| Protocol Title: #Protocol Title# |  |
| --- | --- |
| Protocol Number: #Protocol Number# |  |
| **Compound: #Compound#** |  |
| **Brief Title: #Brief Title#** |  |
| **Study Phase: #Study Phase#** |  |
| **Sponsor Name: #Sponsor Name#** |  |
| **Legal Registered Address: #Legal Registered Address#** |  |
| **Regulatory Agency Identifier Number(s): #Regulatory Agency Identifier Number(s)#** |  |
| **Study Registry Number(s): #Study Registry Number(s)#** |  |
| **Protocol Date: #Protocol Date#** |  |

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Any unauthorized use, reproduction, publication, or dissemination is strictly prohibited.

**Sponsor Signatory:**

|  |  |  |
| --- | --- | --- |
|  |  |  |
| George Nomikos, MD, PhD Vice President, Clinical Development & Strategy Harmony Biosciences Management, Inc.  224-249-9939 gnomikos@harmonybiosciences.com |  | Date |

Investigator’s Agreement

I have read and understood Protocol <<Study Number>> and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

Printed Name of Investigator

Signature of Investigator

Date

Study Center Name

Signature on this page assures the Sponsor that, to the best of the Investigator’s knowledge, the affiliated IRB/IEC/REB operates in accordance with the governing regulations, and that the Investigator understands, and agrees to abide by, all governing regulatory obligations and ICH Guideline for GCP and country and regional (local) requirements while conducting this clinical investigation. Additionally, the Investigator agrees to give access to all relevant data and records to the Sponsor’s monitors, auditors, Sponsor Clinical Quality Assurance representatives, designated agents of the Sponsor, IRBs/IECs/REBs, and regulatory authorities as required.

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List of Abbreviations and Definitions of Terms

| Abbreviation | Definition |
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1. Protocol Synopsis
   1. Synopsis

