, but a trend in recent years is to increase the use of ATD and reduce the use of RAI. This is mainly because RAI is associated with sustained increases in TSH-R-Ab titers and risk for de novo Graves' ophthalmopathy and worsening of pre-existing ophthalmopathy.

The main ATDs are thionamides, such as propylthiouracil, carbimazole, and the active metabolite of the latter, methimazole. Antithyroid drug therapy is indicated as a first-line treatment of GD, particularly in younger subjects, and for short-term treatment of GD before RAI therapy or thyroidectomy (Bartalena, 2013, Davies, et al., 2020). All inhibit the function of thyroperoxidase, reducing oxidation and the organification of iodide. Although ATD does not cure Graves' hyperthyroidism, when given in adequate doses, it is very effective in controlling the hyperthyroidism. The treatment itself might have a beneficial immunosuppressive role, either to primarily decrease thyroid-specific autoimmunity, or secondarily, by ameliorating the hyperthyroid state, which may restore the dysregulated immune system back to normal (Laurberg, 2006). In fact, the rate of remission with ATD therapy is much higher (Abraham 2010) than the historical rates of spontaneous remission (Mazzaferri 1976).

Antithyroid drug therapy reduces TSH-R-Ab levels and enhances rates of remission compared to no therapy. A substantial proportion of patients achieve euthyroidism within 3 to 4 weeks of treatment. Thyrotropin levels often remain suppressed for several months and therefore do not provide a sensitive index of early treatment response. The usual daily maintenance doses of ATD in the titration regimen are 2.5 to 10 mg of methimazole and 50 to100 mg of propylthiouracil.

Treatment with ATD is usually administered for 12 to 18 months according to the American and European guidelines (Abraham 2010, Ross 2016, Kahaly, et al., 2018) with remission rates of 50% to 55% achieved within this period.

Common side effects of ATD are rash, urticaria, and arthralgia. Rare but major side effects include hepatitis; a lupus-like syndrome; and agranulocytosis (neutrophil count <500/mL), which occurs in 0.1% to 1.0% of cases (Yang 2016, Nakamura, et al., 2013). In a study comprising 71,379 ATD initiators (Wang 2014), methimazole was associated in a dose-dependent manner with an increased risk for hepatitis and cholestasis. Antithyroid drug therapy is stopped and not restarted if a patient develops major side effects.

It is recommended to stop the measurement of TSH-R-Ab levels before ATD therapy, as it aids in predicting which patients can be weaned from the medication, with normal levels indicating a greater chance of remission (Ross 2016, Bartalena 2016). Hence, discontinuation of ATD therapy is indicated after reaching both euthyroidism and serological conversion (negative TSH-R-Ab testing). Patients with persistently high TSH-R-Ab at 12 to 18 months can continue methimazole therapy, repeating the TSH-R-Ab measurement after an additional 12 months, or opt for RAI or thyroidectomy.

Relapse is most likely within the first 6 to 12 months after ATD withdrawal but may occur years later. A meta-analysis (Sundaresh 2013) has confirmed the high relapse rate after ATD therapy (52.7%) in comparison with RAI (15%, odds ratio [OR] 6.25) or surgery (10%, OR 9.09), along with a significant rate of adverse effects for ATDs (13%). Another meta-analysis evaluating 54 trials and 7,595 participants showed several risk factors predicting persistence (49%) in GD (Struja 2017). Several factors predict to a certain extent the likelihood of recurrence after ATD. Young age (<40 years), orbitopathy, smoking, large thyroid volume, TSH-R-Ab, and biochemically more severe disease with high free thyroxine (FT4) and total triiodothyronine (T3), were significantly associated with relapse. In a prospective study introducing the quantitative predictive “GREAT” score for GD (Vos 2016), 37% of patients with a first episode of Graves’ hyperthyroidism relapsed within 2 years after ATD withdrawal. Lower age, higher serum TSH-R-Ab and FT4, and larger goiters at diagnosis were independent predictors for recurrence.



Collectively, these data suggest that a treatment for GD targeting the reduction or elimination of circulating stimulating TSH-R-Ab would address the underlying autoimmune pathogenesis of the disease and would restore normal thyroid function.

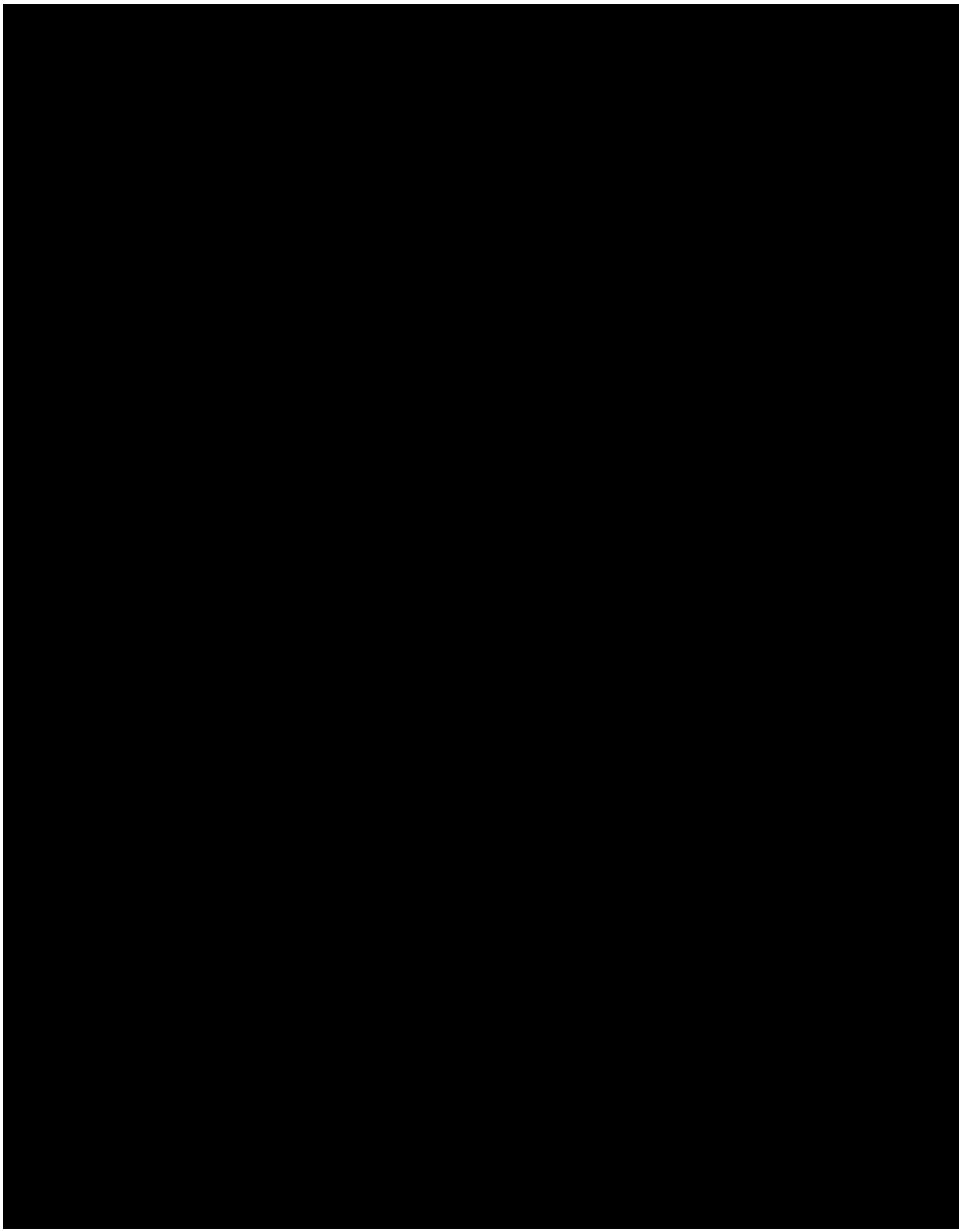
2.2.2. Investigational Product Background: Batoclimab

Targeting the FcRn pathway has been shown to substantially reduce circulating IgG, thus supporting its use in the treatment of autoantibody-mediated autoimmune diseases. Batoclimab functions by inhibiting the binding of IgG to FcRn, resulting in the rapid catabolism of IgG via lysosomal degradation (Pyzik 2019).



Clinical studies in healthy volunteers and participants with autoimmune disease demonstrated rapid decreases in serum IgG levels and levels of pathologic autoantibodies after administration of batoclimab. Due to its ability to reduce IgG, batoclimab is being developed for the treatment of several IgG autoantibody-mediated organ-specific autoimmune diseases (i.e., myasthenia gravis [MG], TED, and warm autoimmune hemolytic anemia [wAIHA]).





[redacted]

2.3. Benefit/Risk Assessment

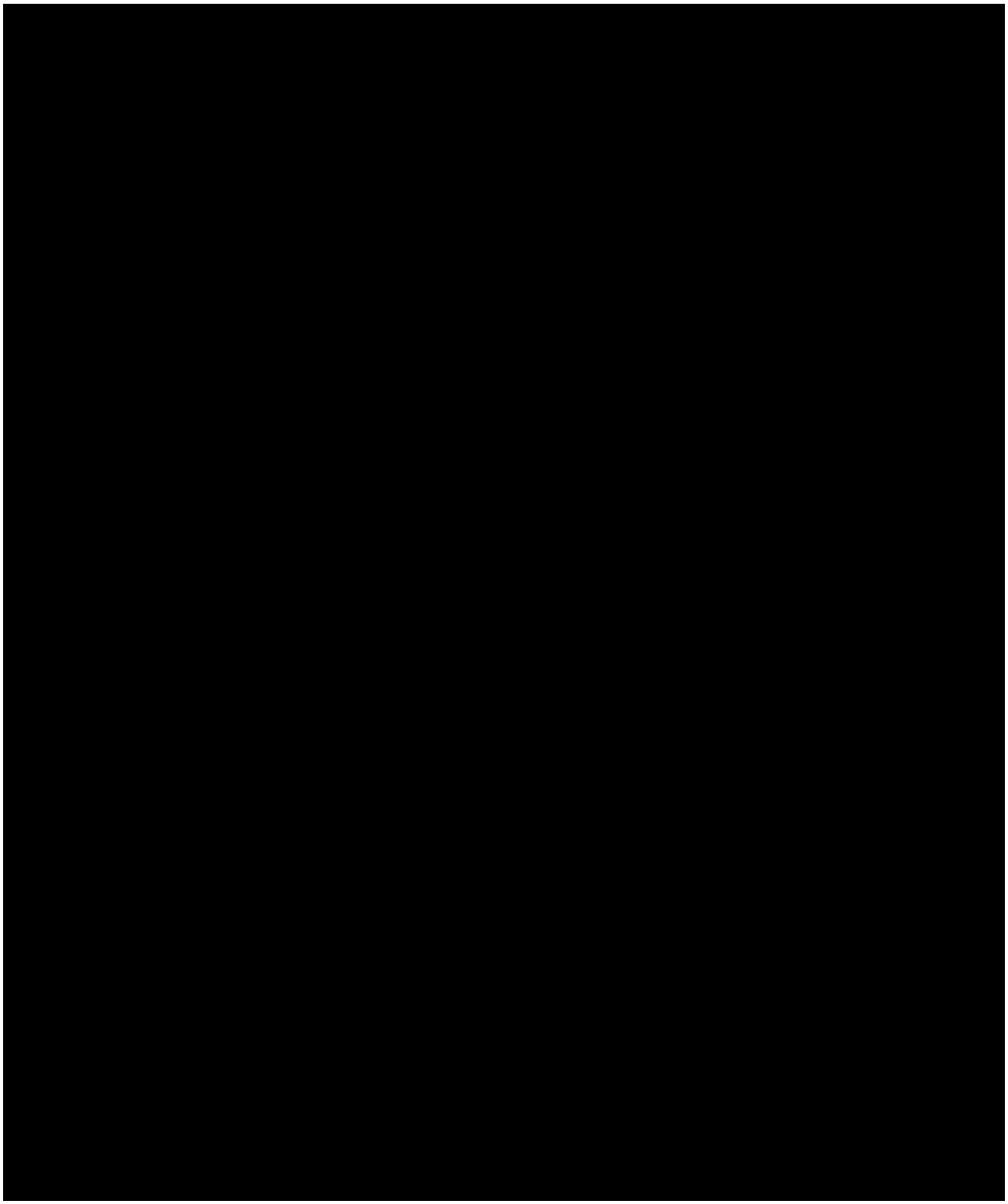
[redacted]

[redacted]

Investigators should refer to the most current local product labels for management of risks associated with ATD.

Table 1. [redacted]

[redacted]



2.3.2. Benefit Assessment

The efficacy of batoclimab for the treatment of IgG autoantibody-mediated organ-specific autoimmune diseases has been evaluated in participants with TED secondary to GD (Study RVT-1401-1002 and Study RVT-1401-2001). Evidence supportive of the efficacy of batoclimab, related to the reduction of pathogenic IgG, has also been generated in other disease states mediated by IgG autoantibodies, such as MG and wAIHA.

