# TITLE PAGE

**Protocol Title:** <FULL TITLE>

**Protocol Number:** <NUMBER>

**Compound:** XXX-123

**Study Phase:** Phase 1

**Short Title:** <SHORT TITLE>

**Acronym:** Not applicable **Sponsor Name:** <SPONSOR> **Legal Registered Address:**

Address Line 1

Address Line 2

Address Line 3

**Regulatory Agency Identifier Number(s):** IND: XXXXXX

## Amendment Number: X.0

**Approval Date:** DD Month YYYY

## Sponsor Signatory:

 

Firstname Lastname

Job Title

## Date

**Medical Monitor Name and Contact Information:** Firstname Lastname; Tel: XXX-XXX-XXXX

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# PROTOCOL SUMMARY

# Synopsis

**Protocol Title:** <FULL TITLE>

**Short Title:** <SHORT TITLE>

## Rationale:

XXX-123 is intended for use in patients with <brief description of disease>.

This Phase 1 study is intended to:

* + - establish safety, tolerability, and pharmacokinetics (PK) for up to XX days of relevant exposure in the single ascending dose (SAD) study in healthy volunteers to support a subsequent repeat-dose exploratory efficacy study in participants with <disease>;
    - obtain PK, safety, and tolerability data in participants with <disease>;
    - explore potential phenotypic, genotypic, and biochemical approaches to identify patients most likely to respond to XXX-123.

## Objectives and Endpoints:

| **Objectives/Endpoints:** The following objectives and endpoints will be evaluated in healthy participants during the SAD component of the study and in participants with <disease> in the repeat-dose component of the study. | |
| --- | --- |
| **Objectives** | **Endpoints** |
| **Primary** |  |
| * To assess the safety and tolerability after X weeks of exposure following single ascending doses of XXX-123 | * Number of participants with serious and other nonserious AEs |
| **Secondary** |  |
| * To assess the safety and tolerability following repeated doses over X weeks of XXX-123 | * Number of participants with serious and other nonserious AEs |
| * To characterize PK of XXX-123 following single ascending doses | * Cmax and AUClast |
| * To characterize the PK of XXX-123 following repeated doses | * Cmax and AUClast |
| **Exploratory** |  |
| * To explore additional PK characteristics of XXX-123 following single ascending doses | * Tmax, Clast, Tlast, AUCinf, CL, V, and t1/2 |
| * To explore additional PK characteristics of XXX-123 following repeated doses | * Tmax, Clast, Tlast, AUCinf, CL, V, and t1/2 |
| * To explore effects of XXX-123 on clinical laboratory assessments, 12-lead ECG, and vital signs following single ascending doses | * Incidence of clinically significant changes in laboratory parameters, 12-lead ECG parameters, and vital signs measurements |
| * To explore effects of XXX-123 on clinical laboratory assessments, 12-lead ECG, and vital signs following repeated doses | * Incidence of clinically significant changes in laboratory parameters, 12-lead ECG parameters, and vital signs measurements |
| * To explore the impact of ADA on the PK profile of XXX-123 following single ascending doses | * Impact of ADA on AUC or impact on overall exposure of XXX-123 |
| * To explore the impact of ADA on the PK profile of XXX-123 following repeated doses | * Impact of ADA on AUC or impact on overall exposure of XXX-123 |
| * To explore the effects on eating behavior in participants following single ascending doses of XXX-123 | * Hunger, satiety, and appetite VAS scores |
| Abbreviations: ADA = antidrug antibodies; AE = adverse event. | |

**Disclosure Statement**: This is a Phase 1, double-blind, randomized, placebo-controlled study with a SAD escalation component to evaluate XXX-123 in healthy volunteers and a repeat-dose component to confirm repeat-dose safety, tolerability, pharmacokinetics, and immunogenicity in participants with <disease>.

## Number of Participants:

*SAD:* A maximum of XX participants will be randomly assigned to study intervention such that approximately XX evaluable participants complete the study.

*Repeat-dose:* A maximum of XX participants will be randomly assigned to study intervention such that approximately X evaluable participants complete the study.

## Intervention Groups and Duration:

*SAD (XXX-123 or placebo single dose subcutaneously [SC]):*

Planned Screening: up to X weeks

Planned study duration (Screening to Follow-up): up to XX weeks *Repeat-dose (XXX-123 or placebo every other week for X doses SC):* Planned Screening: up to X weeks

Planned study duration (Screening to Follow-up): up to XX weeks

**Data Monitoring Committee:** No

# Schema

<insert study schema here>

* 1. **Schedule of Activities (SoA)**

<update tables with the appropriate procedures and time periods. Content below is sample only.>

## Table 1: Schedule of Activities – Single Ascending Dose

| **Study Procedures (Day)** |  | **In-Residence Period** | | | | | | | | | | **Follow-up Period Cohorts 4+** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Follow-up Period Cohorts 1-3** | | | | |  | |
|  | **Screening** | **Day 1** | **Day 2** | **Day 3** | **Day 4** | **Day 5** | **Day 6** | **Day 7** | **Day 8** | **Day 9** | **Day 10** | **Day 11** | **Day 15** | **Day 22** | **Day 29** | **Day 43** | **Day 57** | **Follow-up / ED 71** |
| ***Visit window (Days)*** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Informed consent |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Inclusion/exclusion criteria |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Demographic data |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Medical history/current medical conditions |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Alcohol and drug screen |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Serology |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| FSH test |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Pregnancy testing (females only) |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Height |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Body weight |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Blood sample for DNA |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| **Study residency:** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Check-in |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Check-out |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Nonresidential visit |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| **Study intervention administration:** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Randomization |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| XXX-123 or placebo |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| **Pharmacokinetics:** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Serum PK sampling |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| **Pharmacodynamics:** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Exploratory biomarkers |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Fasting glucose, insulin, C-peptide, and free fatty acids for insulin resistance; adiponectin, leptin,  fasting lipid profile |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |

| **Study Procedures (Day)** |  | **In-Residence Period** | | | | | | | | | | **Follow-up Period Cohorts 4+** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Follow-up Period Cohorts 1-3** | | | | |  | |
|  | **Screening** | **Day 1** | **Day 2** | **Day 3** | **Day 4** | **Day 5** | **Day 6** | **Day 7** | **Day 8** | **Day 9** | **Day 10** | **Day 11** | **Day 15** | **Day 22** | **Day 29** | **Day 43** | **Day 57** | **Follow-up / ED 71** |
| **Safety and tolerability:** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Immunogenicity assessment (ADA) |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Cytokine assessment |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Clinical laboratory evaluations  (chemistry, hematology, and urinalysis) |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Adverse event inquiry |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Prior/concomitant medication monitoring |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Blood pressure, pulse rate, pulse  oximetry/oxygen saturation, respiratory rate |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Body temperature |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Single safety 12-lead ECG |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Triplicate 12-lead ECG |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Physical examination |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |

Abbreviations: ADA = antidrug antibodies; AE = adverse event; SAE = serious adverse event.

## Table 2: Schedule of Activities – Repeat-Dose

| **Study Procedures (Day)** | **Screening** | **Treatment Period** | | | | | | | | | | | | | | | | **Follow-Up Period** | | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **In-Residence Period** | | | | | | | **Nonresidential** | | | **In-Residence Period** | | | | | | **Nonresidential** | | | | | | | |
| **Day 1** | **Day 2** | **Day 3** | **Day 4** | **Day 5** | **Day 6** | **Day 7** | **Day 8** | **Day 15** | **Day 22** | **Day 28** | **Day 29** | **Day 30** | **Day 31** | **Day 32** | **Day 33** | **Day 36** | **Day 39** | **Day 43** | **Day 50** | **Day 64** | **Day 78** | **Day 92 / ED** |
| ***Visit Window (Days)*** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Informed consent |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Inclusion/exclusion criteria |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Demographic data |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Medical history/current medical conditions |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Alcohol and drug screen |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Serology |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| FSH test |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Pregnancy testing (females only) |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Height |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Body weight |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Blood sample for DNA |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| **Study residency:** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Check-in |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Check-out |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Nonresidential visit |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| **Study intervention administration:** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Randomization |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| XXX-123 or placebo |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| **Pharmacokinetics:** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Serum PK sampling |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| **Pharmacodynamics:** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Serum and plasma for  exploratory biomarkers |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |

| **Study Procedures (Day)** | **Screening** | **Treatment Period** | | | | | | | | | | | | | | | | **Follow-Up Period** | | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **In-Residence Period** | | | | | | | **Nonresidential** | | | **In-Residence Period** | | | | | | **Nonresidential** | | | | | | | |
| **Day 1** | **Day 2** | **Day 3** | **Day 4** | **Day 5** | **Day 6** | **Day 7** | **Day 8** | **Day 15** | **Day 22** | **Day 28** | **Day 29** | **Day 30** | **Day 31** | **Day 32** | **Day 33** | **Day 36** | **Day 39** | **Day 43** | **Day 50** | **Day 64** | **Day 78** | **Day 92 / ED** |
| ***Visit Window (Days)*** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Fasting glucose, insulin, C-peptide, and free fatty acids for insulin resistance; adiponectin,  leptin, fasting lipid panel |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Subcutaneous adipose aspirate for exploratory biomarkers *(±1 day)* |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| **Safety and tolerability:** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Immunogenicity assessment (ADA) |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Clinical laboratory evaluations (chemistry, hematology, and  urinalysis) |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Adverse event inquiry |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Prior/concomitant medication monitoring |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Blood pressure, pulse rate, respiratory rate, pulse oximetry/oxygen  saturation |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Body temperature |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Single safety 12-lead ECG |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Triplicate 12-lead ECG |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Physical examination |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |

Abbreviations: ADA = antidrug antibodies; AE = adverse event; SAE = serious adverse event.