|  |  |
| --- | --- |
| **NAME OF SPONSOR:** | Picklist   * Harmony Biosciences Management, Inc. * Zynerba Pharmaceuticals Pty., Ltd. * Epygenix Inc. |
| **NAME OF FINISHED PRODUCT(S):** | Picklist   * EPX-100 * HBS-101 * HBS-102 * HBS-201 * HBS-301 * HBS-401 * ZYN002 |
| **NAME OF ACTIVE INGREDIENT(S):** | Autopopulated  If **NAME OF FINISHED PRODUCT(S)=**   * HBS-101 * HBS-102 * HBS-201 * HBS-301 * HBS-401   Populate with **pitolisant HCl**  If **NAME OF FINISHED PRODUCT(S) =**   * EPX-100   Populate with **clemizole**  If **NAME OF FINISHED PRODUCT(S) =**   * ZYN002   Population with **synthetic cannabidiol** |
| **PHASE OF DEVELOPMENT:** | Picklist   * 1 * 1b * 2 * 3 * 4 * Other: specyfy |
| **PROTOCOL NUMBER:** | <<NAME OF FINISH PRODUCT>>  -CL-  <<Study number>> |
| **PROTOCOL TITLE**: A Phase <<PHASE OF DEVELOPMENT>>, Open-Label, Randomized, 2-Way Crossover Study to Evaluate the Pharmacokinetics of HBS-301 in Healthy Adult Participants | |
| **NUMBER OF PLANNED PARTICIPANTS**: 12 | |
| **STUDY SITES:** <<Single>><<Multicenter>> center<<s>> in <<Countries>> | |
| **STUDY OBJECTIVES AND ENDPOINTS**:   | Objectives | Endpoints | | --- | --- | | **Primary** | | | <<Manual>> | <<Manual>> | | **Secondary** | | | <<Manual>> | <<Manual>> | | |
| **METHODOLOGY:**  <<Manual>>    Study assessments are summarized in Table 1. | |
| **STUDY POPULATION:**  **Inclusion Criteria**  Each participant must meet the following criteria to be eligible for this study:   1. Able to provide voluntary, written informed consent. 2. Male or female 3. Age <<MANUAL ENTRY>> at the time of Screening. 4. <<MANUAL ENTRY OF OTHER CRITERIA>> 5. In generally good health at Screening and Baseline (Day -1), as judged by the Investigator based on the results of medical history, physical examination, vital signs, 12-lead ECG, clinical laboratory test results, and assessment of any condition requiring prescription, OTC, and/or herbal medicines. 6. In the opinion of the Investigator, participant is capable of understanding and complying with the requirements of the protocol and administration of oral study drug.   **Exclusion Criteria**  A participant who meets any of the following criteria will be excluded from enrollment in the study:   1. Manual 2. Manual 3. Any condition or illness that, in the opinion of the Investigator, would compromise participant safety or interfere with the evaluation of the safety of study drug. | |
| **INVESTIGATIONAL PRODUCT, DOSE, AND MODE OF ADMINISTRATION:** | |
| **REFERENCE THERAPY, DOSE, AND MODE OF ADMINISTRATION:** | |
| **DURATION OF TREATMENT:**  Single dose administration of HBS-301 will occur on Day 1 and Day 15. The duration of participation will be up to approximately 56 days (8 weeks), including up to 28 days of Screening, and 26 (+2) days of study participation in Period 1, Period 2, and the safety Follow‑up/EOS Visit. | |
| **STUDY ASSESSMENTS:**  **Efficacy Assessments:**  **Safety Assessments:**  Safety will be assessed by monitoring and recording all AEs from the time of written informed consent through 30 days after the final dose of study drug. Additional safety measures include physical examinations (including height at Screening, weight, and temperature), vital signs (heart rate, systolic and diastolic blood pressure), triplicate 12-lead ECGs, clinical laboratory tests (chemistry, hematology, urinalysis, and pregnancy test [serum and urine] for FCBPs), concomitant medication use, and suicidal ideation and behavior monitoring (using the C‑SSRS).  **Pharmacokinetic Assessments:** | |
| **STATISTICAL METHODS:**  **Determination of Sample Size:**  **Safety Analyses:**  Safety data will be tabulated and listed.  **PK Analyses:**  **Statistical Methods and Planned Analysis** | |