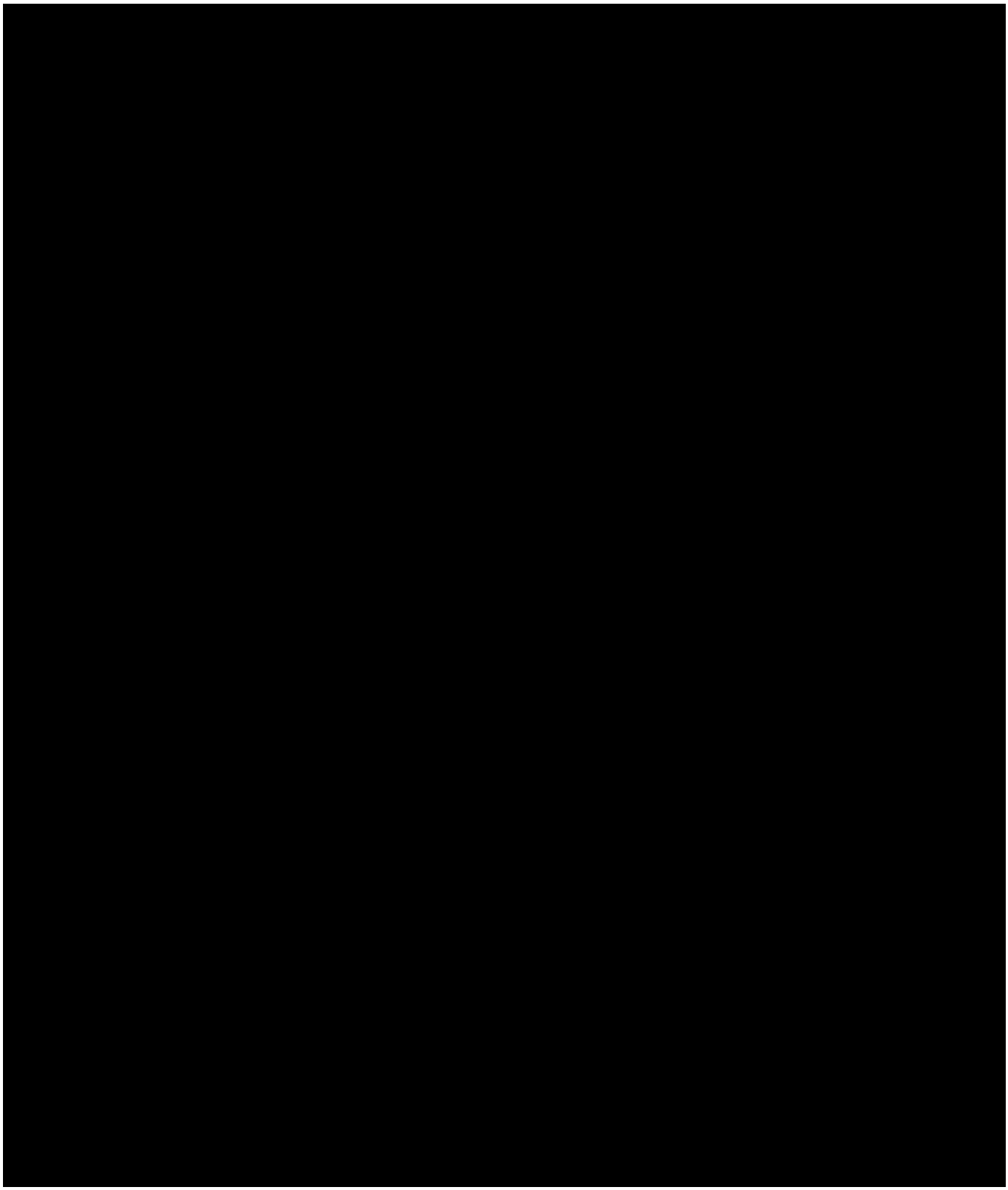


Table 2. [redacted]

[redacted]

Study RVT-1401-2001 (NCT03938545) was a double-blind, placebo-controlled Phase 2b study of batoclimab (255, 340, or 680 mg, or placebo SC weekly for 12 weeks) in participants with active, moderate to severe TED. [redacted]

[redacted]



2.3.3. Overall Benefit: Risk Conclusion

Across [redacted] studies to date, batoclimab administered QW for up to 12 weeks has been generally well tolerated in both healthy volunteers and participants with autoantibody-mediated diseases. No signals of serious risks have been identified. However, the clinical experience with batoclimab remains limited and does not include treatment for the length of time outlined in this study (up to 24 weeks).

[redacted] The study requires frequent assessment of laboratory and other safety measures and includes predefined treatment stopping rules that serve to protect participant safety. The above measures are designed to minimize the risks associated with batoclimab treatment.

A risk-benefit assessment for GD with batoclimab treatment, with the current known risks and protocol mitigation strategies compared to approved GD therapies with established risks and benefits, supports exploration of batoclimab as a potential therapy in GD and the participant enrollment in this study.

2.4. Study Objectives and Endpoints

OBJECTIVES	ENDPOINTS
2.4.1. Primary	
To investigate the effects of batoclimab on thyroid hormone levels in participants with GD as assessed by reduction of FT3 and FT4 at Week 24	Proportion of participants who at Week 24, without increase in ATD dose compared to baseline, have achieved normalization of FT3 and FT4, or haveFT3 and/or FT4 below the LLN.
2.4.2. Secondary	
To investigate the effects of batoclimab on thyroid hormone levels in participants with GD as assessed by reduction of FT3 and FT4 and changes in ATD at Week 24	Proportion of participants who achieve normalization of FT3 and FT4 at Week 24 with ATD dose ≤50% of the baseline ATD dose by Week 24
To investigate the effects of batoclimab on thyroid hormone levels in participants with GD as assessed by reduction of FT3 and FT4 at Week 24 and ATD treatment	Proportion of participants who are off ATD treatment and achieve normalization of FT3 and FT4, or have FT3 and/or FT4 below the LLN at Week 24
[redacted]	

OBJECTIVES	ENDPOINTS
[redacted]	

2.5. Study Design and Dose Rationale

2.5.1. Overall Design

Study IMVT-1401-2501 is a Phase 2a, proof-of-concept, open-label study designed to assess the safety and efficacy of batoclimab in adult participants with biochemically documented hyperthyroidism due to GD who have failed to achieve euthyroidism on ATD.

Approximately 35 participants with GD aged ≥18 years will be enrolled.

The primary efficacy endpoint of the proportion of participants who at Week 24, without increase in ATD dose compared to baseline, have achieved normalization of free triiodothyronine (FT3) and free thyroxine (FT4), or have FT3 and/or FT4 below the lower limit of normal (LLN).

The study includes a screening period of up to 4 weeks, an open-label treatment period [redacted]

2.5.1.1. Screening Period

Only participants meeting all inclusion criteria and no exclusion criteria will be enrolled in the study.

[redacted]

2.5.1.2. Twenty-four-Week Treatment Period

Approximately 35 participants who meet eligibility criteria will receive open-label batoclimab 680 mg SC QW for 12 weeks [redacted] followed by open-label batoclimab 340 mg SC QW for 12 weeks [redacted]

[redacted]

[redacted]

2.5.1.4. Four-Week Safety Follow-up Period

Participants who discontinue prematurely during the 24-Week Treatment Period, [redacted] will undergo a safety follow-up visit 4 weeks after the last dose of batoclimab.

[redacted]

[redacted]

[redacted]

2.6. End of Study

The end of study is defined as the date of the last visit of the last participant in the study [redacted]

Early Discontinuation from Study (Early Termination)

A participant will be considered to have terminated the study if he/she leaves the study [redacted] Any such participant should undergo the ED Visit, followed by a Safety Follow-up Visit 4 weeks after the last dose of batoclimab.

Any participant requiring prohibited medications or procedures should be discontinued from the study [redacted]

Study Termination

The Sponsor or the Sponsor's designated representative may terminate this study prematurely, either in its entirety or at any study site, for a reasonable cause provided that written notice is submitted to Investigators, Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs), and regulatory authorities in accordance with regulatory requirements in advance of the intended termination. Advanced notice is not required if the study is stopped due to safety concerns. If the Sponsor terminates the study for safety reasons, the Sponsor will immediately notify the Investigator and subsequently provide written instructions for study termination.

If the study has been suspended or terminated, prompt notification will be given to Investigators, IRBs/IEC, and regulatory authorities in accordance with respective local regulatory requirements.

3. STUDY POPULATION

Eligibility criteria will be evaluated during the Screening Period. Before any study-specific activities/procedures, the appropriate written informed consent must be obtained (see Section 8.1.3). Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, are not permitted.

A participant may withdraw from the study at any point without any resulting detriment and without having to provide any justification.

3.1. Inclusion Criteria

Participants must meet the following criteria to be eligible for inclusion in the study:

1. Have serologically confirmed GD as documented by presence of elevated stimulatory TSH-R-Ab level (i.e., > specimen-to-reference ratio of 140%) at the Screening Visit.
2. Have active hyperthyroidism due to GD with the following laboratory values at the Screening Visit:
   - TSH < LLN
   - FT3 > upper limit of normal (ULN) and ≤5 × ULN
   - FT4 > ULN and ≤5× ULN

   Note: Participants who have T3 thyrotoxicosis (i.e TSH <ULN, FT3 > ULN and ≤5× ULN, but FT4 within normal range) at the Screening Visit may be enrolled, if they have serologically confirmed GD as per Inclusion Criterion 1.
3. Meet all of the following ATD requirements at the Screening Visit:
   - Have been on an ATD for ≥12 weeks before the Screening Visit.
   - Had starting total daily ATD dose of ≥20 mg of methimazole or carbimazole, or ≥200 mg of propylthiouracil.
   - Are currently treated with a total daily dose of ≥10 mg of methimazole or carbimazole, or ≥100 mg of propylthiouracil.
4. Are willing and capable of giving written informed consent, which includes being able to comply with all aspects of the study treatment and testing schedule.
5. Are willing to not participate in another interventional study while in this study.
6. Are ≥18 years of age at the Screening Visit.

[redacted]

3.2. Exclusion Criteria

Participants must not meet any of the following exclusion criteria:

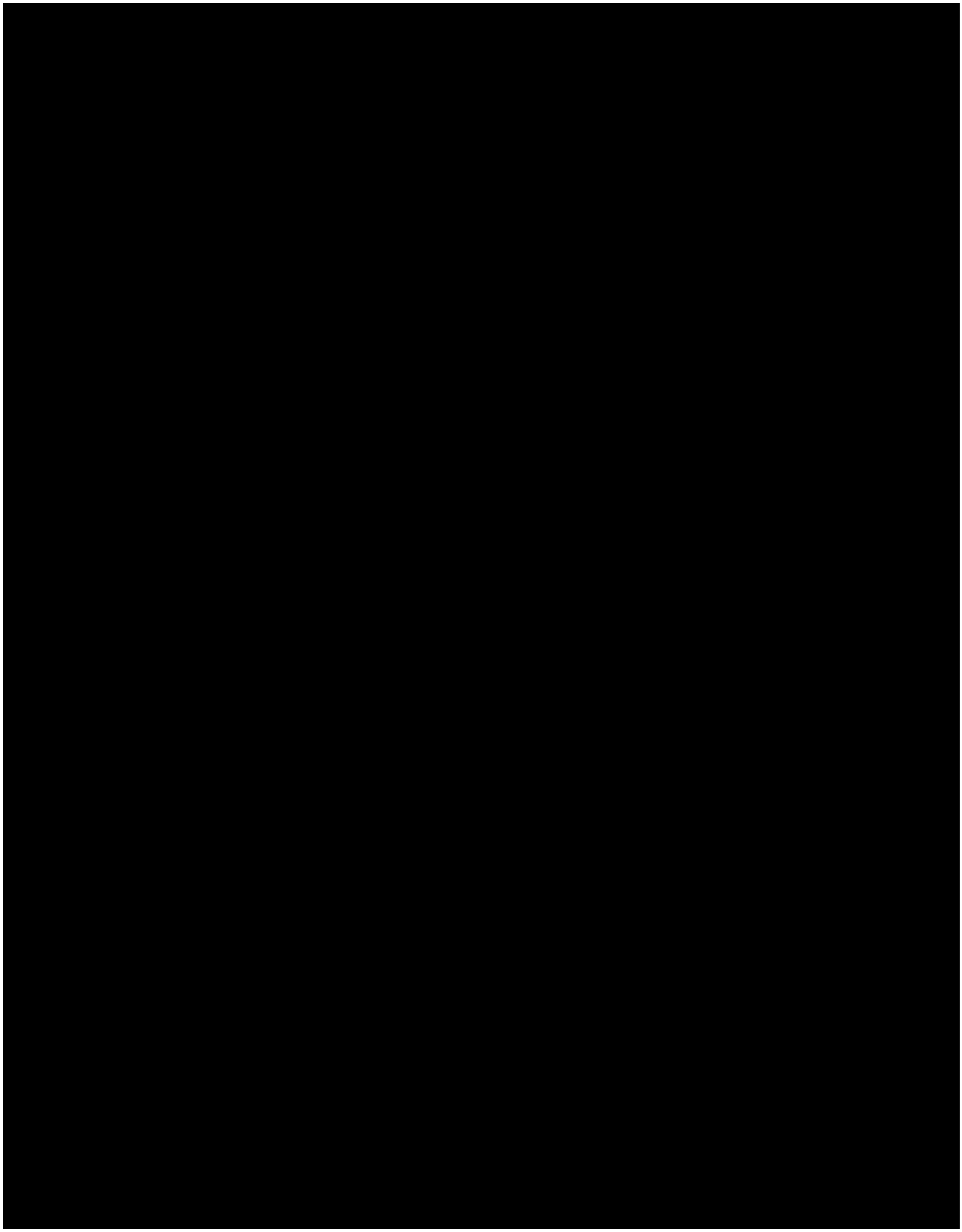
10. Have a history of hyperthyroidism not caused by GD (e.g., toxic adenoma or toxic multinodular goiter), and/or history or presence of thyroid storm.
11. Have a history of treatment with radioactive iodine or thyroid surgery.
    Note: Participants may be enrolled if they meet Inclusion Criteria 2 and 3.
12. Have a total IgG level <6 g/L at the Screening Visit.
13. Have an albumin level <3.5 g/dL (<35 g/L) at the Screening Visit.

[redacted]

[redacted]

15. Have an absolute neutrophil count <1,000 cells/mm^3 at the Screening Visit.

[redacted]



[redacted]

40. Have been enrolled in a previous RVT-1401 or IMVT-1401 clinical trial.
    Note: Participants previously enrolled in an IMVT-1401 clinical trial, with documented assignment to placebo treatment only, may be enrolled in this study.

[redacted]

3.3. Screen Failures and Rescreening

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently assigned to study treatment. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes informed consent, demography, screen failure details, eligibility criteria, and any SAE. [redacted]

[redacted]

4. STUDY TREATMENT(S)

Study treatment is defined as any investigational product, placebo, active comparator, or medical device(s) intended to be administered to a study participant according to the study protocol.

Refer to the Pharmacy Manual for more detailed information regarding the storage, preparation, destruction, and administration of each treatment.

4.1. Study Treatment Administered

4.1.1. Investigational Product

4.1.1.1. Planned Study Treatments

Participants will receive open-label batoclimab 680 mg administered by SC QW injection for 12 weeks followed by 340 mg SC injection for 12 weeks.