# INTRODUCTION

<Provide background information on the disease, the study intervention’s mechanism of action, and a summary of nonclinical results in support, with relevant citations. Suggested length is 1 page. Content below is sample only.>

<Condition> is the leading cause of <disease>, eventually leading to the need for <surgical intervention>. XXX has been the standard of care for many years, and XXX has recently been approved in the European Union and United States (US) as an additional treatment. Even with combination treatment of XXX and XXX, patients with <condition> continue to be at risk for the morbidity, mortality, and impaired quality of life associated with <disease>. Thus, a high unmet medical need remains.

XXX is a G protein-coupled receptor (GPCR), which is characterized by XXX and activated by XXX. XXX activation has also been shown to lead to the phosphorylation and activation of mitogen-activated protein kinases. Compelling evidence from nonclinical studies suggests XXX. XXX is predominantly upregulated in XXX cells in murine models of <disease>. Pharmacological inhibition by XXX ameliorates XXX, inhibits XXX and XXX, and prevents XXX.

XXX-123 is a <description of study intervention>. By targeting XXX, XXX-123 potentially reduces the risk for XXX. XXX also has the advantage of a prolonged time-action profile, allowing the safety and tolerability (and potentially pharmacodynamics [PD]) to be established over 2 to 4 weeks of meaningful exposure even with a single dose (at the high end of the dose range).

# Study Rationale

XXX-123 is intended for use in patients with <describe the target population>.

This Phase 1 study is intended to:

* + - establish safety, tolerability, and PK for up to XX days of relevant exposure in the single ascending dose (SAD) study in healthy volunteers to support a subsequent repeat-dose exploratory efficacy study in participants with <disease>;
    - obtain pharmacokinetic (PK), safety, and tolerability data in participants with <disease>;
    - explore potential phenotypic, genotypic, and biochemical approaches to identify patients most likely to respond to XXX-123.

# Background

XXX-123 is a <description of study intervention>. Monoclonal antibodies typically have a long half-life, which facilitates weekly or monthly dosing, and are generally found to be poorly penetrant to the CNS. By targeting only peripheral receptors, XXX-123 potentially reduces the risk for XXX previously described with XXX.

This is a first-in-human study. It is intended to provide the initial safety, PK, and pharmacology data for XXX-123 in humans.

In nonclinical efficacy models, results of in vitro binding studies indicate that XXX-123 is a potent, selective monoclonal antibody antagonist and inverse agonist of human and monkey XXX. Primary PD studies demonstrated that XXX-123 protects XXX in vitro.

Circulating XXX-123 was pharmacologically active at the end of the dosing period in the

XX-week repeat-dose toxicity study in cynomolgus monkeys, as determined by an ex vivo PD assay. A single dose of XXX-123 in cynomolgus monkeys resulted in a PD response associated with peripheral tissues but not with the brain, consistent with peripheral restriction of drug exposure.

The safety profile of XXX has been extensively studied with XXX in completed Phase 3 clinical studies (<drug name>, <drug name>, and <drug name>). Adverse psychiatric and neurological effects ultimately led to the termination of the development programs. However, outside of the CNS adverse effects, XXX was otherwise reported to be generally safe and well tolerated, with primary adverse effects being gastrointestinal in nature. Furthermore, XXX knockout mice exhibited no serious adverse effects, supporting the general safety of XXX.

# Benefit/Risk Assessment

XXX-123 has not been studied in humans; therefore, the risk-benefit analysis considerations are based on nonclinical data and reports in the literature on similar therapies. The benefits to participants in the XXX-123 clinical program may include contributing to the process of developing new therapies in an area of unmet need and medical evaluations/assessments associated with study procedures (eg, physical examination); participants with <disease> due to <condition> may or may not experience an impact on progression of the disease. The risks of participation are primarily those associated with adverse reactions to the investigational medicinal product, although there may also be some discomfort associated with subcutaneous (SC) injections or study procedures (eg, blood collection).

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of XXX-123 may be found in [Section 2.2](#_17nz8yj) and in the Investigator’s Brochure.

## Risk Assessment

There are no known risks, including CNS-associated risks, that have been observed in nonclinical pharmacology and safety studies of XXX-123.

XXX-123 targets peripheral receptors, potentially reducing the risk for the CNS-associated adverse effects observed in XXX (ie, <effect>, <effect>, and <effect>). Participants in the XXX-123 clinical program will be closely monitored for these CNS-associated risks until sufficient data in the XXX-123 clinical program are available to discharge these risks.

Additional risks observed in clinical studies with XXX include gastrointestinal adverse events (primarily nausea, diarrhea, and vomiting), asthenia/fatigue, hot flushes, and dizziness.

Participants will be monitored closely for the development of adverse effects that may result from study drug administration.

## Benefit Assessment

This is a non-therapeutic study in healthy volunteers (SAD component) and participants with <disease> (repeat-dose component). Potential benefits for participants in the study may include:

* + - * Contributing to the process of developing new therapies in an area of unmet need
      * Medical evaluations/assessments associated with study procedures (eg, physical examination, electrocardiogram [ECG], laboratory assessments).

## Overall Benefit: Risk Conclusion

The prior safety experience documented with XXX, as well as XXX as shown in nonclinical studies, and the lack of significant adverse findings in the XX-week monkey toxicology study, support the conduct of this study. The potential risks identified in association with XXX-123 are justified in consideration of the anticipated benefits to medical and scientific knowledge. The potential risks to the study participants can be minimized by appropriate monitoring and dose escalation during the study.

Based on the available data and the participant population to be studied, the benefit-risk assessment is favorable for participation in this study.

Refer to the Investigator’s Brochure for further details on the nonclinical studies, their findings, and potential risks.

# OBJECTIVES AND ENDPOINTS

| **Objectives/Endpoints:** The following objectives and endpoints will be evaluated in healthy participants during the SAD component of the study and in participants with <disease> in the repeat-dose component of the study. | |
| --- | --- |
| **Objectives** | **Endpoints** |
| **Primary** |  |
| * To assess the safety and tolerability after X weeks of exposure following single ascending doses of XXX-123 | * Number of participants with serious and other nonserious AEs |
| **Secondary** |  |
| * To assess the safety and tolerability following repeated doses over X weeks of XXX-123 | * Number of participants with serious and other nonserious AEs |
| * To characterize PK of XXX-123 following single ascending doses | * Cmax and AUClast |
| * To characterize the PK of XXX-123 following repeated doses | * Cmax and AUClast |
| **Exploratory** |  |
| * To explore additional PK characteristics of XXX-123 following single ascending doses | * Tmax, Clast, Tlast, AUCinf, CL, V, and t1/2 |
| * To explore additional PK characteristics of XXX-123 following repeated doses | * Tmax, Clast, Tlast, AUCinf, CL, V, and t1/2 |
| * To explore effects of XXX-123 on clinical laboratory assessments, 12-lead ECG, and vital signs following single ascending doses | * Incidence of clinically significant changes in laboratory parameters, 12-lead ECG parameters, and vital signs measurements |
| * To explore effects of XXX-123 on clinical laboratory assessments, 12-lead ECG, and vital signs following repeated doses | * Incidence of clinically significant changes in laboratory parameters, 12-lead ECG parameters, and vital signs measurements |
| * To explore the impact of ADA on the PK profile of XXX-123 following single ascending doses | * Impact of ADA on AUC or impact on overall exposure of XXX-123 |
| * To explore the impact of ADA on the PK profile of XXX-123 following repeated doses | * Impact of ADA on AUC or impact on overall exposure of XXX-123 |
| * To explore the effects on eating behavior in participants following single ascending doses of XXX-123 | * Hunger, satiety, and appetite VAS scores |
| Abbreviations: ADA = antidrug antibodies; AE = adverse event. | |

1. **STUDY DESIGN**

# Overall Design

This study will comprise a SAD escalation component in healthy volunteer participants and a repeat-dose component to confirm repeat-dose safety, tolerability, PK, and immunogenicity in participants with <disease>. It will also explore potential XXX activity, participant selection, PD, and differential response biomarkers. This study will be a conducted in a single Phase 1 unit.