* 1. Schedule of Assessments

Table : Schedule of Assessments

| Study Procedures | D-28 to D-2 | D-1\* | D1 | D2 | D3 | D4 | D5 | **D14**\* | **D15** | **D16** | **D17** | **D18** | **D19** | D26 (+2 days) | Notes:  D26 Follow‑up/EOS Visit may be conducted virtually by telephone call.  \*On Days -1 and 14, eligible participants will be admitted to CRU. |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Informed consent |  |  |  |  |  |  |  |  |  |  |  |  |  |  | Section 8.1.1 |
| Informed consent for genetic testing |  |  |  |  |  |  |  |  |  |  |  |  |  |  | Section 8.1.1 |
| Assess/confirm eligibility |  |  |  |  |  |  |  |  |  |  |  |  |  |  | Section 5.1 and Section 5.2 |
| Demographics |  |  |  |  |  |  |  |  |  |  |  |  |  |  | Section 8.1.2 |
| Medical history |  |  |  |  |  |  |  |  |  |  |  |  |  |  | Section 8.1.3 |
| Physical examination |  |  |  |  |  |  |  |  |  |  |  |  |  |  | Section 8.1.4 Height (at Screening), weight, and temperature |
| Targeted physical examination |  |  |  |  |  |  |  |  |  |  |  |  |  |  | Section 8.3.2 Weight and temperature |
| Vital signs |  |  |  |  |  |  |  |  |  |  |  |  |  |  | Section 8.3.3 Prior to blood draw |
| Triplicate 12‑lead ECG |  |  |  |  |  |  |  |  |  |  |  |  |  |  | Section 8.3.4; Screening, Day -1, then Day 1 and Day 15: 4h and 12h postdose; Day 5 and 19: prior to discharge from CRU; |
| Clinical laboratory testing – chemistry, hematology, urinalysis |  |  |  |  |  |  |  |  |  |  |  |  |  |  | Section 8.1.5, Section 8.3.6, and Table 5  On Days 1 and 15, samples will be collected >5 hours post dose, and on other in-clinic days after the morning PK sample. |
| HIV-1, HIV-2, HBsAg, and HCV serology testing |  |  |  |  |  |  |  |  |  |  |  |  |  |  | Section 8.1.5 and Table 5 |
| Urine drug screen/  ethanol screen |  |  |  |  |  |  |  |  |  |  |  |  |  |  | Section 0 and Table 5 |
| Cotinine test |  |  |  |  |  |  |  |  |  |  |  |  |  |  | Section 0 and Table 5 |
| Pregnancy testing |  |  |  |  |  |  |  |  |  |  |  |  |  |  | Section 8.1.5, Section 8.1.6, and Section 8.3.5  FCBPs only; serum test at Screening and urine tests on Days -1 and 14 |
| PGx sample for genotyping |  |  |  |  |  |  |  |  |  |  |  |  |  |  | Section 1.1.1 |
| Admission to CRU |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Study drug administration |  |  |  |  |  |  |  |  |  |  |  |  |  |  | Section 6.1  Participants will end their fast at 4 hours post dose on Days 1 and 15. |
| PK sampling |  |  |  |  |  |  |  |  |  |  |  |  |  |  | Section 8.2 |
| Concomitant medications |  |  |  |  |  |  |  |  |  |  |  |  |  |  | Section 6.5 |
| AE Monitoring |  | | | | | | | | | | | | | |  |
| C-SSRS |  |  |  |  |  |  |  |  |  |  |  |  |  |  | Section 8.1.7 and Section 8.3.7 |
| Discharge from CRU |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |

AE=adverse event; C-SSRS=Columbia-Suicide Severity Rating Scale; CRU=clinical research unit; D=day; ECG=electrocardiogram; EOS=End of Study; FCBPs=female of childbearing potential; HBsAg=hepatitis B virus surface antigen; HCV=hepatitis C virus; PGx=pharmacogenetics; PK=pharmacokinetics

1. Introduction
   1. Background Information

#HC\_AI\_Background\_Information#

* 1. Benefit/Risk Assessment

#HC\_AI\_Benefit\_Risk\_Assessment#

Objectives and Endpoints

Table 2 presents the study objectives and endpoints.

Table : Objectives and Endpoints

| Objectives | | Endpoints |
| --- | --- | --- |
| **Primary** | | |
| #HC\_AI\_Primary\_Objective# | | #HC\_AI\_Primary\_Endpoint# |
| **Key Secondary** | | |
| #HC\_AI\_Key\_Secondary\_Objective# | #HC\_AI\_Key\_Secondary\_Endpoint# | |
| **Secondary** | | |
| #HC\_AI\_Secondary\_Objectives# | | #HC\_AI\_Secondary\_Endpoint# |

Study Design

This is a Phase X, *multicenter, randomized, double-blind, parallel-group, placebo-controlled*, clinical study to assess efficacy and safety of XX in adult patients (ages ≥XX years) with XX. The study will consist of a Screening Period (XX days) and a X-week *Double-Blind Treatment* Period. An overall schematic of the study design is provided in [Figure 1 .](#_bookmark29)

After completion of the Screening Period, approximately XX participants who meet all eligibility criteria and provide written informed consent will be enrolled in the study. X. Patients will be randomized 1:1 to blinded study drug (XX or matching placebo).