[redacted]

4.1.1.2. Identity of Investigational Product

Study treatment name:	Batoclimab
Supplier:	[redacted]
Dose formulation:	Sterile solution for injection.
Unit dose strength:	Each prefilled syringe contains batoclimab 340 mg [redacted]
Dosage levels:	340 mg: [redacted] batoclimab in 1 syringe for a total of [redacted] 680 mg: [redacted] batoclimab in 2 syringes for a total of [redacted]
Route of administration:	Subcutaneous injection
Dosing instructions:	The detailed methods are indicated in the Pharmacy Manual.
Dose preparation:	The preparation procedure and expiry details will be included in the Pharmacy Manual/product label.

4.1.1.3. Preparation/Handling/Storage/Accountability

A description of the methods and materials required for preparation will be detailed in the Pharmacy Manual.

The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit and storage for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.

Only participants enrolled in the study may receive study treatment and only authorized site staff may prescribe study treatment. Study treatment must be administered by a delegated health care professional.

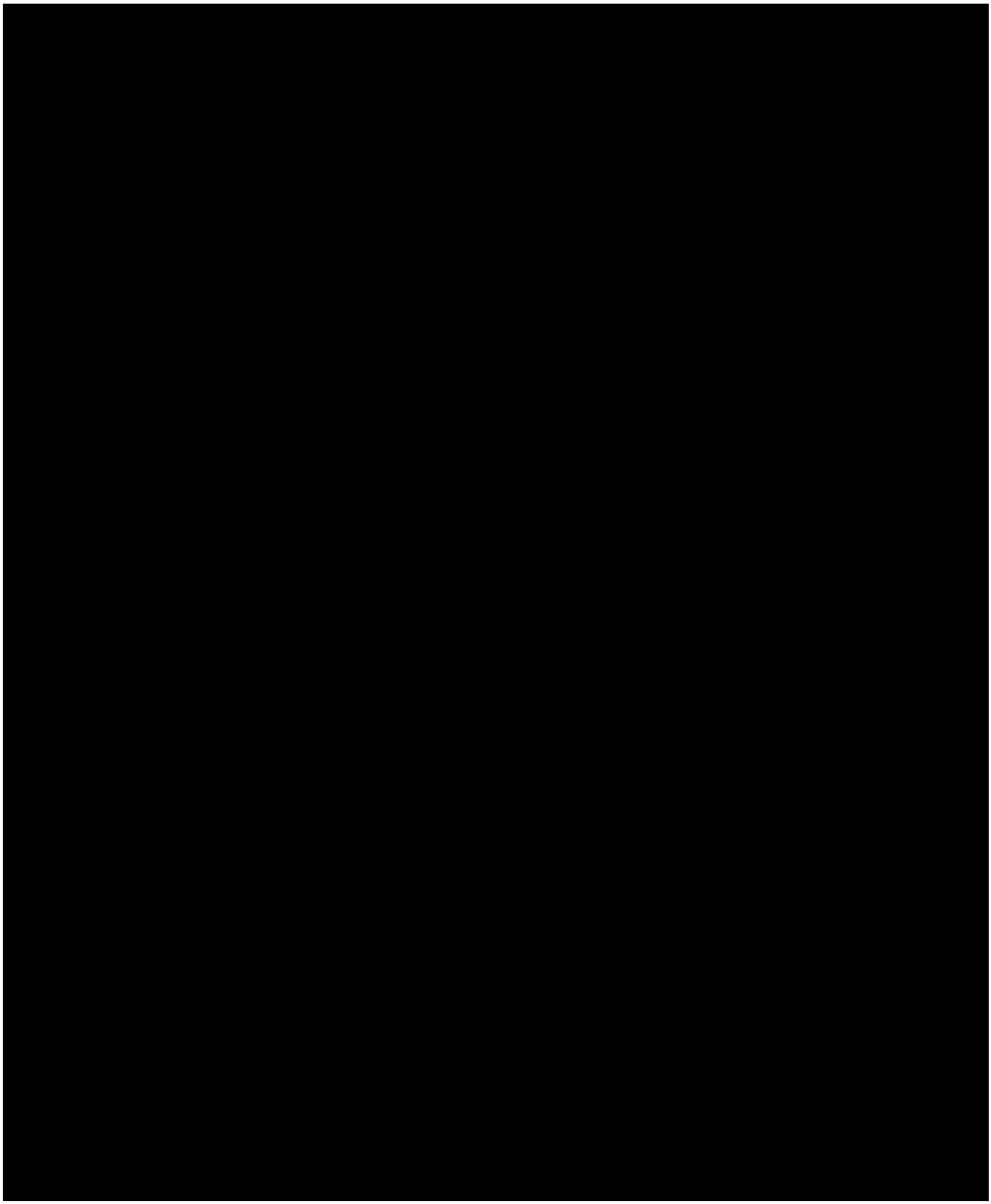
All study treatment must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions [redacted]

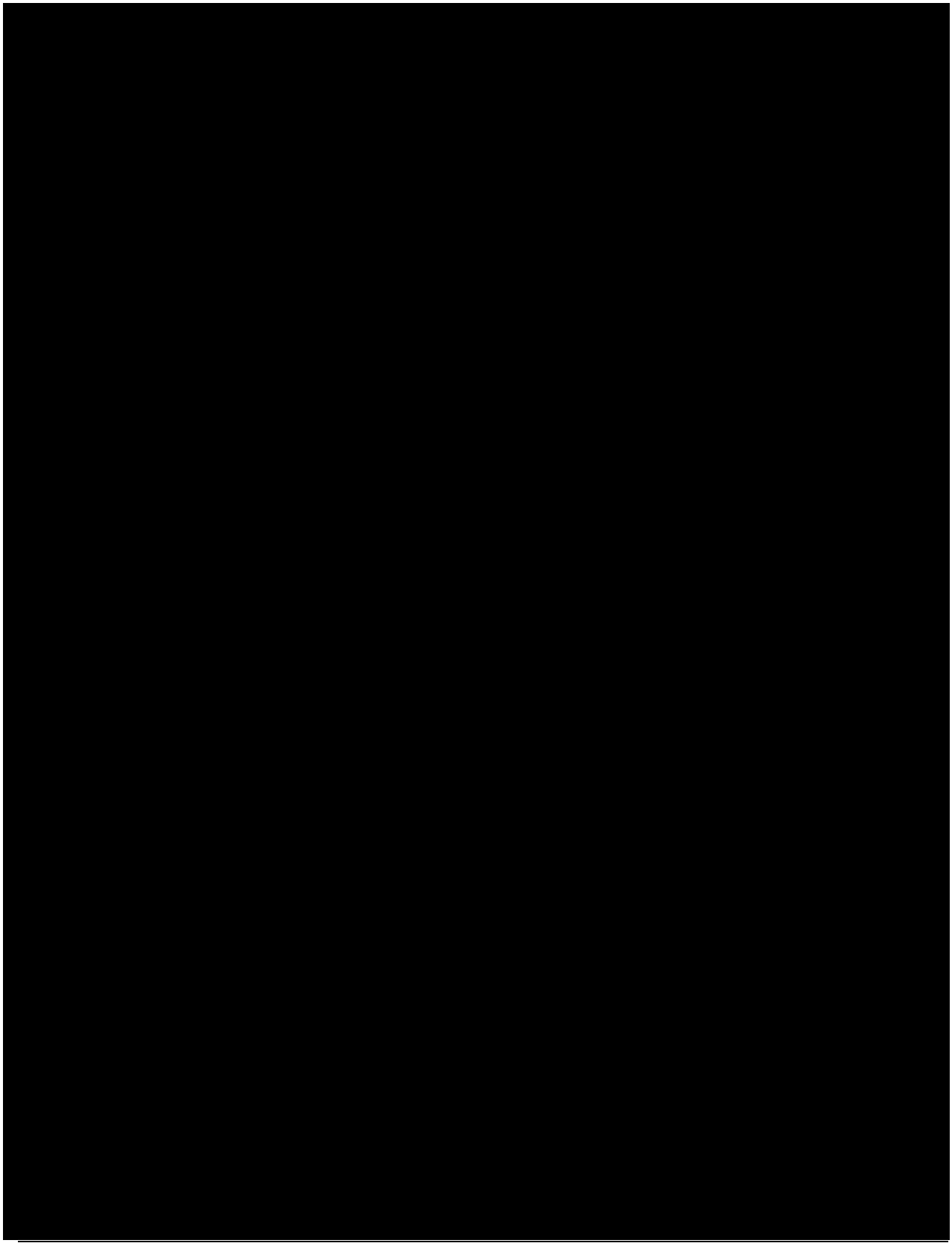
The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

4.1.2. Comparator Product(s)

Not applicable

[redacted]





[redacted]

4.3. Study Treatment Compliance

Batoclimab will be administered as a SC injection via a prefilled syringe.

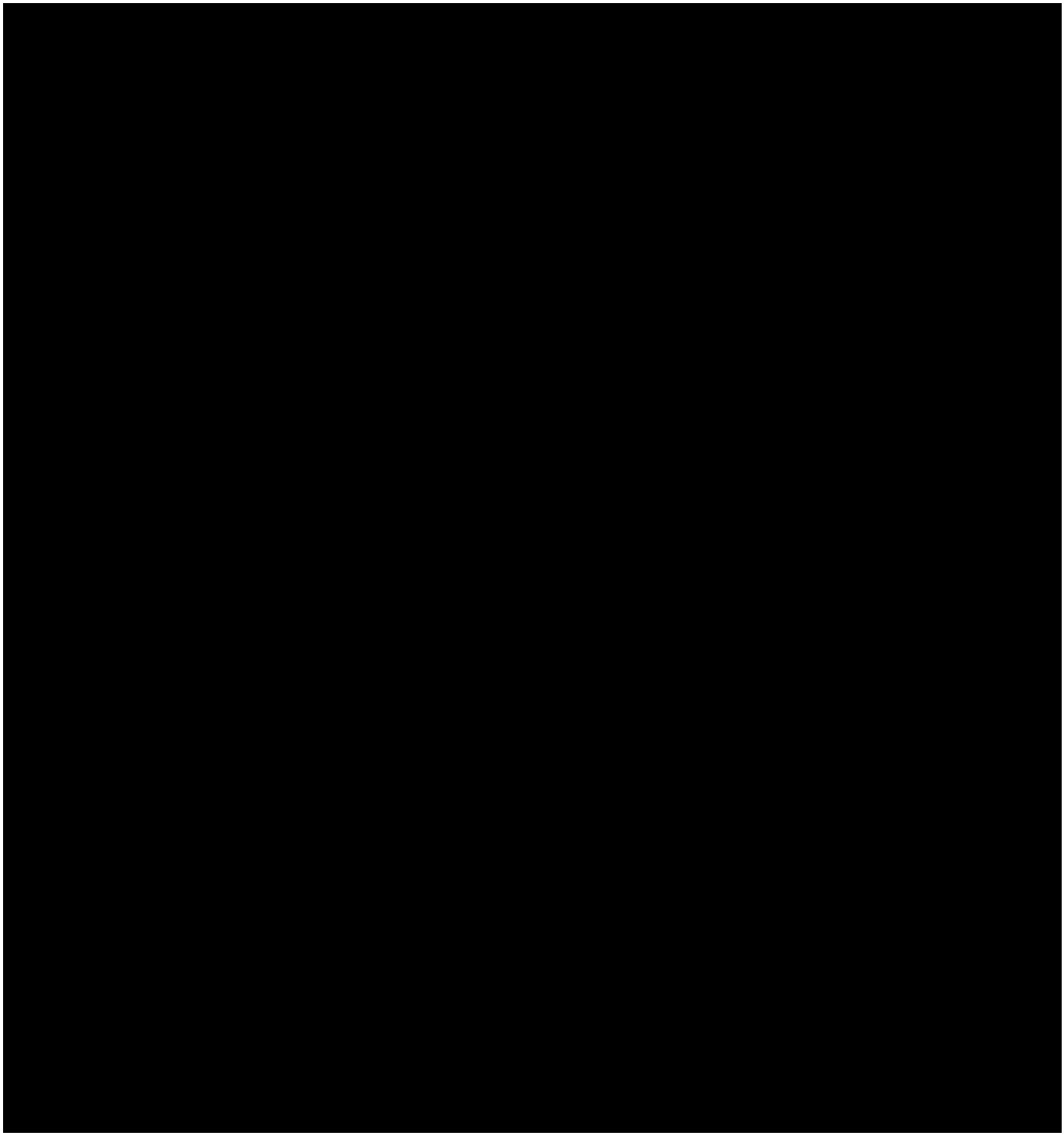
[redacted]

Further guidance on study treatment compliance and management is provided in the Pharmacy Manual.

4.4. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Generic drug name
- Reason for use
- Dates of administration including start and end dates
- Dosage information including route of administration, dose, and frequency



5. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

5.1. Discontinuation of Study Treatment

In rare instances, it may be necessary for a participant to permanently discontinue study treatment.

If study treatment is permanently discontinued during the 24-Week Treatment Period, the participant will be asked to proceed to the ED Visit and 4-week Safety Follow-Up Period.

Potential reasons for a participant's early discontinuation of study treatment may include any of the following:

- Adverse event (see Section 6.4.1).
- Individual stopping criteria listed in Section 5.1.1)
- Pregnancy (see Section 6.4.7).
- Major protocol deviation
- Use of a prohibited medication or procedure [redacted]
- Participant requests to discontinue study treatment
- Lost to follow-up
- Investigator decision
- Sponsor decision
- Other

[redacted]

A participant may withdraw from the study without any resulting detriment and without having to provide any justification.