Refer to S[ection 10.3 (Appendix](#_2qk79lc) 3) for mitigation strategies if changes may be required to procedures as a result of a public health emergency (eg, coronavirus disease 2019 [COVID-19]).

## Single Ascending Dose

The SAD portion of the study is double-blind, randomized, placebo-controlled, single ascending dose design in up to X cohorts of healthy participants.

All screening tests establishing eligibility will be performed following informed consent and within XX days prior to study intervention administration. Each participant will be enrolled in

1 dose cohort only; participants will reside at the Clinical Research Unit (CRU) from Day X to Day X. In each cohort, participants will receive a subcutaneous (SC) dose of XXX-123

(X participants) or placebo (X participants) on Day 1. To assure safety and tolerability of the starting dose, 2 sentinel participants will be dosed first in Cohort 1 (1 active drug and 1 placebo to maintain study blinding); the remaining Cohort 1 participants may be dosed at least XX hours later, after initial safety of the sentinel participants is confirmed by the Phase 1 Unit Principal Investigator in consultation with the Sponsor.

Following Check-out from the CRU, all participants will return for Follow-up study visits up to X weeks post dosing in the first 3 cohorts and XX weeks post dosing in the remaining cohorts as shown in the Schedule of Assessments (SoA; S[ection 1.3](#_3j2qqm3)).

Blood samples for PK and blood and urine samples for biomarkers are planned to be collected prior to dosing and at specific post-dose time points per the SoA. Timing of the blood sample collection for PK may change based on availability of new data from completed study cohorts.

Safety measurements, including 12-lead ECG; vital sign monitoring including blood pressure, pulse rate, respiratory rate, and body temperature; clinical laboratory tests (chemistry, hematology, lipid profile, cytokine assessments); physical examinations; mental health assessment; and other metrics, will be obtained at specific time points per the SoA. Adverse events and concomitant medication use will be monitored throughout the study.

The study Investigator and Medical Monitor will monitor the safety of participants in a blinded fashion throughout the study on an ongoing basis to determine whether to continue dosing, whether to escalate dose, and whether to initiate dosing in various cohorts. The allocation of participants to various cohorts may be adjusted based on the ongoing data review.

Dose escalation to the next cohort (ie, dose level) will not take place until the Sponsor, in conjunction with the Principal Investigator, has determined that adequate safety, tolerability, and PK (if available) from the previous cohort have been demonstrated to permit proceeding to the next cohort.

Dose escalation to the next cohort may occur only following review of all available clinical, laboratory safety, and any other relevant data through X days post-dose from a minimum of

X participants in the currently dosed cohort as well as all available clinical, laboratory safety, and PK data from the previous cohorts. The planned dose increment during the SAD phase of the study will not exceed half-log increments (approximately 3.3-fold). Refer to [Section 4.3](#_1mrcu09) for further details on dose selection and S[ection 6.6](#_39kk8xu) for further details on dose modifications.

Duration of participation is up to XX weeks (including up to X weeks of Screening) for the SAD.

## Repeat-Dose

The repeat-dose portion of the study is a double-blind, randomized, placebo-controlled design in 1 cohort of participants with <disease>.

All screening tests establishing eligibility will be performed following informed consent and within XX days prior to study intervention administration. Participants will reside at the CRU from Day X to Day X and Day XX to Day XX and will receive SC XXX mg XXX-123 (X participants) or placebo (X participants) every other week for X doses. The actual dose and regimen selected for this part of the study will be based on the safety, tolerability, and PK of XXX-123 as determined during the ongoing SAD component of the study. To account for anticipated accumulation, the dose selected for the repeat-dose cohort will not exceed 50% of a dose that has previously been shown to be safe and well tolerated in the single-dose cohort. Sentinel dosing is not required during this part of the study. Participants must not have been enrolled in the SAD component.

All participants will return for Follow-up study visits through X weeks following the last dose as shown in the SoA (see Section 1.3).

Blood samples for PK and blood and urine samples for biomarkers are planned to be collected prior to dosing and at specific post-dose time points per the SoA. Timing of the blood sample collection for PK may change based on availability of new data from completed study cohorts.

Safety measurements, including 12-lead ECG; vital sign monitoring including blood pressure, pulse rate, respiratory rate, and body temperature; clinical laboratory tests (chemistry, hematology, lipid profile); physical examinations; mental health assessment; and other metrics, will be obtained at specific time points per the SoA. Adverse events and concomitant medication use will be monitored throughout the study. Refer to [Section 6.6](#_39kk8xu) for further details on dose modifications.

Duration of participation is up to XX weeks (including up to X weeks of Screening) for the repeat-dose portion of the study.

# Scientific Rationale for Study Design

The SAD portion of this study is a standard design for first-in-human testing with a monoclonal antibody. In addition, a 4-week repeated dose cohort will allow confirmation of the safety, tolerability, and repeat-dose PK and immunogenicity in the target population prior to proceeding to subsequent repeat-dose studies in a patient population.

# Justification for Dose

The planned clinical starting dose in healthy volunteers (HVs) is a single dose of X mg of XXX-123 administered as an SC injection. The planned maximum dose is XXX mg.

The clinical starting dose is based on an integrated approach supported by the Good Laboratory Practice (GLP) toxicology study approach, the minimal cytokine change, expected 10% receptor occupancy (RO) attained at maximum observed serum concentration (Cmax), and utilizing the minimal anticipated biological effect level (MABEL) based on the half-maximal inhibitory concentration (IC50) of XXX-123 on binding and inhibition of XXX.

The XX-week GLP toxicology study was conducted in cynomolgus monkey, as this is the most relevant species for evaluation based on in vitro cross-reactivity (<nonclinical study number>). The no observed adverse effect level (NOAEL) in this study was XXX mg/kg. In addition, there is a X-fold difference in binding of XXX-123 in monkey to human XXX; therefore, the human equivalent dose of the NOAEL is XXX mg/kg. Based on the maximum recommended starting dose (MRSD) guidance, a factor of 10 can be used to determine the maximum allowable starting dose, with an estimated maximum starting dose of XX mg/kg of XXX-123.

The planned starting dose of X mg given as a single SC injection in HVs is expected to be XXX-fold lower than the dose supported by the GLP toxicology study. Starting at the dose of X mg will ensure full characterization of safety, PK, and PD of XXX-123.

# Start and End of Study Definitions

The start of the study is defined as the date the first participant signs an informed consent form (ICF).

The end of the study is defined as the date of the last participant’s last assessment (scheduled or unscheduled).

# STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

To be considered for enrollment in this study, participants must meet all the following Inclusion Criteria and none of the Exclusion Criteria. Retesting of eligibility assessments previously not met may be permitted once upon discussion with the Medical Monitor.

# Inclusion Criteria

1. Understands study procedures and voluntarily provides written informed consent.
2. Willing and able to abide by the study restrictions, including the lifestyle considerations in [Section 5.3](#_3ygebqi).
3. Willing and able to complete all study visits, in-residence requirements, and procedures.
4. XX to XX years of age at the time of signing informed consent.
5. Body mass index (BMI) between XX and XX kg/m2, inclusive, at Screening.
6. Female participants will be of non-childbearing potential (refer to [Section 10.5](#_4gjguf0) [A[ppendix 5](#_4gjguf0)] for definition of non-childbearing potential).
7. Male participants will agree to use contraception while on study intervention and for at least X months after the last dose of study intervention.
8. SAD cohorts only: Participants must be in good health, determined by no clinically significant findings from medical history, physical examination, 12-lead ECG, vital signs measurements, and clinical laboratory evaluations (see exclusion criteria for criteria for specific labs) at Screening as assessed by the Investigator. Clinical laboratory assessments may be repeated once at the Investigator’s discretion if laboratory error is suspected.
9. Repeat-dose cohort only: <disease> treated with XXX or XXX and in otherwise good health except for well-controlled common conditions associated with <disease>, such as <condition> or <condition>. Clinical laboratory assessments may be repeated once at the Investigator’s discretion if laboratory error is suspected.