* 1. Overall Study Design

#HC\_AI\_Study\_Design#

* 1. Duration of Study Participation

#HC\_AI\_Duration\_of\_Study#

* 1. Study Completion

#HC\_AI\_Study\_Completion#

1. Study Population

Approximately 12 participants will be enrolled at a single study site in Australia.

#HC\_AI\_Study\_Population#

Study Drug(s) and Concomitant Therapy

* 1. Study Drug

#HC\_AI\_Study\_Drug\_Overview#

* 1. Study Drug Preparation, Storage, and Accountability

#HC\_AI\_Drug\_Preparation\_Storage\_Accountability#

* 1. Blinding

#HC\_AI\_Blinding\_And\_Unblinding#

* 1. Dose Modification

#HC\_AI\_Dose\_Modification\_And\_Discontinuation#

* 1. Prior and Concomitant Therapy

#HC\_AI\_Concomitant\_Therapy#

1. Discontinuation Of Study Drug/Participant Withdrawal From Study
   1. Participant Withdrawal Criteria

Each participant has the right to withdraw from the study at any time without prejudice. If a participant withdraws from the study, the reason(s) must be recorded on the eCRF, and evaluations scheduled for the EOS Visit should be performed.

The Investigator may discontinue any participant’s participation if he or she feels it is necessary for any reason, including any AE or failure to comply with the protocol.

Participants who withdraw from the study will not be replaced. All efforts will be made to ensure that the follow‑up procedures scheduled for Day 26 (Table 1) are completed at the time of discontinuation.

* 1. Discontinuation of Study Drug

Table 4: Findings Requiring Discontinuation of Study Drug

| Finding | Discontinue for |
| --- | --- |
| ECG finding based on the mean of triplicate 12‑lead ECGs | Mean QTcF >500 msec  or  Mean QTcF increase from Screening >60 msec AND mean QTcF >470 msec  Note: ECG finding should be promptly addressed by the Investigator with correction of any factors that may have contributed to QT prolongation. |
| Renal function | ESRD (eGFR <15 mL/min/1.73 m2) at any time during the study  Participants who develop eGFR <60 mL/min/1.73 m2 during Period 1 will be monitored carefully and will be excluded from participation in Period 2. |
| Hepatic function | Severe hepatic impairment (Child-Pugh C) at any time during the study  Participants who develop moderate hepatic impairment (Child-Pugh B) during Period 1 will be monitored carefully and will be excluded from participation in Period 2. |
| C‑SSRS | Suicidal behavior or suicidal ideation at any time during the study, or a positive response to any question at any time after Baseline (Section 8.3.7). |
| Pregnancy test | A positive pregnancy test at any time during the study. |
| Other | At the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons. |

C‑SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; eGFR=estimated glomerular filtration rate; ESRD=end‑stage renal disease; QTcF=QT interval corrected according to the method of Fridericia

1. Study Assessments, Procedures, And Visits

The following sections describe study procedures and assessments that will be performed during the study. Study procedures and timing are summarized in the SOA (Table 1).

Urgent safety concerns should be discussed with the Medical Monitor immediately upon occurrence or upon awareness to determine next steps.

Adherence to study design requirements, including those specified in the SOA (Table 1), is essential and required for study conduct.

All Screening evaluations must be completed and reviewed by the Investigator or designee 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 not meeting eligibility criteria, as applicable.

* 1. Administrative and General/Baseline Procedures
     1. Informed Consent Process

Instructional text: For studies with pediatric participants, change this text to have “Assent” and “Parental Permission” and the “parent/caregiver/LAR”

Informed consent will be obtained at the Screening Visit for all participants. The informed consent form will be signed before any study procedures are undertaken for the determination of the participants’ eligibility for this study. A separate informed consent that is specific for genetic testing will be obtained at Baseline (Day -1) before collecting the PGx sample.