5.1.1. Individual Stopping Criteria

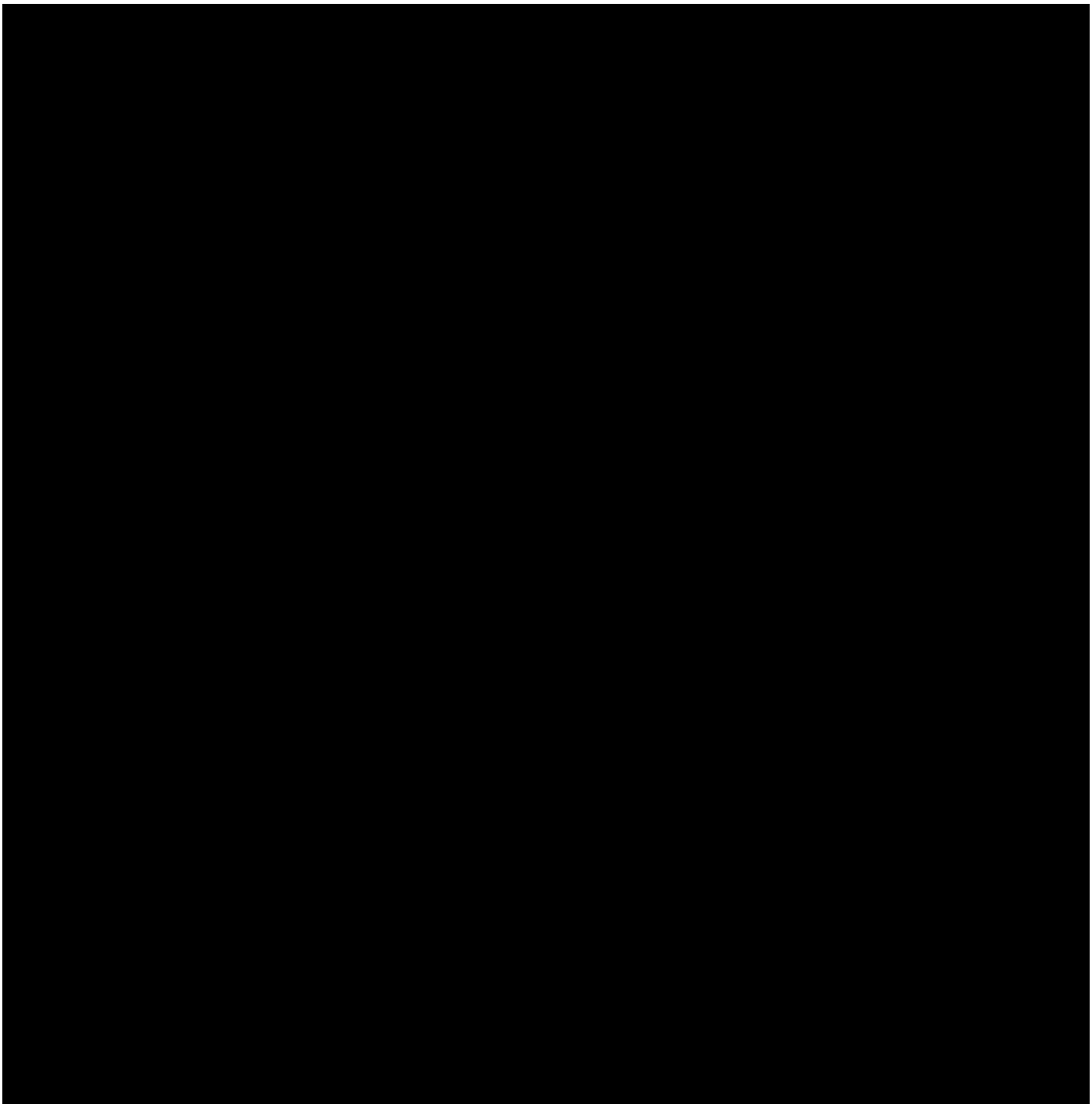
5.1.1.1. Liver Enzyme Stopping Criteria

To ensure participant safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring, and evaluation of liver enzyme abnormalities is to be followed. This process is in alignment with the Food and Drug Administration (FDA) Guidance for Industry: Drug-Induced Liver Injury: Premarketing Clinical evaluation (FDA, July 2009).

Refer to Appendix E for complete definitions of liver laboratory triggers, liver events and thresholds of liver enzyme abnormalities that require discontinuation of study treatment.

An event of this nature should be reported as an SAE and the Medical Monitor must be notified within 24 hours of knowledge of the event. The participant requires appropriate clinical follow-up (including further evaluation and repeat laboratory tests) until resolution of the event as described in Appendix E.

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



5.2. Discontinuation/Withdrawal from the Study

A participant may withdraw from the study at any point without any resulting detriment and without having to provide any justification.

The Investigator may discontinue or withdraw a participant from the study for the following reasons:

- Investigator decision
- Sponsor decision
- Participant withdrawal of consent from study
- Participant noncompliance
- Lost to follow-up
- AE
- Use of a prohibited medication or procedure [redacted]
- Death

All discontinued participants should complete the ED and the 4-Week Safety Follow-up visits (Section 2.6 [redacted] the decision to prematurely discontinue study treatment occurs after the participant completed the [redacted] visit and before the next prespecified study visit, the participant should not undergo the full list of ED Visit procedures [redacted] Instead, the participant should have an abbreviated ED Visit and undergo only those assessments that were not done at the last visit on study treatment (e.g., [redacted] TED assessments), followed by the 4-Week Safety Follow-up Visit.

[redacted]

If the participant withdraws consent for disclosure of information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, they may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

5.3. Lost to Follow-up

A participant will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The study site must attempt to contact the participant and reschedule the missed visit as soon as possible and 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.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.

A participant may withdraw from the study at any point without any resulting detriment and without having to provide any justification.

Discontinuation of specific sites or of the study are handled in Section 8.1.11.

6. STUDY ASSESSMENTS AND PROCEDURES

[redacted] Protocol waivers or exemptions are not allowed.

Important safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.

Adherence to the study design requirements, [redacted] is essential and required for study conduct.

6.1. Study Periods

6.1.1. Screening

[redacted]

Written informed consent must be obtained before any study-related procedures are performed.

[redacted]

[redacted]

6.1.4. End of Study Visit

A participant will be considered as having completed the 24-Week Treatment Period after having completed assessments at Week 24.

[redacted]

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure [redacted] for the last participant in the study.

[redacted]

6.2.1. Laboratory Assessments

[redacted]

The actual date and results for each blood sample collection will be recorded in the eCRF.

Instructions for the collection, handling, storage, and shipping of biological samples will be included in the Laboratory Manual. After analysis, samples may be stored for 10 years, and then destroyed per laboratory standard operating procedures (SOPs).

Total blood volume will be specified in the informed consent form (ICF).

[redacted]

[redacted]

6.3. Safety Assessments

Time points for all safety assessments are provided [redacted]

6.3.1. Concomitant Medications

Concomitant medications, [redacted] will be documented for each participant at each scheduled visit.

At each study visit, participants will be asked whether they have taken any medication other than study treatment. All medications taken from the time of informed consent through the last follow-up visit must be documented.

[redacted]

6.3.2. Physical Examinations

A complete physical examination will include, at minimum, assessments of the skin, cardiovascular, respiratory, gastrointestinal, and neurological systems. A brief physical examination will include, at minimum, assessments of the skin, abdomen (liver and spleen), and respiratory and cardiovascular systems. In addition, height and body weight (with shoes off) will be measured and collected.

[redacted]

6.3.3. Vital Signs

Vital signs, including systolic and diastolic blood pressures (mmHg), pulse rate (beats/minute), respiratory rate, and temperature, will be obtained and recorded. All vital sign measures will be obtained with the participant in the seated position and having rested for at least 5 minutes. Vital signs will be taken prior to blood draws and administration of study treatment.

[redacted]

6.3.4. Electrocardiograms

Twelve-lead ECGs will be obtained using an ECG machine that automatically calculates the heart rate and measures PR, QT, RR, and QTcF intervals; QRS duration; and P, QRS, and T axes (in degrees). [redacted] Electrocardiograms will be performed before blood draws and administration of study treatment.

[redacted]

6.3.5. Clinical Safety Laboratory Assessments

[redacted] All protocol-required laboratory assessments must be conducted in accordance with the Laboratory Manual [redacted] Details of how blood and urine samples will be collected, processed, and stored are provided in the laboratory manual. Safety samples will be destroyed per laboratory SOP after analysis and data transfer.

Participants will fast (only water intake is permissible) [redacted]

The Investigator must review the laboratory report, document this review, and record in the AE section of the eCRF any clinically relevant changes occurring during the study. The laboratory reports must be filed with the source documents.

All abnormal laboratory tests with values considered clinically significant during participation in the study should be repeated until the values are no longer considered clinically significant by the Investigator or are considered stable or chronic. If deemed clinically significant by the Investigator, non-protocol specified laboratory assessments performed at the institution's local laboratory that are needed to manage a participant should be reported as an AE (or SAE). See Section 6.4.

6.3.6. Adverse Events

Adverse event collection will begin from time of informed consent and continue through the completion of a participant's post study treatment safety follow-up visit. Adverse events will be documented at each clinic visit but can be collected at any time. Any AE that meets the definition of a SAE will also be reported on a separate form to the Sponsor.

Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.

See Section 6.4.5 for information regarding AE collection.

6.4. Adverse Events and Other Safety Aspects

6.4.1. Definition of Adverse Events

An AE is defined as any untoward medical occurrence in a participant administered a study treatment or who has undergone study procedures, and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. Any pre-existing symptom or sign are to be captured as an AE if they worsen in severity.

Some countries may have additional local requirements for events that are required to be reported as AEs or in an expedited manner similar to an SAE. In these cases, it is the Investigator's responsibility to ensure these AEs or other reporting requirements are followed and the information is appropriately recorded in the eCRF accordingly.

An abnormality identified during a medical test (e.g., laboratory parameter, vital sign, ECG data, physical exam) should be defined as an AE only if the abnormality meets 1 of the following criteria:

- Induces clinical signs or symptoms
- Requires active intervention
- Requires interruption or discontinuation of study treatment
- The abnormality or investigational value is clinically significant in the opinion of the Investigator [redacted]

Any finding assessed by the Investigator to be associated with the participant's underlying GD, unless judged by the Investigator to be more severe than expected for the participant's condition, will not be reported as an AE.

6.4.2. Criteria for Defining the Severity of an Adverse Event

Adverse events, including abnormal clinical laboratory values, will be graded using the National Cancer Institute (NCI)-CTCAE guidelines (Version 5.0). The items that are not stipulated in NCI-CTCAE Version 5.0 will be assessed according to the criteria in Table 5 and recorded in the eCRF.

Table 5. NCI-CTCAE Guidelines (Version 5.0) Criteria

Grade	Assessment Standard
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	Medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
4-Life Threatening	Life-threatening consequences; urgent intervention indicated
5-Death	Death related to adverse event

CTCAE = Common Terminology Criteria for Adverse Events; NCI = National Cancer Institute.

6.4.3. Criteria for Causal Relationship to the Study Treatment

The Investigator will provide the causality assessment for an AE. The definitions in Table 6 are to be used for the relationship of the AE to study treatment:

Table 6. Criteria for Causal Relationship

Causal Relationship to the Study Treatment	Criteria for Causal Relationship
Not Related	A clinical event, including laboratory test abnormality, with a temporal relationship to treatment administration which makes a causal relationship improbable, and/or in which other drugs, chemicals or underlying disease provide plausible explanations.
Possible	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the treatment, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
Probable	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the treatment, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on re-administration (rechallenge) or withdrawal (dechallenge).

6.4.4. Definition of a Serious Adverse Event

An AE is considered "serious" if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Results in death.
- Is life threatening (an AE is considered "life-threatening" if, in the view of either the Investigator or Sponsor, its occurrence places the participant at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death).
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions.
- Results in congenital anomaly, or birth defect.
- Requires inpatient hospitalization or leads to prolongation of hospitalization (hospitalization for treatment/observation/examination caused by AE is to be considered as serious).
- Other medically important events.

Medical and scientific judgment should be exercised in deciding whether an event is serious (and requires expedited reporting) in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent 1 of the other outcomes listed in the definition above. These events, including those that may result in disability/incapacity, should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

In accordance with regulatory guidance, specific events suggestive of liver injury should be reported as SAEs. These events are described in Section 5.1.1.

Safety events of interest on the medicinal products administered to the participant as part of the study (e.g., study treatment, pretreatment regimen) that may require expedited reporting and/or safety evaluation include, but are not limited to:

- Overdose of the medicinal product(s).
- Suspected abuse/misuse of the medicinal product(s).
- Inadvertent or accidental exposure to the medicinal product(s).
- Medication error involving the medicinal product(s) (with or without participant exposure to the Sponsor medicinal product, e.g., name confusion).

All the events of interest noted above should be recorded in the eCRF. Any situation involving these events of interest that also meets the criteria for an SAE should be recorded on the AE page of the eCRF and marked 'serious.'

6.4.5. Reporting of Serious Adverse Events (SAEs)

All SAEs will be collected from the signing of the ICF through a participant's poststudy treatment safety follow-up visit. If an Investigator becomes aware of an SAE after the participant's last visit that is believed to be related to study treatment or to a study procedure, it should be reported as an SAE.

In the case of any SAE, the Investigator must contact the Sponsor or designee immediately (within 24 hours of awareness). The Investigator is to complete and submit an SAE Report Form containing all information that is required by the regulatory authorities to the Sponsor designee (within 24 hours of awareness).

If there are any questions, or if clarification is needed regarding the SAE, please contact the Sponsor's Medical Monitor or their designee [redacted].

Follow-up information for the event should be sent promptly (within 7 days of the initial notification).

Full details of the SAE are to be recorded in the medical records and in the eCRF.

The following minimum information is required:

- International Study Number/Study number.
- Participant number, biological sex, and age.
- The date of report.
- A description of the SAE (event, seriousness of the event).
- Investigator's assessment of causal relationship to the study treatment.

The Sponsor has a legal responsibility to record and notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to ensure that the regulatory authority, IEC, and Investigators are informed within the applicable timeframe. Documentation of the submission to and receipt by the IEC of expedited safety reports is to be retained by the study site.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary. SUSARs will be submitted to the IRB(s)/IEC(s) according to the local requirements and, in the EU, will be reported through EudraVigilance and other applicable authorities.

6.4.6. Follow-up of Adverse Events and Serious Adverse Events

After the initial AE/SAE report, the Principal Investigator is required to proactively follow each event at subsequent visits/contacts until resolved or judged to be no longer clinically significant, or until they become chronic to the extent that they can be fully characterized in the opinion of the Investigator. Where necessary, repeated laboratory testing should be requested to confirm resolution. If during AE follow-up, the AE progresses to an "SAE," or if a participant experiences a new SAE, the Investigator must immediately report the information to the Sponsor. Ongoing AEs where no further information is likely to be available may be closed after consultation between the Sponsor and Medical Monitor.