# Exclusion Criteria

1. History of, or treatment for, XXX, including XXX or XXX within X years of the Screening visit.
2. History of XXX.
3. Blood pressure >155 mmHg systolic or >95 mmHg diastolic.
4. Known heart disease or clinically significant abnormalities identified in the 12-lead ECG at Screening. Specific exclusion criteria are:
   1. QT interval corrected for heart rate using Fridericia’s method (QTcF) >450 msec (males) or >470 msec (females) confirmed by calculating the mean of the original value and 2 repeats.
   2. QRS duration >120 msec confirmed by calculating the mean of the original value and 2 repeats.
   3. PR interval >220 msec confirmed by calculating the mean of the original value and 2 repeats.
   4. Findings that would make corrected QT (QTc) measurements difficult or QTc data uninterpretable.
   5. Family history of long QT syndrome.
5. Female participant with a positive pregnancy test or who is lactating at Screening.
6. History of alcoholism or drug/chemical abuse within 2 years prior to Screening.
7. Prior exposure to XXX-123 or <therapy type>.
8. Participation in a clinical study involving administration of an investigational drug (new chemical entity) in the past XX days or X half-lives of last dose (whichever is longer) prior to first dosing.
9. History of significant hypersensitivity, intolerance, or allergy to more than one class of drugs.
10. Aspartate aminotransferase, alanine aminotransferase, or total bilirubin >2 × upper limit of normal.
11. Positive hepatitis panel and/or positive human immunodeficiency virus test. Participants whose results are compatible with prior immunization may be included.
12. Have previously completed or withdrawn from this study. Alternates for prior cohorts who were not assigned to treatment and did not receive study intervention are considered eligible.
13. SAD cohorts only: Fasting glucose >XX mg/dL.

# Lifestyle Considerations

Donation of sperm is not permitted for male participants from Check-in until X months after the last dose of study intervention.

Donation of blood is not permitted from X weeks (XX weeks for double red cell donation) prior to Screening until XX days after the final Follow-up visit.

Use of tetrahydrocannabinol, cannabidiol (CBD), or other cannabinoid is not permitted for XX days prior to Screening through the end of participation in the study.

Any vaccinations anticipated during the course of the study should be completed at least XX days prior to Screening.

SAD Cohorts: Use of any prescription or nonprescription medications/nutritional products including vitamins (except ongoing multivitamin supplement), minerals, and phytotherapeutic/herbal/plant-derived preparations is not permitted from Screening until the end of the study, unless deemed acceptable by the Investigator. Saline, lidocaine, or other medications required by study procedures are permitted at the Investigator’s discretion. Paracetamol/ acetaminophen (X g/day for up to X consecutive days) is allowed as needed.

Repeat-Dose Cohort: Study participants will continue to receive their usual <disease treatment> throughout the study. Concomitant medications for XXX, XXX, and XXX must be stable for at least XX days prior to Screening and may not be changed from time of Screening until end of study, unless deemed acceptable by the Investigator. Saline, lidocaine, or other medications required by study procedures are permitted at the Investigator’s discretion. Paracetamol/ acetaminophen (X g/day for up to X consecutive days) is allowed as needed.

## Meals and Dietary Restrictions

SAD cohort only: Participants must be willing and able to adhere to <dietary requirements> as described in S[ection 8.2.3](#_3rnmrmc).

SAD and repeat-dose cohorts: Participants must be willing and able to fast for at least XX hours prior to fasting laboratory tests.

## Caffeine, Alcohol, and Tobacco

* + - 1. Participants will abstain from ingesting caffeine- or xanthine-containing products (eg, coffee, tea, cola drinks, and chocolate) from XX hours before Check-in until Check-out from the CRU.
      2. Participants will abstain from alcohol from XX hours before Check-in until Check-out from the CRU.
      3. Participants who use tobacco products will be instructed that use of nicotine-containing products (including nicotine patches) will not be permitted while they are in the CRU.

## Activity

Participants should avoid strenuous activity within XX hours prior to Check-in and subsequent return visits. Participants may engage in light recreational activities during the study (eg, watching television, reading). Study participants in the repeat-dose cohort may continue their usual exercise/activity regimen but should not increase intensity during the study.

# Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but do not meet study entry criteria and are not subsequently randomly assigned to study intervention. 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 (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened upon discussion with the Medical Monitor. If a participant is inside the Screening window and repeating a single out-of-range assessment, the participant’s original participant number should be retained. If a participant is outside the Screening window and repeating all assessments, a new participant number should be assigned.

# STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), or placebo intended to be administered to a study participant according to the study protocol.

**Test Product**: XXX-123 injection is supplied in a X mL vial containing XXX mg/mL XXX-123. Administration route: subcutaneous.

SAD: Proposed starting dose level: X mg with approximate half-log escalations.

Repeat-dose: Proposed dose level: XXX mg every other week for 3 doses.

The actual dose and regimen for the repeat-dose component will be determined based on safety, tolerability, and PK data from the SAD component of this study.

**Placebo Product**: Matching placebo injection is supplied in a X mL vial. Administration route: subcutaneous.

# Study Intervention(s) Administered

| **Arm Name** | **XXX-123** | **Placebo** |
| --- | --- | --- |
| **Intervention Name** | XXX-123 | Placebo (blinded) |
| **Type** | <type> | NA |
| **Dose Formulation** | Injectable solution | Injectable solution |
| **Unit Dose Strength(s)** | XXX mg/mL | Matching placebo |
| **Dosage Level(s)** |  |  |
| **SAD** | X mg with approximate half-log escalations | NA |
| **Repeat-dose** | Proposed dose level: XXX mg every other week for X doses (to be confirmed based on SAD data) | NA |
| **Route of Administration** | Subcutaneous | Subcutaneous |
| **Use** | Experimental | Placebo |
| **IMP and NIMP** | IMP | IMP |
| **Sourcing** | Provided centrally by the Sponsor | Provided centrally by the Sponsor |
| **Packaging and Labeling** | XXX-123 will be provided in glass vials. Each vial will be labeled as required per FDA requirements. | Placebo will be provided in matching glass vials. Each vial will be labeled per FDA requirements. |

Abbreviations: FDA = Food and Drug Administration; IMP = investigational medicinal product; NA = not applicable; NIMP = noninvestigational medicinal product.

Injections will be administered by the Investigator (or qualified designee). Injections may be administered in the abdomen. The injection site may be divided into quadrants and the quadrants rotated for each injection for the repeat-dose component of the study. Injection sites will be carefully monitored.

# Preparation/Handling/Storage/Accountability

* + 1. The Investigator or designee must confirm that frozen conditions (≤ -60°C) have been maintained during transit for all study intervention received, and any temperature excursions are reported and resolved before use of the study intervention.
    2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) ≤ -60°C freezer in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.
    3. Prior to dosing, the study intervention will be removed from the freezer and placed on the pharmacy counter until all contents in the vial(s) are completely thawed. The Investigator will follow all procedures as outlined in the Pharmacy Manual for handling and dosing the study intervention. XXX-123 product following preparation for administration should be stored for no more than 4 hours at room temperature or 24 hours at 2-8°C per FDA recommendation.
    4. The Investigator is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records). The Investigator (or designee) will maintain an accurate record of the study supplies received. In addition, an accurate drug disposition record will be kept, specifying the amount dispensed to each participant and the date of dispensing. This drug accountability record will be available for inspection at any time. At the completion of the study, the original drug accountability record will be available for review by the Sponsor upon request.
    5. Further guidance and information for the final disposition of unused study intervention are provided in the Pharmacy Manual.

# Measures to Minimize Bias: Randomization and Blinding

The following controls will be employed to maintain the double-blind status of the study:

* The placebo solution vial and label will be indistinguishable in appearance to XXX-123.
* With the exception of the site pharmacy staff, the Investigator and other members of site staff involved with the study will remain blinded to the treatment randomization code during the study.
* The bioanalytical laboratory personnel responsible for assaying PK samples will be unblinded but will provide XXX-123 concentration data to selected contract research organizations (CRO) and the Sponsor in a blinded manner.
* The CRO and Sponsor PK, absorption, distribution, metabolism, and excretion (ADME), biomarker, or clinical scientists who are not directly involved with study management or in direct contact with the site personnel may be unblinded for the purposes of exploratory biomarker evaluation and development of PK and PD response models during the course of the study.

Participants will be randomly assigned in a X:1 ratio (XXX-123: placebo) to receive study intervention.

To maintain the blind, each participant will receive an assigned treatment (active or placebo) based on the randomization schedule prepared by the unblinded statistician.

The treatment assignment should be unblinded at the clinic only in the case of an emergency, when knowledge of the study intervention assignment is absolutely necessary for the clinical management or welfare of the participant, or where necessary to determine if dose-limiting toxicity (DLT) criteria have been met ([Section 6.6.1](#_39kk8xu)). Breaking of the blind at the clinic under any other circumstances will be considered a protocol deviation. The Investigator is strongly encouraged to contact the Sponsor before unblinding the study intervention assignment prior to the scheduled assessment of tolerance and safety data unless there is an urgent safety issue that must be addressed as a priority. If the blind is broken for any reason, the Investigator must notify the Sponsor within 24 hours, and an SAE form must be completed, if appropriate. In addition, the Investigator will record the date and reason for revealing the blinded study intervention assignment for that participant in the source documents and appropriate electronic case report form (eCRF) page(s).

In the event of a Quality Assurance audit, the auditor(s) will be allowed access to unblinded study intervention records at the site(s) to verify that randomization/dispensing has been done accurately.

# Study Intervention Compliance

Participants are to be dosed at the site and will receive study intervention directly from the Investigator or their designee, under medical supervision. The date and time of each dose administered in the clinic as well as the injection location will be recorded in the source documents and recorded in the eCRF. Study participant identification and the dose of study intervention will be confirmed at the time of dosing by the person administering the study intervention and by another member of the study site staff.

# Concomitant Therapy

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

* Reason for use
* Dates of administration including start and end dates
* Dosage information including dose and frequency

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

## 6.5.1. Rescue Medicine

Not applicable.

# Dose Modification

## Dose Escalation and Stopping Criteria

Dose escalation will proceed in no greater than half-log (approximately X-fold) increments. As described in [Section 4.](#_vx1227)1, the Sponsor and Principal Investigator will be responsible for reviewing safety and tolerability data and making dose escalation decisions for each cohort. A smaller dose escalation increment may be chosen for any cohort. A dose escalation increment greater than the planned half-log increment is not permitted.

If any of the dose escalation stopping criteria are met, dose escalation will be put on hold pending further review of the data, which may include assessing data from any cohort (eg, evaluating for laboratory test trends) and unblinding of 1 or more participants per the procedures outlined in [Section 6.3](#_2iq8gzs). Dosing may be suspended in the current or in other cohorts if deemed necessary. Based on the review, the Sponsor and Principal Investigator may recommend resuming the planned escalation, modifying the dose escalation in subsequent cohorts, or terminating further dose escalation. Once dose escalation is terminated, subsequent cohorts may be dosed at the maximum tolerated or lower doses to obtain additional safety and PK data at the discretion of the Sponsor. The data review may also result in changes to safety monitoring or eligibility criteria to ensure the safety of the participants. The results of the review will be communicated to the Institutional Review Board (IRB) prior to resuming dose escalation.

Dose-limiting toxicities will be defined as follows:

| **Toxicity** | **Criteria for Stopping Dosing in Any Participant (as applicable) – Repeat Dose** | **Dose Escalation Stopping Rules – Single Dose** |
| --- | --- | --- |
| TEAEs | * Drug-related SAE * Drug-related severe TEAE | * 1 or more drug-related SAEs in XXX-123-treated participants * 1 or more drug-related severe TEAEs or >50% similar drug-related moderate TEAEs in XXX-123- treated participants |
| Hepatic (criteria do not apply to elevations with an extrahepatic etiology) | * ALT or AST >5×ULN for greater than 2 weeks * ALT or AST >3×ULN and (TBL   >2×ULN or INR >1.5)  (confirmed by repeat testing)   * ALT or AST >3×ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%) (confirmed by repeat testing) | * >1 drug-related events in XXX-123- treated participants with ALT or AST >5×ULN for greater than   2 weeks   * 1 drug-related event in XXX-123- treated participants with ALT or AST >3×ULN and (TBL >2×ULN or INR >1.5) * 1 drug-related event in XXX-123- treated participants with ALT or AST >3×ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, |

| **Toxicity** | **Criteria for Stopping Dosing in Any Participant (as applicable) – Repeat Dose** | **Dose Escalation Stopping Rules – Single Dose** |
| --- | --- | --- |
|  | Refer to [Section 10.6](#_gtnh0h) (Appendix 6) for guidance on the management and follow- up of these events. | fever, rash, and/or eosinophilia (>5%) |
| Other toxicity | * Any other adverse clinical or laboratory adverse effects that would, in the judgment of the Investigator, present significant risk to the participant | * Any other adverse clinical or laboratory effects that would, in the judgment of the Sponsor or Principal Investigator, present significant risk to participants administered higher doses |

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; INR = international normalized ratio; SAE = serious adverse event; TBL = total bilirubin; TEAE = treatment-emergent adverse event; ULN = upper limit of normal.

Consultation with a relevant clinical or other specialist for adjudication of any of these cases may be obtained as appropriate.

If study intervention is withheld in an individual participant due to AEs, scheduled visits and all assessments should continue to occur. In the repeat-dose component, the participant may resume dosing at the same or lower dose based on the discretion of the Investigator and discussion with the Medical Monitor provided that resuming treatment would not pose a significant risk to the participant.

## Maximum Tolerated Dose

The maximum tolerated dose is defined as the highest dose tested in the SAD component of the study at which dose escalation stopping criteria are not met and that is deemed safe with acceptable PK.

# Intervention After the End of the Study

No intervention following the end of the study is planned.

# DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

# Discontinuation of Study Intervention

See the SoA (Section 1.3) for data to be collected at the time of intervention discontinuation and Follow-up and for any further evaluations that need to be completed.

## Individual Participant Discontinuation

A participant may stop treatment at any time for any reason. Treatment discontinuations may be initiated by a participant due to scheduling difficulties, dissatisfaction with study requirements or treatment, or medical necessity due to AEs or other issues.

The Investigator in consultation with the Sponsor should determine if the participant can continue participation in the trial if modifications to his/her treatment and/or SoA can be accommodated.

A participant who permanently discontinues treatment will have an early discontinuation (ED) visit and will have the reason for treatment discontinuation recorded on the eCRF. The participant will be encouraged to complete the remaining study visits.

A participant may temporarily interrupt or discontinue study intervention for any reason including those listed below:

* + - * Participant decides to discontinue due to annoyance or discomfort due to a nonserious AE which is not otherwise determined to be an undue hazard.
      * Continuing study intervention places the participant at undue hazard as determined by the Investigator (eg, a safety concern that is possibly, probably, or likely related to study intervention)
      * SAE
      * Liver test abnormalities meeting criteria for permanent discontinuation (see Section 6.6.1 and [Section 10.6 [Appendix](#_gtnh0h) 6])
      * Participant meets DLT criteria (S[ection 6.6.1](#_39kk8xu))
      * Death
      * Reasons unrelated to medical condition (provide detail and review AE history with participant)
      * Withdrawal of informed consent (complete written withdrawal of consent form)
      * Loss to follow-up
      * Pregnancy
      * Termination of all or part of the trial by the Sponsor

If the participant temporarily interrupts or discontinues study intervention due to an AE, the Investigator, or other trial personnel, will make every effort to follow the AE until it has resolved or stabilized.

## Withdrawal of Consent

All participants have the right to withdraw their consent from further participation in the trial at any time without prejudice. Unless the participant provides their written withdrawal of consent or there is other written documentation by the Investigator confirming the participant’s verbal intent to completely withdraw from the trial, participants should be followed for all

protocol-specified evaluations and assessments.

Complete withdrawal of consent requires a participant’s refusal of ALL of the following methods of follow-up:

* + - * Participation in all follow-up procedures specified in the protocol (whether in clinic, by telephone, or by an in-home visit).
      * Participation in a subset of protocol-specified follow-up procedures (by a frequency schedule and method as agreed by participant and staff).
      * Contact of the participant by trial personnel, even if only by telephone, mail, or email, to assess current medical condition and obtain necessary medical or laboratory reports relevant to the trial’s objectives.
      * Contact of alternative person(s) who have been designated in source records as being available to discuss the participant’s medical condition, even if only by telephone, mail, or email (eg, family, spouse, partner, legal representative, friend, neighbor, physician).
      * Access to medical information from alternative sources (eg, hospital/clinic medical records, referring doctor’s notes, public records, social media sources).

The reasons for the participant’s intended withdrawal need to be completely understood, documented, and managed to protect the rights of the participant and the integrity of the trial.

Only participants who withdraw their permission for all of the above degrees of follow-up are considered to have completely withdrawn their consent to participate in the study.

If the participant withdraws consent for disclosure of future 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, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

Participants who are withdrawn for reasons not related to study intervention may be replaced following discussion between the Investigator and the Sponsor. Participants withdrawn as a result of AEs thought to be related to the study intervention will not be replaced.

## Procedures to Encourage Continued Trial Participation

In all cases of impending study intervention discontinuation, Investigators will be given instructions to meet and discuss with the participant their options of continuing in the trial or not, preferably on therapy. The Investigator should clearly highlight that any decision is solely the participant's, and there would be no repercussions if they choose to leave the trial. The

Investigator should ensure understanding and documentation of the reasons for the participant’s desire to withdraw consent.