6.4.7. Pregnancy

If a female participant or partner of a male participant becomes pregnant during the study, the Investigator will report the information to the Sponsor/delegated CRO using the SAE reporting process and forms. The expected date of delivery or expected date of the end of the pregnancy, last menstruation, estimated conception date, pregnancy result and neonatal data, etc., should be included in this information.

The Investigator will follow the medical status of the mother, as well as the fetus, as if the pregnancy is an SAE and will report the outcome to the Sponsor.

When the outcome of the pregnancy falls under the criteria for SAEs (spontaneous abortion, induced abortion, stillbirth, death of newborn, congenital anomaly [including anomaly in a miscarried fetus]), the Investigator should respond in accordance with the report procedure for SAEs. Additional information regarding the outcome of a pregnancy (which is categorized as an SAE) is mentioned below.

- "Spontaneous abortion" includes miscarriage, abortion, and missed abortion.
- Death of an infant within 1 month after birth should be reported as an SAE regardless of its relationship with the study treatment.
- If an infant dies more than 1 month after the birth, the death should be reported if a relationship between the death and intrauterine exposure to the study treatment is judged as "possible" by the Investigator.
- In the case of a delivery of a living newborn, the "normality" of the infant is evaluated at the birth and followed for 1 year.
- Unless a congenital anomaly is identified prior to spontaneous abortion or miscarriage, the embryo or fetus should be assessed for congenital defects by visual examination where possible.

If during the conduct of a clinical trial, a male participant impregnates his partner, the participant is asked to report the pregnancy to the Investigator. The Investigator will report the pregnancy to the Sponsor/delegated CRO as an SAE and follow-up as required.

See Appendix D for additional details.

[redacted]

6.5. Treatment of Overdose

[redacted]

[redacted] The Medical Monitor is to be notified and the quantity of the excess dose, as well as the duration of the overdose, is to be documented 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.

[redacted]

6.6. Product Quality Complaints and Medical Device Reporting

Product complaints will be reported to the Sponsor. See the Pharmacy Manual for instructions on complaint reporting.

Medical devices (i.e., drug-device combination) are being provided for use in this study as the study treatment is supplied in prefilled syringes. In order to fulfill regulatory reporting obligations worldwide, the Investigator is responsible for the detection and documentation of complaints and/or related events that occur during the study with such devices. The Investigator and Sponsor will comply with the local regulatory medical device reporting requirements.

The Investigator will report within 24 hours of discovery any product quality complaints/device complaints occurring with the supplied prefilled syringe to the Sponsor. The Investigator should report the product quality event by completing the Product Quality Complaint Form to the Sponsor. This must be used to report initial or any follow-up product quality complaints within 24 hours of the receipt of any new/updated information.

Medical device deficiencies or malfunctions of the device that result in an incident will be detected, documented, and reported during all periods of the study in which the medical device is used.

If the Investigator learns of any device deficiency at any time after a participant has been discharged from the study, and such incident is considered reasonably related to a medical device provided for the study, the Investigator will promptly notify the Sponsor.

6.7. Pharmacokinetics

[redacted]

[redacted] After analysis, pharmacokinetics (PK) samples may be stored for up to 10 years and then destroyed per laboratory SOP.

[redacted]

[redacted]

7. STATISTICAL CONSIDERATIONS

The statistical considerations summarized in this section describe the protocol-defined plan for data analysis of this study. Complete details of data handling and analysis procedures will be documented in the SAP, which will be finalized before the primary database lock of the study treatment period.

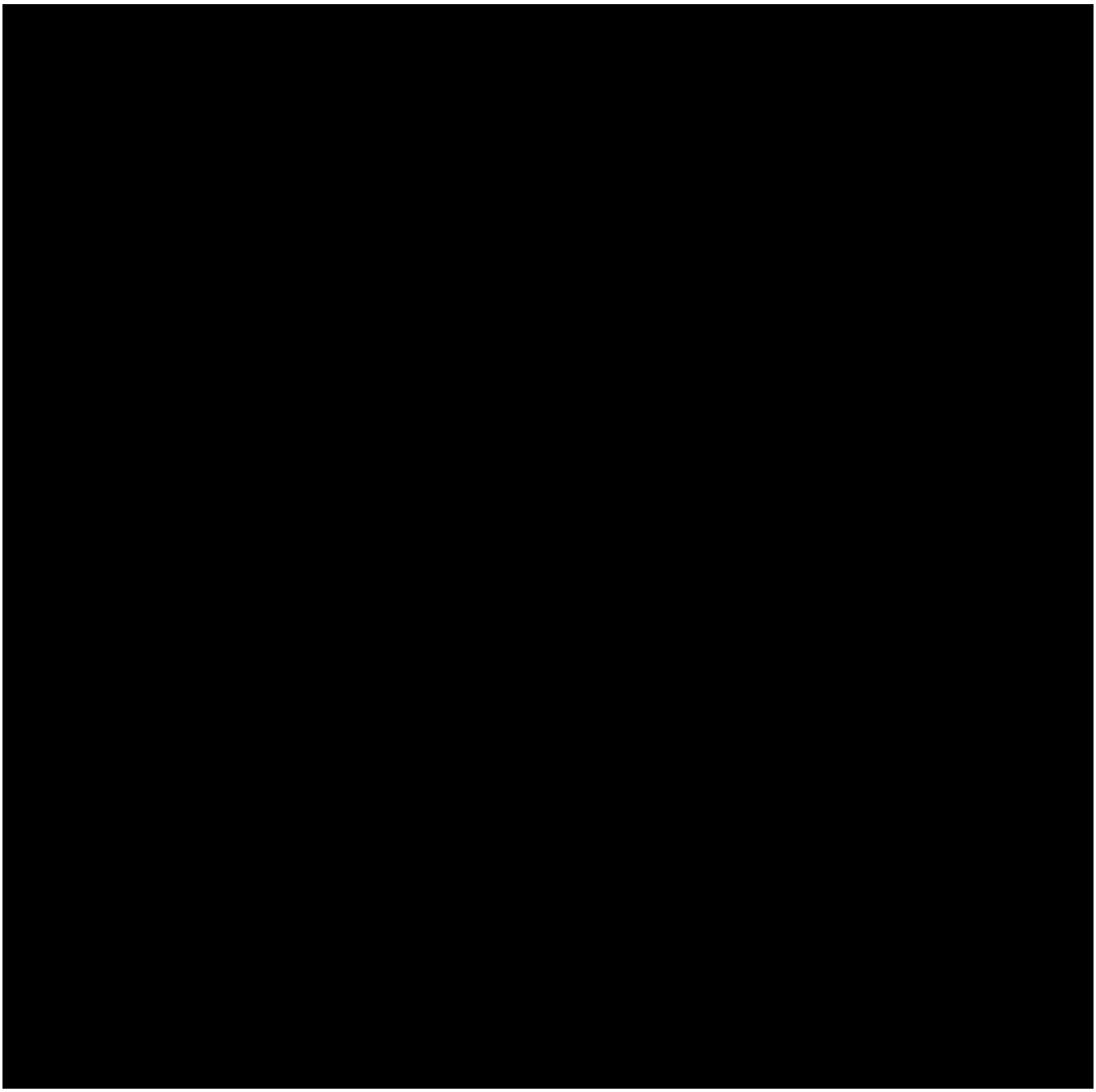


Table 7. [redacted]

[redacted]

7.3. Study Analysis Populations

7.3.1. Safety Analysis Population

The safety analysis set (SAF) includes all participants who received any study treatment. The SAF will be used for all safety and efficacy analyses.

7.3.2. Pharmacokinetic (PK) Population

The PK analysis set (PKAS) includes all participants who received any study treatment and had at least one non-missing post-dose PK result of batoclimab following the administration of the study treatment. The PKAS will be used in the PK analyses.

[redacted]

7.4. Disposition, Demographic, and Baseline Data

7.4.1. Participant Disposition

The number and percentage of participants screened, enrolled, treated, completed, early discontinued, and the primary reason for discontinuation will be summarized.

7.4.2. Demographic and Baseline Characteristics

Demographic variables (including age, gender, race, body weight, and height), region, country, baseline characteristics, [redacted] disease history, diagnoses, and prior and concomitant therapies will be summarized either by descriptive statistics or categorical tables.



7.5.3. Subgroup Analyses

Details of subgroup analyses will be provided in the SAP.

7.6. Safety Analysis

Adverse events, ECGs, vital signs, and safety laboratory data will be reviewed and summarized on an ongoing basis during the study to evaluate the safety of participants.

Summaries of safety data will be provided.

7.6.1. Safety Variables of Analysis

7.6.1.1. Adverse Events

Adverse events/SAEs will be coded and tabulated using the latest version of MedDRA at the time of the database lock. Each AE will be classified by system organ class (SOC) and preferred term.

Treatment-emergent AEs are defined as those AEs that start or worsen on or after the first dose of study treatment. Only TEAEs will be summarized. The incidence of TEAEs will be presented by the number and percentage of participants who experience the TEAE.

Each participant will be counted only once in the incidence for each term (overall incidence, SOC, or preferred term). The incidence of TEAEs, treatment-related TEAEs, SAEs, treatment-related SAEs, and TEAEs leading to study treatment discontinuation will be summarized by SOC and preferred term.

In addition, the incidence of TEAEs will be summarized by SOC, preferred term, maximum severity, and relationship to study treatment.

Refer to Section 6.4.1, Section 6.4.4, [redacted] for the definitions of AEs, SAEs, [redacted] respectively.

Adverse events variables of analysis will include:

- Proportions of participants with TEAEs by decreasing frequency of preferred term.
- Proportions of participants with TEAEs by SOC and preferred term.
- Proportions of participants with treatment withdrawals due to AEs.
- Proportions of participants with death, SAEs, any TEAE, and discontinuation due to an AE.

Tables summarizing the incidence of TEAEs by treatment groups and overall will be generated for each of the following:

- Overall (overview) summary of TEAEs.
- All TEAEs by SOC and preferred term.
- All TEAEs by descending frequency of preferred term.
- All treatment-related TEAEs by SOC and preferred term.
- All TEAEs by maximum severity.
- All serious TEAEs by SOC and preferred term.
- All treatment-related serious TEAEs by SOC and preferred term.
- All Grade 5 TEAEs (deaths) by SOC and preferred term.
- All TEAEs leading to treatment withdrawals.

7.6.1.2. Vital Signs

Vitals sign measurements of blood pressure and pulse will include summary statistics of the actual values and the change from baseline by visit.

7.6.1.3. Clinical Laboratory

Clinical laboratory hematology and clinical chemistry variables of analysis include:

- Proportions of participants with treatment-emergent abnormalities for selected parameters.
- Proportions of participants meeting DILI criteria per FDA Guidance for Industry: “Drug-Induced Liver Injury: Premarketing Clinical evaluation” (FDA, July 2009).
- Summary statistics of actual values and change from baseline by visit.

7.6.1.4. Electrocardiography

Summary statistics of numerical ECG variables and change from baseline by visit will be reported.

In addition, the proportion of participants with maximum postbaseline absolute QTc (QT correction with Bazett's formula and QTcF) intervals that fall into the categories will be summarized. The categories will be based on the International Council for Harmonisation (ICH) E14 Guideline: "Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Nonantiarrhythmic Drugs" (ICH, October 2005).

7.7. Other Analyses

7.7.1. Pharmacokinetic Data

Serum batoclimab concentrations will be listed and summarized over time. Summary statistics for drug concentrations will include the number of nonmissing values (n), number of participants with concentrations below the lower limit of quantification, arithmetic mean, SD, standard error (SE), coefficient of variation (CV), median, minimum, maximum, first and third quartiles, and geometric mean.

[redacted]

7.7.3. Interim Analysis

No formal interim analysis is planned during the study. Preplanned data reviews to review all available efficacy and safety data will occur periodically.

7.7.4. Handling of Missing Data

The study will involve diligent collection of all the data as planned. [redacted]

Sensitivity analyses will be evaluated and explored for the primary endpoint under different assumptions for the missing data, such as last observation carried forward and completer analysis (disregarding the missing data), etc.

[redacted]

Details of the handling of missing data will be specified in the SAP.

Unless otherwise specified, safety data will not be imputed.

8. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

8.1. Regulatory, Ethical, and Study Oversight Considerations

8.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines.
- Applicable ICH Good Clinical Practice (GCP) Guidelines.
- Applicable laws and regulations (including 21 Code of Federal Regulation and EU Clinical Trials Regulation [CTR] No. 536/2014).

The protocol, protocol amendments, ICF, Investigator's Brochure, and other relevant documents (e.g., participant recruitment advertisements) must be submitted to an IRB/IEC for review and approval by the IRB/IEC before the study is initiated at a clinical trial site.

Any substantial amendments to the protocol will require regulatory and IRB/IEC approval before implementation of changes made to the study design at the clinical trial site, except for changes necessary to eliminate an immediate hazard to study participants.

If there is significant public emergency (e.g., pandemic, environmental), the continuity of clinical trial conduct, and oversight may require implementation of temporary or alternative mechanisms. Examples of such mechanisms may include, but are not limited to, any of the following: phone contact, virtual visits, telemedicine visits, online meetings, noninvasive remote monitoring devices, use of local clinic or laboratory locations, and home visits by skilled staff. Important: no waivers will be granted for study entry criteria. All temporary mechanisms utilized, and deviations from planned study procedures are to be documented as being related to the public emergency and will remain in effect only for the duration of the public emergency.

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IEC.
- Taking appropriate urgent safety measures to protect participants against any immediate hazard and notify the Sponsor promptly
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures and in parallel the Sponsor.
- Providing oversight of the conduct of the study at the study site and adherence to requirements of 21 Code of Federal Regulations, ICH guidelines, the IEC, the EU CTR No. 536/2014 for clinical studies when the latter comes into operation, and all other applicable local regulations.

New information that becomes available and is relevant to the management and care of a participating participant will be communicated promptly to all participating Investigators.

8.1.2. Financial Disclosure

Investigators and Sub-Investigators will provide the sponsor with sufficient, accurate financial information, as requested, to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

8.1.3. Informed Consent Process

The Investigator or his/her representative will explain the nature of the study to the participant and answer all questions regarding this study. Prior to any study-related screening procedures being performed on the participant, the informed consent statement will be reviewed, voluntarily signed and dated by the participant or his/her guardian or legal representative, the person who administered the informed consent, and any other signatories according to local requirements. A copy of the signed ICF will be given to the participant. An entry must also be made in the participant's dated source documents to confirm that informed consent process was completed and signed informed consent was obtained prior to any study-related procedures and that the participant received a signed copy.