# Lost to Follow-up

A participant will be considered lost to follow-up if he or 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 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 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.
* Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

# STUDY ASSESSMENTS AND PROCEDURES

* Study procedures and their timing are summarized in the SoA ([Section 1.3](#_3j2qqm3)). Protocol waivers or exemptions are not allowed.
* Immediate safety concerns should be discussed with the Medical Monitor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
* Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
* All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
* Procedures conducted as part of the participant’s routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.
* Refer to S[ection 10.3 (Appendix 3](#_2qk79lc)) for mitigation strategies if changes may be required to procedures as a result of a public health emergency (eg, COVID-19).

# Pharmacokinetic Assessments

## Sample Collection and Processing

Blood samples for PK and biomarkers will be collected by venipuncture or cannulation at the times indicated in the SoA (Section 1.3). Furthermore, up to 3 additional blood samples may be taken from each participant per treatment period. Any changes to the scheduled times of PK assessments will be agreed with the Sponsor and documented in the Trial Master File (TMF).

Procedures for collection, processing, and shipping of PK blood samples will be detailed in a separate document.

## Analytical Methodology

Serum concentrations of XXX-123 will be determined using validated analytical procedures. Specifics of the analytical methods will be provided in separate documents.

# Pharmacodynamic Assessments

This study will collect samples for biomarker as[sessments in all](#_3j2qqm3) participants (where not prohibited by local regulations). For biomarker assessments, whole blood, serum, and plasma will be collected from all enrolled participants (where not prohibited by local regulations or policies). The results may help to inform dose selection, monitor baseline and post-treatment responses, and possibly further characterize the mechanism of action and/or determine potential prognostic and/or predictive biomarkers to assist in any research related to XXX-123, <disease>, and for potential diagnostic development. Based on emerging data or for operational reasons, certain samples may not be collected and/or analyzed. All analyses will be conducted by the Sponsor or designee.

## Exploratory Biomarkers

Blood sampling will be conducted for analysis of exploratory PD and safety biomarkers. The timings of all PD assessments to be performed during the study are indicated in the SoA (S[ection 1.3](#_3j2qqm3)) and may be subject to change based on the ongoing review of the data. Furthermore, up to 3 additional blood samples may be taken from each participant per treatment period (where applicable). Any changes to the scheduled times of PD assessments will be agreed with the Sponsor and documented in the TMF.

# Immunogenicity Assessments

Antibodies to XXX-123 will be evaluated in serum samples collected from all participants according to the SoA (Section 1.3). Additionally, serum samples should also be collected at the final visit from participants who discontinued study intervention or were withdrawn from the study. These samples will be tested by the Sponsor or Sponsor's designee.

Serum samples will be screened for antibodies binding to XXX-123, and the titer of confirmed positive samples will be reported. Other analyses may be performed to verify the stability of antibodies to XXX-123 and/or further characterize the immunogenicity of XXX-123.

The detection and characterization of antibodies to XXX-123 will be performed using a validated assay method by or under the supervision of the Sponsor. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of the study intervention(s). Samples may be stored for at least X years (or according to local regulations) following the last participant’s last visit for the study at a facility selected by the Sponsor to enable further analysis of immune responses to XXX-123.

# Pharmacogenomics

Where local laws and regulations allow, a blood sample will be collected for genetic analysis, as outlined in the SoA ([Section 1.3](#_3j2qqm3)) and described under the main ICF.

This sample may be used to investigate the impact of genetic variation on the safety, efficacy, ADME of XXX-123 and similar therapies and to further our understanding of drug response and the genetics of XXX, XXX, XXX, and other aspects of <disease> and traits of interest to the Sponsor. Information obtained will not have clinical diagnostic or therapeutic implications for the participant and will not be provided to the participant or the Investigator.

To ensure participant confidentiality, samples will be coded and identified by a participant identification number and will be stored in a secure location chosen by the Sponsor. Samples will be stored for a maximum of XX years, until they are exhausted, or until the Sponsor requests the destruction of samples, whichever is sooner.

# Safety Assessments

Planned time points for all safety assessments are provided in the SoA.

Every effort will be made to schedule and perform the procedures as closely as possible to the nominal time, considering appropriate conditions, practical restrictions, and the other procedures to be performed at the same time point. Actual times are to be recorded in the eCRF.

The suggested order of assessments of pre-dose procedures is as follows:

* ECG
* Vital signs
* Blood samples
* Any other procedures
* Dosing

The suggested order of assessments of post-dose procedures is as follows:

* ECG
* Vital signs
* Blood samples
* Any other procedures

## Physical Examinations

A full physical examination will be performed at the time points specified in the SoA ([Section 1.3](#_3j2qqm3)).

* + - * A full physical examination will include, at a minimum, assessments of head, eyes, ears, nose, and throat (HEENT), neck, chest, skin, cardiovascular system, respiratory system, gastrointestinal system/abdomen, genitourinary system (at discretion of Investigator), lymphatic system, musculoskeletal system, and neurological system.
      * Investigators should pay special attention to clinical signs related to previous serious illnesses.

## Vital Signs

* + - * Temperature, pulse rate, respiratory rate, blood pressure, oximetry, and pulse oximetry will be assessed.
      * Blood pressure and pulse measurements will be assessed while the participant is supine.
      * Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones).
      * Vital signs will consist of 1 pulse and 1 blood pressure measurement; vital sign measurements may be repeated at the discretion of the Investigator.

## Body Weight

Body weight (in light clothing or a gown and without shoes) will be recorded at the times indicated in the SoA.

Body weight will be measured using a consistent scale at each visit (calibrated when possible). When feasible, participants should be weighed fasting at approximately the same time of day on the same scale. Participants should urinate prior to being weighed.

## Height

Height will be recorded at Screening only and used to calculate BMI.

Height should be measured without shoes using a consistent device for all participants.

## Electrocardiograms

* + - * 12-lead ECG will be obtained as outlined in the SoA (see S[ection 1.3](#_3j2qqm3)) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals.
      * At each time point at which triplicate ECG are required, 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart. The full set of triplicates should be completed in less than 4 minutes when possible. During the residential phase, these may be collected from 12-lead ECG telemetry, if available.

## Clinical Safety Laboratory Assessments

* + - * See S[ection 10.2 (Appendix 2](#_3c9z6hx)) for the list of clinical laboratory tests to be performed and the SoA for the timing and frequency.
      * The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant’s condition.
      * All laboratory tests with values considered clinically significantly abnormal during participation in the study or within XX weeks after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or Medical Monitor.
        + If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified, and the Sponsor notified.
        + All protocol-required laboratory assessments, as defined in Section [10.2](#_3c9z6hx) (Appendix 2), must be conducted in accordance with the SoA and any applicable Laboratory or Procedures Manual SoA.
        + If laboratory values from non-protocol-specified laboratory assessments performed at the institution’s local laboratory require a change in participant management or are considered clinically significant by the Investigator (eg, SAE or AE or dose modification), the results must be recorded in the eCRF.

# Adverse Events and Serious Adverse Events

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue study intervention (see [Section 7](#_40ew0vw)).

The Investigator must evaluate the clinical significance of a finding prior to grading and recording it as an AE.

## Time Period and Frequency for Collecting AE and SAE Information

All AEs will be collected from the signing of the ICF until the last study visit or XX days after the last dose of study intervention, whichever is longer.

Medical occurrences that begin before signing of the ICF will be recorded in the Medical History/Current Medical Conditions section of the eCRF, not in the AE section. Any worsening of a medical occurrence after signing of the ICF is to be reported as an AE.

All SAEs will be recorded and reported to the Sponsor or designee immediately (S[ection 10.4 [Appendix 4](#_3pp52gy)]), and under no circumstance should this exceed 24 hours. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AEs or SAEs after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the Investigator must promptly notify the Sponsor.

## Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Section [10.4](#_3pp52gy) (Appendix 4).

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

AE occurrences. Participants will also be encouraged to spontaneously report AEs occurring at any other time during the study.

## Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in

Section 7.2). Further information on Follow-up procedures is provided in Section [10.4](#_3pp52gy) (Appendix 4).

## Regulatory Reporting Requirements for SAEs

* + - * Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
      * The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/Independent Ethics Committees (IECs), and Investigators.
      * For all studies, Investigator safety reports must be prepared for suspected unexpected [serious adve](#_279ka65)rse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.
      * An Investigator who receives an Investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will

review and then file it along with the Investigator’s Brochure and will notify the IRB/IEC, if appropriate, according to local requirements.

## Pregnancy

* + - * If a pregnancy is reported in a study participant or the partner of a male study participant, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in S[ection 10.5](#_4gjguf0)

([Appendix 5](#_4gjguf0)).

* + - * Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

Study intervention should be discontinued if positive or indeterminate pregnancy testing results are obtained.

# Treatment of Overdose

The Sponsor does not recommend specific treatment for an overdose. In the event of an overdose, the Investigator should:

* + 1. Contact the Medical Monitor immediately.
    2. Closely monitor the participant for any AE/SAE, laboratory abnormalities, and PK per protocol.
    3. Document the quantity of the excess dose as well as the duration of the overdose 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.