The signed consent forms will be retained by the Investigator and made available (for review only) to the study monitor and auditor, regulatory authorities, and other applicable individuals upon request.

A reconsent is required to be signed prior to any rescreening activities.

8.1.3.1. Supply of New and Important Information Influencing the Participant's Consent and Revision of the Written Information

The Investigator or his/her representative will inform the participant verbally as soon as possible or whenever new information becomes available from the Sponsor that may be relevant to the participant's consent or may influence the participant's willingness to continue to participate in the study (e.g., report of serious adverse drug reaction). The communication must be documented in the participant's source documents and must document whether the participant is willing to remain in the study or not.

The Investigators must update their ICF and submit it for approval to the IRB/IEC. The Investigator or his/her representative must obtain written informed consent from the participant on all updated ICFs throughout his/her participation in the study. The Investigator or his/her designee must re-consent participants with the updated ICF even if relevant information was provided verbally. The Investigator or his/her representative who obtained the written informed consent and the participant should sign and date the ICF. A copy of the signed ICF will be given to the participant and the original will be placed in the participant's medical record. An entry must be made in the participant's records documenting the re-consent process.

8.1.4. Data Protection

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information that would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The Investigator must ensure that the participant's confidentiality is maintained for documents submitted to the Sponsor.
- For SAEs reported to the Sponsor, participants are to be identified by their unique participant identification number, initials (for faxed reports, in accordance with local laws and regulations), and age (in accordance with local laws and regulations).
- Documents that are not submitted to the Sponsor (e.g., signed ICFs) are to be kept in confidence by the Investigator, except as described below.
- In compliance with governmental regulations/ICH GCP Guidelines, it is required that the Investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IRB/IEC direct access to review the participant's original medical records for verification of study related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study.
- The Investigator is obligated to inform and obtain the consent of the participant to permit such individuals to have access to his/her study related records, including personal information.
- The Investigator and CRO are obligated to inform the Sponsor within an agreed timeframe set out in specific agreements of any personal data breach impacting study participants. As per its SOP on data breach management, Sponsor staff are required to notify its Data Protection Officer, the Investigator, and CRO, and evaluate the severity of the impact on the privacy of affected persons/individuals according to the number of data subjects concerned, their type and level of vulnerability, the type and amount of data, and any other factors relevant to the breach. The relevant parties will then implement appropriate mitigations (to be determined on a case-by-case basis) to reduce any possible harm to individuals and consider ongoing risks that may be associated with the breach, including an assessment of potential adverse consequences for individuals and their likelihood, extent, and seriousness. The Sponsor will maintain a data breach log and record the results of any risk assessments

and associated mitigations. Where required, the Sponsor and Investigator may both be under an obligation to notify the relevant Data Protection Authority of a data breach within a certain timeframe (e.g., 72 hours under both the EU and the United Kingdom General Data Protection Regulation). Where this is the case, the Investigator and Sponsor will cooperate with one another, but remain separately responsible for complying with such obligation. Where data protection legislation requires that data subjects be notified of the data breach, the Investigator will be responsible for contacting the relevant data subjects on behalf of the Investigator and the Sponsor to ensure Sponsor does not receive any identifiable personal data. All decisions made with regard to the data breach shall be recorded in the Sponsor's breach log, alongside identification of lessons learned from the breach and what measures have been implemented to prevent a reoccurrence.

8.1.5. Notification of Serious Breach

The Sponsor is responsible for ensuring compliance of the study with the applicable laws and the approved study protocol. The Sponsor will notify the relevant country-specific regulatory authority or authorities of a serious breach of the applicable laws or the approved study protocol within required timeframe of becoming aware of the breach. Whether or not a notification should be submitted will be based on an assessment of whether the breach will likely affect to a significant degree the safety and rights of a trial participant, or the reliability and robustness of the data generated in the clinical trial. To this end, the study sites, Investigators, and the relevant ancillary staff as well as contractors are required to fully cooperate with the Sponsor to render such an assessment.

8.1.6. Data Management

Data management will be coordinated by the Sponsor. All study specific processes and definitions will be documented by Data Management. Electronic case report form completion will be described in the eCRF completion guidelines. Coding of medical terms and medications will be performed using MedDRA and World Health Organization Drug Dictionary, respectively.

All participant data relating to the study will be recorded on eCRFs unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.

The Sponsor shall archive the content of the clinical trial master file according to the type of study and applicable regulation (e.g., at least 25 years after the end of the clinical study for studies under the EU CTR).

8.1.7. Clinical Monitoring

The Sponsor or delegated CRO is responsible for monitoring the clinical trial to ensure that participant's human rights, safety, and well-being are protected, that the study is properly conducted in adherence to the current protocol and GCP, and study data reported by the Investigator/Sub-Investigator are accurate and complete and that they are verifiable with study-related records such as source documents. The Sponsor is responsible for assigning study monitor(s) to this study for proper monitoring. They will monitor the study in accordance with planned monitoring procedures.

Retention of study documents will be governed by the Clinical Trial Agreement.

Quality tolerance limits (QTLs) will be predefined and will be monitored during the study. Any important deviations from the QTLs and remedial actions taken will be summarized in the clinical study report.

8.1.8. Protocol Deviations

A protocol deviation is generally an unplanned excursion from the protocol that is not implemented or intended as a systematic change. The Investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol and must protect the rights, safety, and welfare of participants. The Investigator should not implement any deviation from, or changes of, the protocol, unless it is necessary to eliminate an immediate hazard to trial participants.

For the purposes of this protocol, deviations requiring notification to the Sponsor are defined as any participant who:

- Entered the study even though he/she did not satisfy entry criteria.
- Developed withdrawal criteria during the study and not withdrawn.
- Received incorrect dose or wrong treatment (includes participant consuming investigational product determined to be not fit for use).
- Received excluded concomitant treatment.

When a deviation from the protocol is identified for an individual participant, the Investigator or designee must ensure the Sponsor is notified. The Sponsor will follow-up with the Investigator, as applicable, to assess the deviation and the possible impact to the safety and/or efficacy of the participant to determine participant continuation in the study.

If a deviation impacts the safety of a participant, the Investigator must contact the Sponsor immediately.

The Investigator will also ensure that deviations meeting IRB/IEC and applicable regulatory authorities' criteria are documented and communicated appropriately. All documentation and communications to the IRB/IEC and applicable regulatory authorities will be provided to the Sponsor and maintained within the Trial Master File.

NOTE: Other deviations outside of the categories defined above that are required to be reported by the IRB/IEC in accordance with local requirements will be reported, as applicable.

8.1.9. Source Documents

- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF including description of procedures for the identification of data to be recorded directly on the CRF considered as source data.
- The Investigator is responsible for ensuring that the source data are attributable, legible, contemporaneous, original, accurate, and complete whether the data are hand-written on paper or entered electronically.
- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections, and provide direct access to source data documents.

8.1.10. Quality Assurance

The Sponsor (or designee) is implementing and maintaining quality assurance systems with written standard operating procedures to ensure that trials are conducted, and data are generated, documented, recorded, and reported in compliance with the protocol, GCP, and applicable regulatory requirement(s).

The Sponsor or Sponsor's designee may arrange to audit the clinical trial at any or all investigational sites and facilities. The audit may include remote or on-site review of regulatory documents, case report forms, participants' medical charts, files, and health medical records (paper and/or electronic), and source documents as allowed by local laws and regulations. Direct access to these documents including electronic systems will be required by the auditors.

8.1.11. Study and Site Start and Closure

The study start date is the date on which the clinical trial will be open for recruitment of participants.

The first act of recruitment is the first site activated (as defined by completion of site initiation visit and approval to receive study treatment).

The Sponsor reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of participants by the Investigator.
- Discontinuation of further study treatment development.

If the study is prematurely terminated or suspended, the Sponsor will promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator will promptly inform the participant and must ensure appropriate participant therapy and/or follow-up.

8.1.12. Publication Policy

Publication of the study results is discussed in the Clinical Trial Agreement. The Sponsor will submit a clinical trial summary report to the relevant regulatory authorities following the end of the study within 1 year of the completion of the study or earlier if required by the Agency or other health authorities.

9. REFERENCES

Abraham P, Avenell A, McGeoch SC, Clark LF, Bevan JS. Antithyroid drug regimen for treating Graves' hyperthyroidism. Cochrane Database Syst Rev 2010 Jan 20;(1): CD003420.

Bartalena L. Diagnosis and management of Graves' disease: a global overview. Nat Rev Endocrinol. 2013 Dec;9(12): 724–34.

[redacted]

Bartalena L, Burch HB, Burman KD, Kahaly GJ. A 2013 European survey of clinical practice patterns in the management of Graves' disease. Clin Endocrinol (Oxf.) 2016 Jan;84(1): 115-20.

Biondi B, Kahaly GJ. Cardiovascular involvement in patients with different causes of hyperthyroidism. Nat Rev Endocrinol. 2010 Aug;6(8):431-43.

[redacted]

Davies TF, Andersen S, Latif R, Nagayama Y, Barbesino G, Brito M, et al. Graves' disease. Nat Rev Dis Primers. 2020 Jul 2;6(1):52.

FDA. Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). Guidance for Industry Drug-induced liver injury: premarketing clinical evaluation. July 2009. Available from: https://www.fda.gov/media/116737/download.

[redacted]

International Council for Harmonisation (ICH) E14 Guideline: Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Nonantiarrhythmic Drugs (October 2005).

Investigator's Brochure RVT-1401.

[redacted]

Laurberg P. Remission of Graves' disease during anti-thyroid drug therapy. Time to reconsider the mechanism? Eur J Endocrinol. 2006 Dec;155(6):783-6.

[redacted]

Mazzaferri EL, Reynolds JC, Young RL, Thomas CN, Parisi AF. Propranolol as primary therapy for thyrotoxicosis. Arch Intern Med. 1976 Jan;136(1):50-6.

[redacted]

Morshed SA, Davies TF. Graves' disease mechanisms: the role of stimulating, blocking, and cleavage region TSH receptor antibodies. Horm Metab Res. 2015 Sep;47(10):727-34.

Nakamura H, Miyauchi A, Miyawaki N, Imagawa J. Analysis of 754 cases of antithyroid drug-induced agranulocytosis over 30 years in Japan. J Clin Endocrinol Metab 2013 Dec; 98(12): 4776-83.

Pyzik M, Sand KM, Hubbard JJ, Andersen JT, Sandlie I, Blumberg RS. The neonatal Fc receptor (FcRn): A misnomer? Front. Immunol. 2019 Jul 10;10:1540.

Rare Disease Database: Graves' Disease. National Organization for Rare Disorders Web site: https://rarediseases.org/rare-diseases/graves-disease/. Accessed August 30, 2022.

[redacted]

Ross DS, Burch HB, Cooper DS, Greenlee MC, Laurberg P, Maia AL, et al. 2016 American Thyroid Association guidelines for diagnosis and management of hyperthyroidism and other causes of thyrotoxicosis. Thyroid. 2016 Oct;26(10):1343-1421.

[redacted]

Struja T, Fehlberg H, Kutz A, Guebelin L, Degen C, Mueller B, et al. Can we predict relapse in Graves' disease? Results from a systematic review and meta-analysis. Eur J Endocrinol. 2017 Jan;176(1):87-97.

Sundaresh V, Brito JP, Wang Z, Prokop LJ, Stan MN, Murad MH, et al. Comparative effectiveness of therapies for Graves' hyperthyroidism: a systematic review and network meta-analysis. J Clin Endocrinol. Metab 2013 Sep;98(9):3671-7.

Vos XG, Endert E, Zwinderman AH, Tijssen JG, Wiersinga WM. Predicting the risk of recurrence before the start of antithyroid drug therapy in patients with Graves' hyperthyroidism. J Clin Endocrinol Metab. 2016 Apr;101(4):1381-9.

Wang MT, Lee WJ, Huang TY, Chu CL, Hsieh CH. Antithyroid drug-related hepatotoxicity in hyperthyroidism patients: a population-based cohort study. Br J Clin Pharmacol 2014 Sep;78(3):619-29.

[redacted]

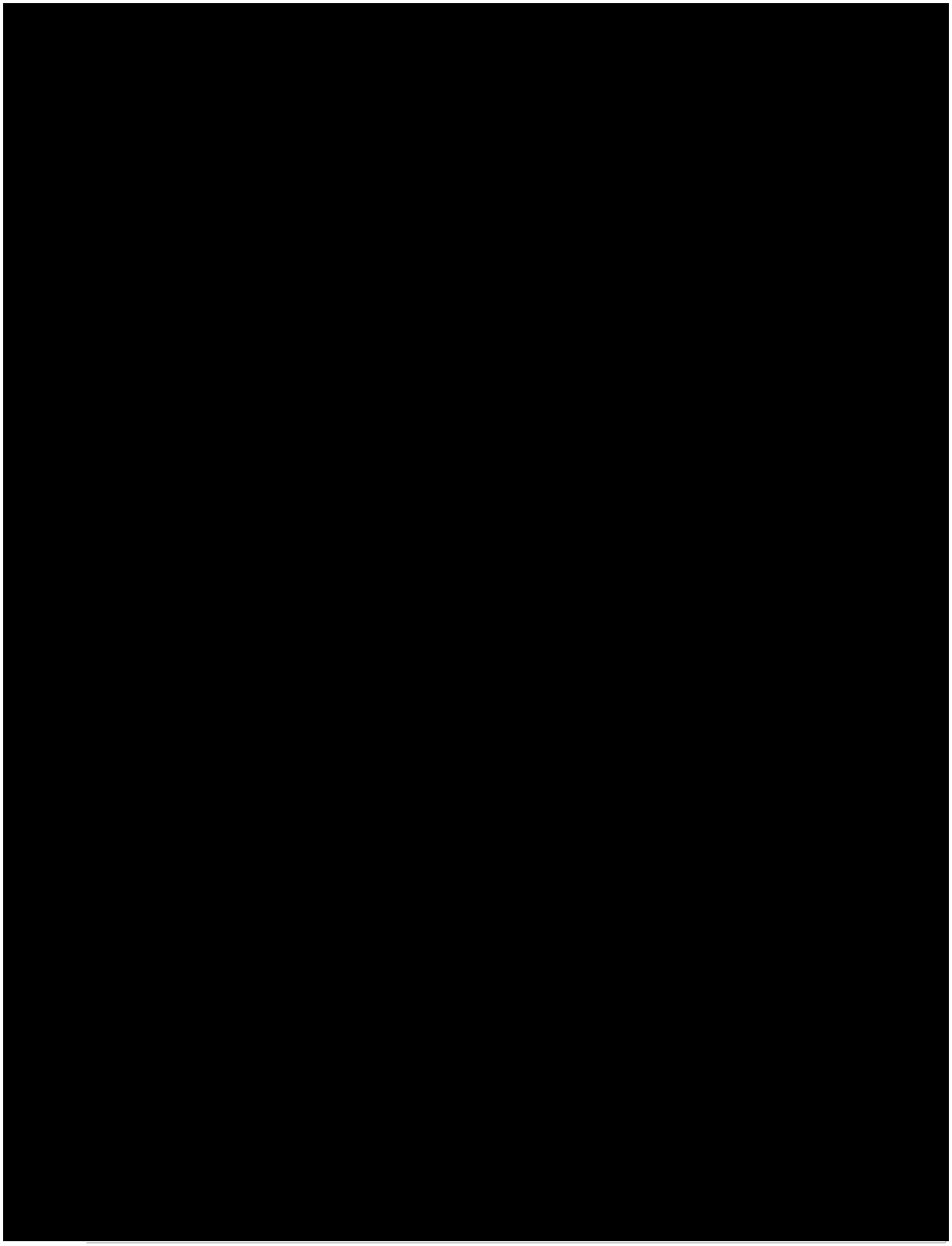
Weetman AP. Graves' disease. N Engl J Med. 2000 Oct 26;343(17):1236-48.

Yang J, Zhu YJ, Zhong JJ, Zhang J, Weng WW, Liu ZF, et al. Characteristics of antithyroid drug-induced agranulocytosis in patients with hyperthyroidism: a retrospective analysis of 114 cases in a single institution in China involving 9690 patients referred for radioiodine treatment over 15 years. Thyroid. 2016 May;26(5):627-33.

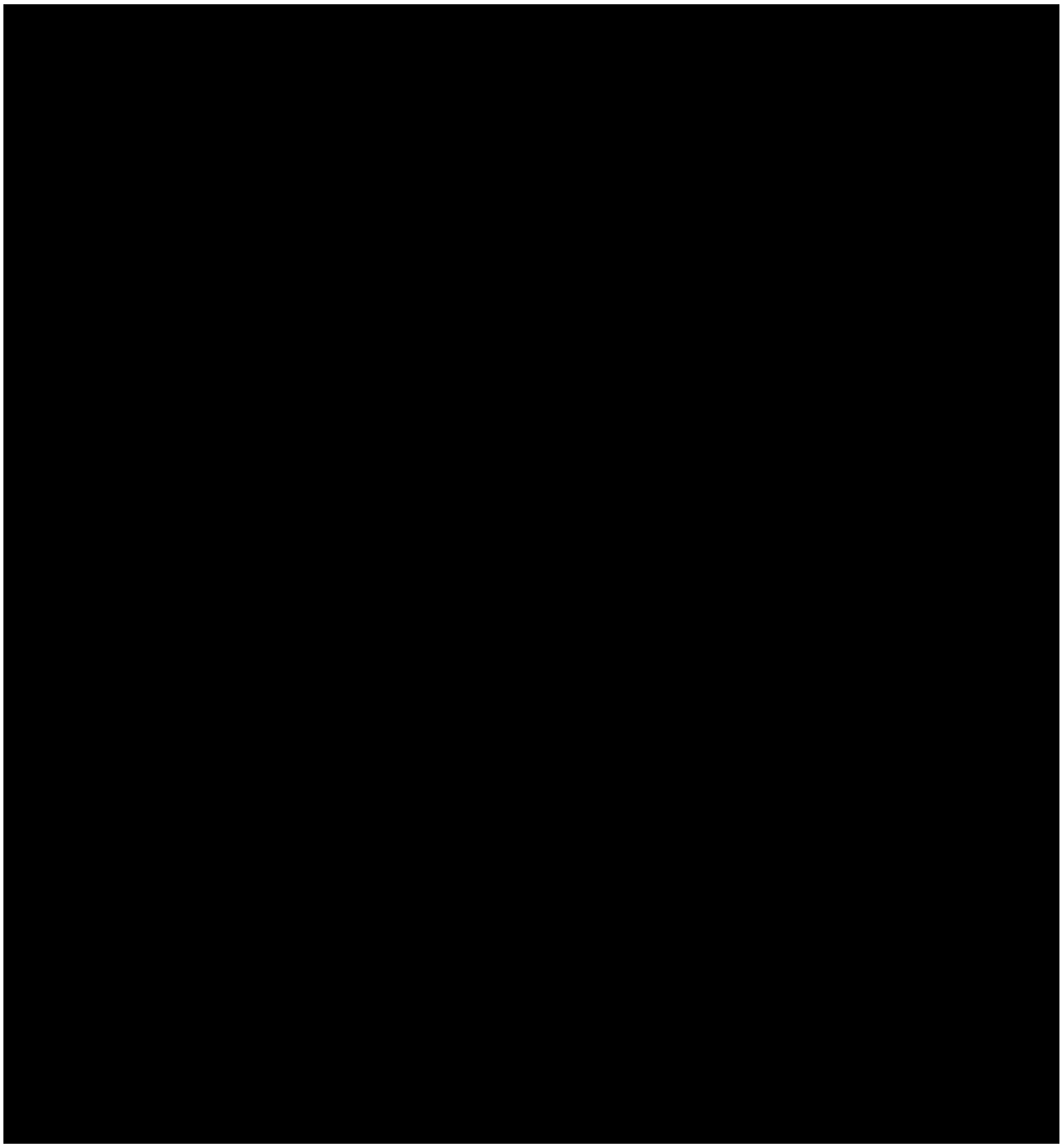
Appendix A: Clinical Laboratory Tests

- [redacted] Safety samples will be destroyed per laboratory SOP after analysis and data transfer. [redacted] samples may be stored for up to 10 years after analysis and then destroyed per laboratory SOP.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 3 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

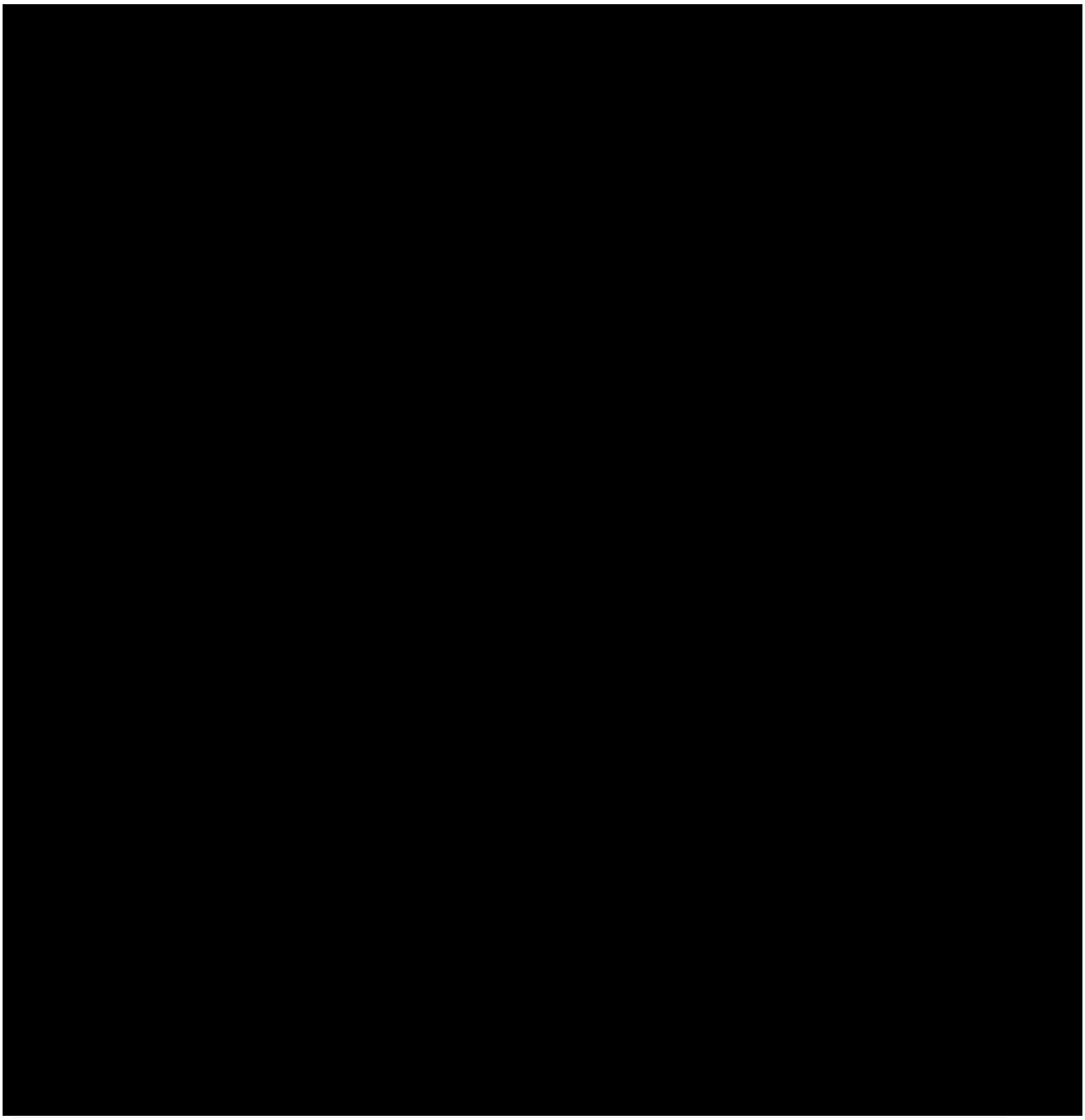
Table 8. [redacted]



Copyright © Torquil Watt, Copenhagen University Hospital, Denmark



Copyright © Torquil Watt, Copenhagen University Hospital, Denmark



Copyright © Torquil Watt, Copenhagen University Hospital, Denmark
3



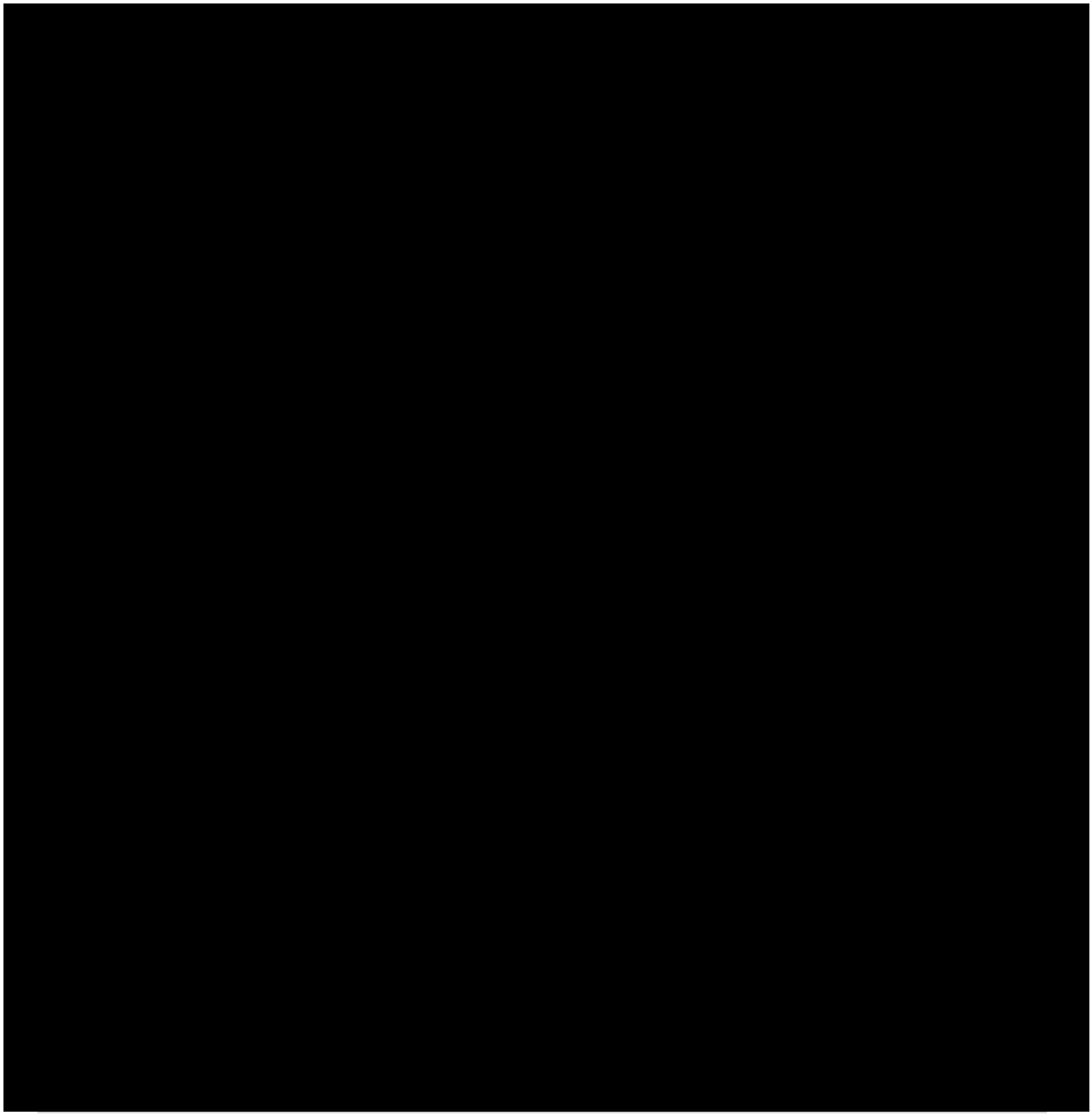
Copyright © Torquil Watt, Copenhagen University Hospital, Denmark
4