# Medical Resource Utilization and Health Economics

Not applicable.

# STATISTICAL CONSIDERATIONS

# Statistical Hypotheses

The statistical analyses do not investigate prior hypotheses, but instead, the analyses are a way of highlighting and estimating the size of possible effects.

# Sample Size Determination

Single Ascending Dose: X cohorts of X participants per cohort are planned; however, enrollment of up to XX participants will be permitted, including replacements.

Repeat-dose: X participants in a single cohort are planned; however, enrollment of up to XX participants will be permitted, including replacements.

For this early development study, formal statistical calculations of sample size are not appropriate. The number of participants per cohort is the customary sample size employed in early development studies, which is expected to allow clinical judgment of safety and tolerability and assessment of the PK profile. If an AE occurs at the rate of 1% or 10%, then the chance of observing such an AE among X participants receiving that dose of active study intervention will be X% or XX%, respectively. If no AE of a given type is observed in any of the participants at a given dose of active study intervention, then with XX% (XX%) confidence the true incidence of the AEs at that dose is at most XX% (XX%).

# Populations for Analyses

The following populations are defined:

| **Population** | **Description** |
| --- | --- |
| Enrolled | All participants who sign the ICF |
| PK | All participants who received at least 1 dose of XXX-123 and have concentration data for at least 1 post-baseline time point and no major protocol deviations |
| PD | All participants who received at least 1 dose of study intervention (XXX-123 or placebo) and have at least 1 PD measurement and no major protocol deviations |
| Safety | All participants randomly assigned to study intervention and who receive at least 1 dose of study intervention. Participants will be analyzed according to the intervention they actually received. |

Abbreviations: ICF = informed consent form; PD = pharmacodynamic; PK = pharmacokinetic.

# Statistical Analyses

The statistical analysis plan (SAP) will be finalized prior to database lock and it will include a more technical and detailed description of the statistical analyses described in this section. In the case of any deviation from the planned analyses described in the protocol, the SAP takes precedence, in which the reasons for the change and impact on study results should be carefully described.

## Initial Participant Characteristics

For all participants who received at least 1 dose of study intervention, descriptive statistics (mean, standard deviation, median, minimum, maximum) will be performed for age, BMI, weight, and height function. Sex will be listed and tabulated.

## Pharmacokinetic Analyses

Individual and summary serum concentration versus time profiles will be plotted using linear and semi-logarithmic scales for each dose level. The PK parameters for XXX-123 will be calculated using noncompartmental methods and presented in summary tables using descriptive statistics (mean, standard deviation, minimum, median, maximum, coefficient of variation, and geometric mean, and geometric coefficient of variation where applicable).

Dose proportionality of XXX-123, the area under the serum concentration-time curve (AUC) from time zero to infinity (AUCinf), AUC from time zero to the last measurable concentration (AUClast), and Cmax will be evaluated using descriptive statistics and visual inspection of the scatter plots of these parameters versus dose level. In addition, dose proportionality will be evaluated using a power model approach.

## Pharmacodynamic Analyses

Pharmacodynamic parameters will be listed and summarized using descriptive statistics. No formal statistical analysis of PD data is planned. Association between PK and PD will be evaluated using appropriate statistical methods. These exploratory analyses will be detailed in the SAP. Combined with PK and safety data, the analyses will aid in study design in the future, including dose selection and identification of a population that may specifically benefit from treatment with XXX-123.

## Safety Analysis

Adverse events will be summarized using descriptive methodology by association with the study intervention, severity, and/or frequency. Clinical laboratory test data will be summarized by descriptive statistics, including change from baseline, and will be categorized based on severity grade. Shift tables will be provided for clinical laboratory test data and 12-lead ECGs. The incidence of clinically relevant post-baseline vital sign abnormalities will be summarized by number and percentage of participants.

## Immunogenicity

Individual serum concentrations of anti-XXX-123 antibodies and their incidence or persistence will be listed, tabulated separately for each dose level and sampling time, and summarized using descriptive statistics.

# Interim Analyses

In order to facilitate planning of the next clinical study, an unblinded interim analysis will be performed when the last participant dosed has completed at least X days of follow-up. The interim analysis will include safety, PK, biomarker, and other data as needed to inform the design and initiation of subsequent studies.

# Data Monitoring Committee

Not applicable

# SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

# Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

## 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 (CIOMS) International Ethical Guidelines
      * Applicable International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
      * Applicable laws and regulations

The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants or changes to the PK sample timing.

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 IRB/IEC
      * Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
      * Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

## Financial Disclosure

The provision of financial disclosure in accordance with 21 CFR (US), or as applicable in the country to conduct, by applicable parties is required and will be addressed via a standalone agreement.

## Informed Consent Process

* + - * The Investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
      * Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
      * The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
      * Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
      * A copy of the ICF(s) must be provided to the participant or the participant’s legally authorized representative.

## 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.

## Dissemination of Clinical Study Data

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

## Data Quality Assurance

The following data quality steps will be implemented:

* + - * All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
      * The Investigator must maintain complete and accurate documentation (source data) that supports the information entered in the eCRF.
      * The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
      * Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk- Based Monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the TMF.
      * The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
      * The Sponsor will provide oversight for actions delegated to other individuals (eg, CRO).
      * Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
      * Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 2 years (or until final marketing authorization approval) after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

## Source Documents

* + - * 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 reported on the eCRF or 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.

## Study and Site Start and Closure

The first act of recruitment is the first site open and will be the study start date.

The Sponsor designee 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.

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

## Publication Policy

* + - * The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
      * The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.
      * Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

# Appendix 2: Clinical Laboratory Tests

* The tests detailed in [Table 4](#_3c9z6hx) will be performed by the local laboratory.

## Table 4: Clinical Laboratory Evaluations

| **Clinical chemistry:** | **Hematology:** | **Urinalysis:** |
| --- | --- | --- |
| Alanine aminotransferase Aspartate aminotransferase Gamma-glutamyl transferase Alkaline phosphatase  Total bilirubin (with direct and indirect if elevated) Albumin  Total protein  Blood urea nitrogen Creatinine (with eGFR by CKD-EPI a)  Sodium Potassium Chloride  Total CO2 (measured as bicarbonate)  Calcium Phosphorus Magnesium Glucose  Creatine phosphokinase C-reactive protein | RBC count Hemoglobin Hematocrit  Mean cell volume Mean cell hemoglobin  Mean cell hemoglobin concentration RBC distribution width  Platelet count WBC count WBC differential: Basophils Eosinophils Lymphocytes Monocytes Neutrophils  **Coagulation profile:**  Activated partial thromboplastin time International normalized ratio Prothrombin time | Bilirubin Blood  Color and appearance Glucose  Ketones Leukocyte esterase Nitrite  pH Protein  Specific gravity Urobilinogen  Microscopic examination (if protein, leukocyte esterase, nitrite, or blood is positive) |
| **Serology:** | **Drug screen:** | **FSH test:** |
| Anti-hepatitis B surface antibody  Anti-hepatitis B core antibody  Hepatitis B surface antigen Hepatitis C antibody Human immunodeficiency (HIV-1 and HIV-2)  antibodies and p24 antigen | Including but not limited to: Amphetamines/methamphetamines Barbiturates  Benzodiazepines Cocaine (metabolite) Methadone Phencyclidine Opiates  Tetrahydrocannabinol/ Cannabinoids  Alcohol breath/urine test | Follicle-stimulating hormone |
| **Other:** | **Biomarkers:** | **Cytokine assessment:** |
| COVID-19 test (as applicable per local regulations) Pregnancy testing (hCG) a | Adiponectin, leptin, fasting lipid profile (total cholesterol, triglycerides, HDL, LDL), fasting glucose, insulin, free fatty acids, and C-peptide (calculation of insulin resistance) Urinary MCP-1 | IL-8  TNF-alpha IFN-gamma |

Abbreviations: CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; CLIA = Clinical Laboratory Improvement Amendments; CO2 = carbon dioxide; COVID-19 = coronavirus disease 2019; eGFR = estimated glomerular filtration rate; FSH = follicle-stimulating hormone; hCG = human chorionic gonadotropin; HDL = high-density lipoprotein; HIV = human immunodeficiency virus; LDL = low-density lipoprotein; MCP-1 = monocyte chemotactic protein-1; RBC = red blood cell; T2DM = type 2 diabetes mellitus; WBC = white blood cell.

a Clinical Laboratory Improvement Amendments (CLIA) waived test.

Investigators must document their review of each laboratory safety report.

# Appendix 3: Guidelines for Public Health Emergencies, Including Infectious Disease Outbreaks

In the event of a public health emergency, including infectious disease outbreaks (eg, COVID-19), the following mitigation strategies may be enacted, as applicable per local and institutional standards.

* If participants are unable to come into the clinic for any visit other than the in- residence visit as outlined in the SoA ([Section 1.3](#_3j2qqm3)), the site may complete the assessments at the home of the participant using alternate methods, such as home collections, an alternate laboratory location, a home healthcare nurse, via telephone, or other telemedicine options.
  + If the visit is not conducted at the site, information on how the visit was conducted (eg, the location of the participant) should be collected.
  + For visits conducted via home nursing or telemedicine, a symptom-directed physical examination is acceptable.
  + Participants may be administered study intervention at home by a qualified home healthcare nurse if necessary (repeat-dose portion of the study only).
  + Participants may consent to revisions to the ICF using an approved alternate method.

For all remotely conducted assessments, the site will have appropriate procedures and safeguards in place to maintain the participant’s privacy as well as to confirm the identity of the participant.

Remote monitoring visits may be conducted if local or institutional guidelines prohibit on-site monitoring at clinical sites.

The Sponsor will collect detailed information if any of the above mitigation strategies is enacted and will assess the impact of these changes on the study analyses prior to database lock. Any deviation from the protocol (altered procedures, missed visits, etc.) due to COVID-19 will be identified in the eCRF as such.

If any additional measures not listed here are required per local or institutional standards on public health emergencies, those measures should be documented. The Investigator should make every effort to minimize impact to the integrity of the clinical trial while ensuring the safety and well-being of trial participants.

If a public health emergency is declared, each study will have a continuity plan that defines the mitigation strategy, including local or institutional requirements for COVID-19 (or other) testing.

Additional sites may be used if needed to complete enrollment due to impact of the COVID-19 pandemic (or other public health emergency) at the study site.

# Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

## Definition of AE

| **AE Definition** |
| --- |
| * An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. * NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention. |

| **Events Meeting the AE Definition** |
| --- |
| * Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease). * Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. * New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. * Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. * Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. |

| **Events NOT Meeting the AE Definition** |
| --- |
| * Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant’s condition. * The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant’s condition. * Medical or surgical procedure (eg, endoscopy, appendectomy, tooth extraction): the condition that leads to the procedure is the AE. * Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). * Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen. |

* + 1. **Definition of SAE**

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

| **An SAE is defined as any untoward medical occurrence that, at any dose:** |
| --- |
| **1. Results in death** |
| **2. Is life-threatening**  The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe. |
| **3. Requires inpatient hospitalization or prolongation of existing hospitalization**  In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician’s office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether “hospitalization” occurred or was necessary, the AE should be considered serious.  Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE. |
| 1. **Results in persistent disability/incapacity**    * The term disability means a substantial disruption of a person’s ability to conduct normal life functions.    * This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption. |
| **5. Is a congenital anomaly/birth defect** |
| 1. **Other situations:**    * Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate 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 medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.    * Examples of such events include invasive or malignant cancers, 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. |

## Recording and Follow-Up of AE and/or SAE

| **AE and SAE Recording** |
| --- |
| * When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event. * The Investigator will then record all relevant AE/SAE information in the eCRF. * It is not acceptable for the Investigator to send photocopies of the participant's medical records to the Sponsor (or designee) in lieu of completion of the AE/SAE eCRF pages. * There may be instances when copies of medical records for certain cases are requested by the Sponsor (or designee). In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor (or designee). * The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE. |
| **Assessment of Intensity** |
| The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:   * Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities. * Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities. * Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe. * An event is defined as ‘serious’ when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe. |

| **Assessment of Causality** |
| --- |
| * The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. * A “reasonable possibility” of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. * The Investigator will use clinical judgment to determine the relationship. * Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated. * The Investigator will also consult the Investigator’s Brochure and/or Product Information, for marketed products, in his/her assessment. * For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality. |

| **Assessment of Causality** |
| --- |
| * There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data. * The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment. * The causality assessment is one of the criteria used when determining regulatory reporting requirements. |

| **Follow-up of AEs and SAEs** |
| --- |
| * The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor (or designee) to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. * If a participant dies during participation in the study or during a recognized Follow-up period, the Investigator will provide the Sponsor (or designee) with a copy of any post-mortem findings including histopathology. * New or updated information will be recorded in the originally completed eCRF. * The Investigator will submit any updated SAE data to the Sponsor (or designee) within 24 hours of receipt of the information. |

* + 1. **Reporting of SAEs**

| **SAE Reporting via Paper CRF** |
| --- |
| * Facsimile transmission or electronic transmission of a scanned copy of the SAE paper CRF is the preferred method to transmit this information to the CRO’s SAE coordinator. * In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service. * Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE CRF pages within the designated reporting time frames.   Contacts for SAE reporting can be found in the Safety Plan. |

# Appendix 5: Contraceptive Guidance and Collection of Pregnancy Information

## Definitions:

**Woman of Childbearing Potential (WOCBP)**

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

## Women in the following categories are not considered WOCBP

* + 1. Premenarchal
    2. Premenopausal female with 1 of the following:
       - Documented hysterectomy
       - Documented bilateral salpingectomy
       - Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), cause should be documented, and Investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel’s: review of the participant’s medical records, medical examination, or medical history interview.

* + 1. Postmenopausal female
       - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
         * A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement consistent with postmenopausal status is required.
       - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

## Contraception Guidance:

Female Participants

Female participants who are of non-childbearing potential will not be required to use contraception.

Male Participants

All fertile male participants (even males with a history of vasectomy) will be required to use a male condom with spermicide in addition to a second method of acceptable contraception from Check-in until 6 months after the final Follow-up visit. Sexual intercourse with female partners who are pregnant, or breastfeeding should be avoided unless condoms are used from the time of the first dose until 6 months after the final Follow-up visit. Acceptable second methods of contraception for female partners include:

* + - * hormonal injection
      * combined oral contraceptive pill or progestin/progestogen-only pill
      * combined hormonal patch
      * combined hormonal vaginal ring
      * surgical method (bilateral tubal ligation or Essure® [hysteroscopic bilateral tubal occlusion])
      * hormonal implant
      * hormonal or non-hormonal intrauterine device
      * over-the-counter sponge with spermicide
      * cervical cap with spermicide
      * diaphragm with spermicide

## 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 study intervention.
      * 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 6 to 8 weeks 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 participants who become pregnant while participating in this study. The initial 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 6 to 8 weeks 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.
      * While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE. A spontaneous abortion (occurring at <22 weeks gestational age) or still birth (occurring at ≥22 weeks gestational age) is always considered to be an SAE and will be reported as such. Any post-study

pregnancy-related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as described in [Section 8.6.4](#_4kx3h1s). 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 intervention.

# Appendix 6: Liver Safety: Suggested Actions and Follow-up Assessments

Elevations of liver enzymes (eg, alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) may be related to hepatic and extrahepatic causes and may be an indicator of drug- induced liver injury. In evaluating cases of potential hepatic injury, other contributing factors capable of causing the observed laboratory abnormalities should be considered. These include viral hepatitis A, B, C, cytomegalovirus, or Epstein-Barr virus, muscle injury, alcohol use, nonalcoholic steatohepatitis, cholecystitis, other drugs (eg, acetaminophen).

Testing for hepatic injury through monitoring liver enzymes will be conducted per the SoA ([Section 1.3](#_3j2qqm3)).

Participants with elevations in liver enzymes (ALT and/or AST) of >3 × upper limit of normal (ULN) should return to the clinical site within 72 hours to repeat liver chemistries, and to conduct a detailed history (including recent alcohol, acetaminophen, drug-use, recent travel, contact with sick individuals, etc.) and physical examination. Participants should be followed until resolution of the event or return to baseline state.

Laboratory tests to be collected include: ALT, AST, total bilirubin, direct and indirect bilirubin, alkaline phosphatase, gamma glutamyltransferase, creatine phosphokinase, international normalized ratio, and serum PK sample. A liver ultrasound should be performed, and collection of blood for acetaminophen toxicity and viral causes of hepatitis should be collected if appropriate.

Participants should discontinue study intervention and other concomitant medications that may be associated with liver injury. Any consideration for resuming study intervention should be discussed with the Medical Monitor.

# Appendix 7: Country-specific Requirements

Not applicable.

# Appendix 8: Abbreviations

<insert all abbreviations used throughout the document>

| **Term** | **Definition** |
| --- | --- |
| ADA | antidrug antibodies |
| ADME | absorption, distribution, metabolism, and excretion |
| AE | adverse event |
| AUC | area under the serum concentration-time curve |
| AUCinf | area under the serum concentration-time curve from time zero to infinity |
| AUClast | area under the serum concentration-time curve from time zero to the last measurable concentration |
| CL | clearance |
| Clast | last observed serum concentration |
| Cmax | maximum observed serum concentration |

# REFERENCES

<insert bibliography>