Copyright © Torquil Watt, Copenhagen University Hospital, Denmark
5

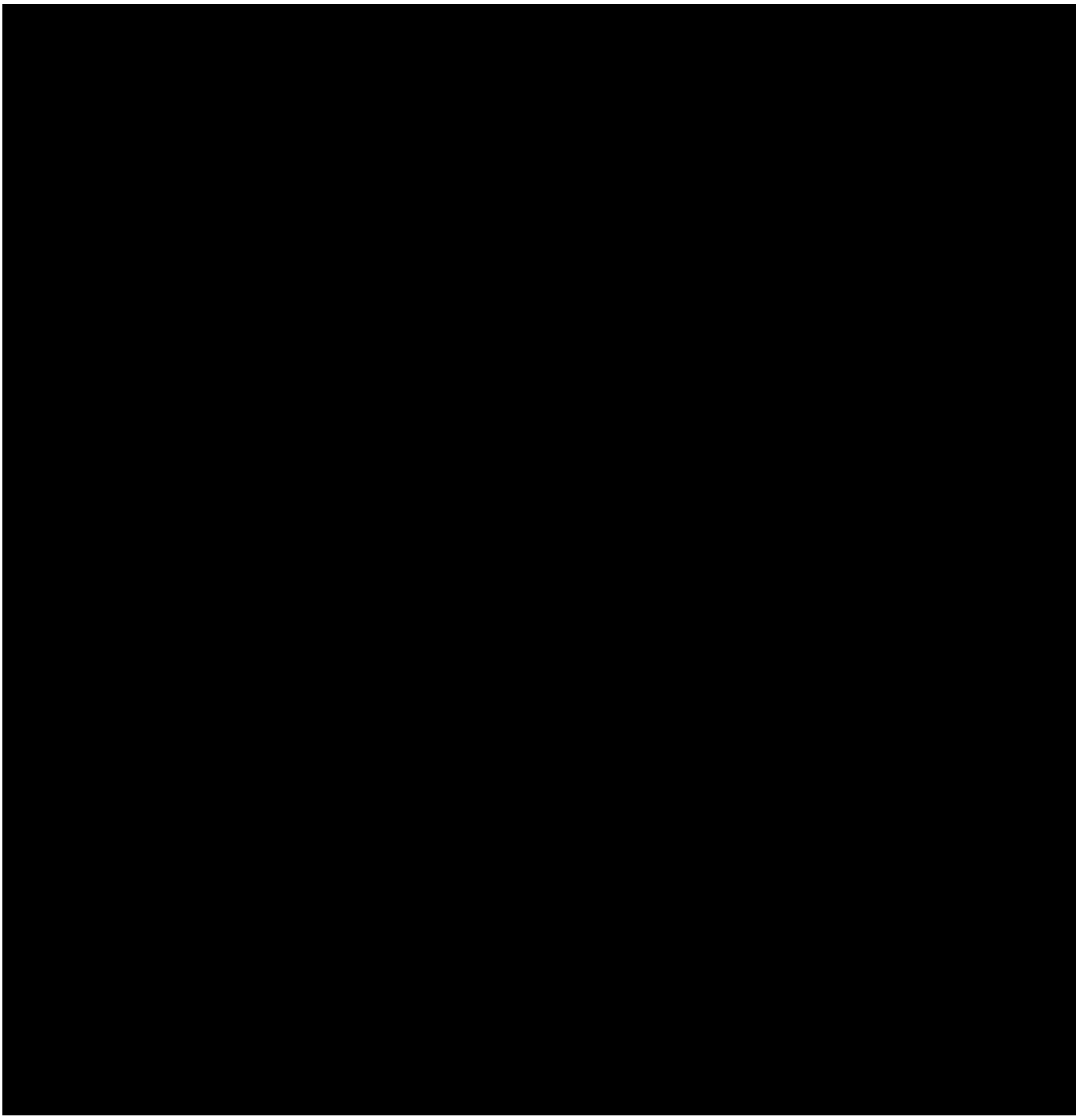
[redacted]

Copyright © Torquil Watt, Copenhagen University Hospital, Denmark
6



Copyright © Torquil Watt, Copenhagen University Hospital, Denmark
7





Appendix D: Collection of Pregnancy Information

Male Participants with Partners Who Become Pregnant

The Investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive batoclimab.

After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 1 year following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female Participants Who Become Pregnant

The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy.

The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 1 year beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

A spontaneous abortion (occurring at <22 weeks gestational age) or stillbirth (occurring at >22 weeks gestational age) is always considered to be a serious adverse event (SAE) and will be reported as such.

Any poststudy pregnancy-related SAE considered reasonably related to the study treatment by the Investigator will be reported to the Sponsor as described in Section 6.4.5. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating in the study will discontinue study treatment.

Appendix E: Liver Safety Required Actions and Follow up Assessments

Table 9. Definition of Liver Enzyme Abnormality Stopping Criteria / Additional Monitoring Criteria

	Definition/ threshold
LIVER ENZYME ABNORMALITIES REQUIRING ADDITIONAL MONITORING	ALT or AST >3 × to ≤8 × ULN (asymptomatic and without associated TBL or INR abnormality) TBL >1.5 × ULN in the absence of known Gilbert syndrome, and not associated with ALT or AST elevation Any adverse event potentially indicative of a liver toxicity[a]
LIVER ENZYME ABNORMALITIES STOPPING CRITERIA	Potential severe drug induced liver injury meeting the following criteria: ALT or AST >3 × ULN and TBL >2 × ULN ALT or AST >8 × ULN ALT or AST >5 × ULN for > 2 weeks ALT or AST >3 × ULN and INR >1.5 ALT or AST >3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%) Persistent TBL >2 × ULN Any clinical event of jaundice (or equivalent term)

ALT = alanine aminotransferase; AST = aspartate aminotransferase; INR = international normalized ratio; TBL = total bilirubin; ULN = upper limit of normal.

[a] These events include: hepatic failure, fibrosis, cirrhosis, and other liver damage-related conditions; noninfectious hepatitis; benign, malignant, and unspecified liver neoplasms.

The following evaluation should be performed to establish causality of the liver enzyme abnormalities:

- Obtain a more detailed history of symptoms and prior or concurrent diseases. Record the appearance or worsening of clinical symptoms of hepatitis (fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia) on the adverse event (AE) electronic case report form (eCRF).
- Obtain a history of concomitant drug use (including nonprescription medications such as acetaminophen, and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.
- Obtain a history of exposure to environmental chemical agents.
- Perform a physical examination.
- Exclude causes of underlying liver disease, as specified in Exclusion Criteria (Section 3.2).

- Perform laboratory evaluation including:
  - Viral hepatitis serology including hepatitis A immunoglobulin M (IgM) antibody, hepatitis B surface antigen and hepatitis B core antibody (IgM), and hepatitis C ribonucleic acid.
  - Obtain serum creatine phosphokinase lactate dehydrogenase, and complete blood count with differential for eosinophilia.
  - Consider the following additional testing if appropriate: cytomegalovirus IgM antibody, Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, a heterophile antibody or monospot testing), serum acetaminophen (paracetamol) level, antinuclear antibodies, anti-smooth muscle antibodies, anti-liver/kidney microsomal-1 antibodies.
- Perform liver imaging with abdominal ultrasound, computed tomography or magnetic resonance imaging, as appropriate.
- Consider gastroenterology or hepatology consultations.
- Consider liver biopsy in conjunction with gastroenterology or hepatology consultant if appropriate.

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

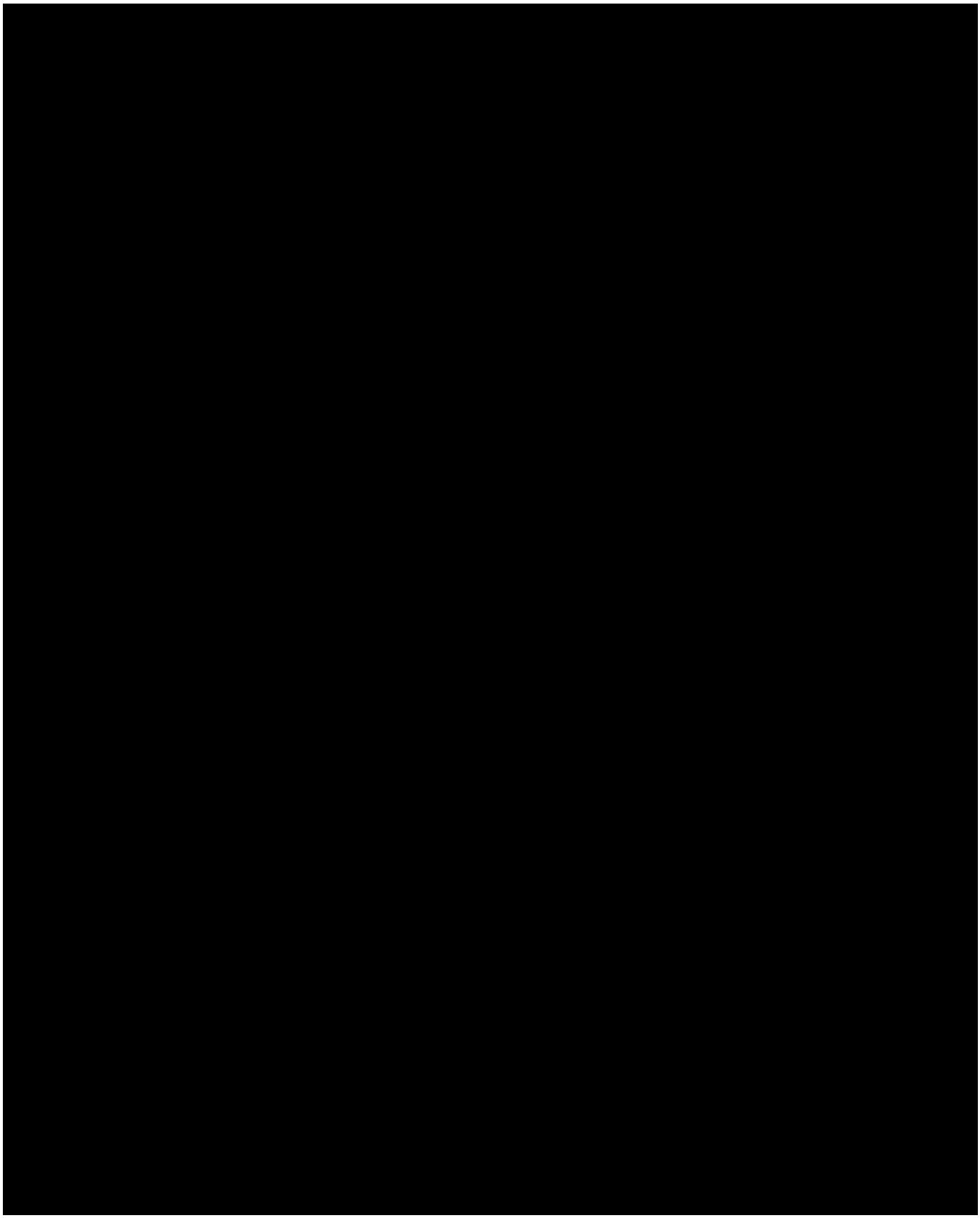
Table 10. Follow-up Requirements for Liver Enzyme Abnormalities

Criterion	Actions required	Follow-up monitoring
AST/ALT		
ALT or AST >3 × ULN and TBL >2× ULN ALT or AST >8 × ULN ALT or AST >5 × ULN for ≥2 weeks ALT or AST >3 × ULN and INR >1.5 ALT or AST >3 × ULN accompanied by symptoms[a] Jaundice (or equivalent)	• Discontinue the study treatment immediately • Hospitalize if clinically appropriate • If not hospitalized, make every reasonable attempt to have participant return to the clinic within 24 hours for repeat liver chemistries, additional testing, and close monitoring (with specialist or hepatology consultation recommended). • Establish causality	ALT, AST, TBL, direct bilirubin, albumin, PT/INR, ALP, and GGT until resolved, stabilized, or return to baseline values (frequency initially should be 2-3 times weekly. Frequency of retesting can decrease to once a week or less at Investigator discretion if abnormalities stabilize and the participant is asymptomatic)
ALT or AST >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	ALT, AST, TBL, albumin, PT/INR, ALP, and GGT until resolution[b] (after first repeat test at 48 hours, frequency at Investigator discretion)

Criterion	Actions required	Follow-up monitoring
ALT or AST >3 to ≤5 × ULN and total bilirubin and INR are normal (participant is asymptomatic)	• Repeat LFT within 48 to 72 hours • If elevation persists, initiate close observation of the participant • Establish causality	After first repeat test within 48 to 72 hours, monitor LFT within 1 to 4 weeks, at Investigator discretion
TBL (isolated)		
>2 × ULN (in the absence of known Gilbert syndrome)	• Repeat LFT within 48 hours • If elevation persists, discontinue the study treatment immediately • Hospitalize if clinically appropriate • Establish causality	ALT, AST, TBL, direct bilirubin, albumin, PT/INR, ALP, and GGT until resolution[b] (after first repeat test at 48 hours, frequency at Investigator discretion) Test for hemolysis (e.g., reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
>1.5 to ≤2 × ULN (participant is asymptomatic)	• Repeat LFT within the next week • If elevation is confirmed, initiate close observation of the participant • If elevation persists, establish causality	After first repeat test within the next week, monitor LFT within 1 to 4 weeks, or at next visit at Investigator discretion
Any AE potentially indicative of a liver toxicity[c]	• Consider study treatment interruption or discontinuation • Hospitalize if clinically appropriate • Establish causality	Investigator discretion

AE = adverse event; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = gamma glutamyl transferase; INR = international normalized ratio; LFT = liver function test; PT = prothrombin time; TBL = total bilirubin; ULN = upper limit of normal.

a. Malaise (general), fatigue, abdominal pain, nausea or vomiting, or rash with eosinophilia.
b. Resolution is defined as 1 of the following: (1) return to baseline values, (2) stable values at 3 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.
c. These events include hepatic failure, fibrosis, cirrhosis, and other liver damage-related conditions; noninfectious hepatitis; and benign, malignant, and unspecified liver neoplasms.





Appendix G: Sponsor Signatory

I, the undersigned, have approved the original version of the clinical trial protocol V8.0 with the date of 20 November 2024.

[redacted]	**Signature and Date**
[redacted]	
[redacted]	
[redacted]	