* Investigators or Investigators’ designees will explain the nature of the study to participants and answer all questions regarding the study.
* Participants must be informed that study participation is voluntary. Participants will be required to sign statements of informed consent that meet the requirements of 21 CFR 50, local regulations, ICH guidelines, or HIPAA (where applicable), and the IRB/IEC or study center. Specifically, participants will sign a statement of informed consent.
* The medical record must include a statement that written informed consent, as required by local laws and regulations, was obtained before enrollment in the study. The medical record must also include the date of the informed consent process. The authorized person conducting the informed consent process must be documented.
* Throughout the study, when informed consent forms are updated, participants must be reconsented using the most current version of the form.
* A copy of the relevant informed consent form must be provided to the participant.
  + 1. Demographic Information Collection

Demographic information will be collected at the Screening Visit and documented in the eCRF.

* + 1. Medical History
    2. Physical Examination
    3. Screening Laboratory Testing
    4. Pregnancy Test
    5. Columbia-Suicide Severity Rating Scale
    6. Study Drug Compliance Data Collection

The dates and times of study drug administration will be recorded in the eCRF.

* 1. Pharmacokinetic Assessments
  2. Safety Assessments

Safety assessments are to be performed as indicated in the SOA (Table 1).

* + 1. Adverse Event Monitoring

All AEs, regardless of causality or seriousness, will be collected from the time of written informed consent through 30 days after the final dose of study drug. Additional safety information, including the definition of an AE/SAE and reporting requirements, is provided in Section 9.

Clinically significant laboratory test results, vital signs, ECGs, and physical assessments should be recorded as AEs; a clinical diagnosis, rather than the changes in laboratory analyte or other assessment, should be recorded as detailed in Section 9.1.1.

* + 1. Targeted Physical Examination
    2. Vital Signs Measurements
    3. Triplicate 12-Lead Electrocardiograms
    4. Pregnancy Testing
    5. Clinical Laboratory Assessments

Clinical laboratory tests include serum chemistry, hematology, urinalysis, and urine drug screen as detailed in Table 5. Timing of sample collection for clinical laboratory tests are detailed in the SOA (Table 1). Clinical laboratory tests may be repeated at the discretion of the Investigator.

The Laboratory Manual provides detailed instructions on sample collection, processing, and shipping procedures.

Participants are not required to fast prior to having blood or urine samples taken. Pharmacokinetic sample collection (Section 8.2) should be given priority; therefore, on Days 1, 5, 14 and 19, clinical laboratory samples will be collected >5 hours post dose; (Section 8.2).

Laboratory test results will be reviewed by the Investigator. Any laboratory value outside of the normal reference range will be evaluated for clinical significance and, if deemed clinically significant, should be reported as an AE with an appropriate diagnosis. Abnormal test results deemed not clinically significant by the Investigator should be documented as such in the medical records.

Table : Clinical Laboratory Tests

| Screening Serology:  -HIV-1, HIV-2, HBsAg, and HCV  Urine Drug Screen  -amphetamine -barbiturates -benzodiazepines -cocaine -methadone -methamphetamine -morphine -opiates -phencyclidine -THC, marijuana -tricyclic antidepressants -cotinine  Urinalysis  -bilirubin -blood, erythrocytes -epithelial cells -glucose -ketones -leucocyte esterase -nitrite -pH -protein -specific gravity -urobilinogen  Pregnancy Testing (FCBPs only)  -serum (at Screening) -urine (after Screening])  Postmenopausal females -FSH | Serum Chemistry  -albumin -alkaline phosphatase -alanine aminotransferase -aPTT -aspartate aminotransferase -anion gap -bicarbonate -bilirubin (total, direct, and indirect) -calcium -chloride -creatinine -creatinine kinase -eGFR -gamma-glutamyl transferase -globulin -glucose -INR -lactate dehydrogenase -high-density lipoprotein -low-density lipoprotein -magnesium -phosphorus -potassium -PT -sodium -total cholesterol -total protein -triglycerides -urea -uric acid  Hematology  -hematocrit -hemoglobin -mean cell hemoglobin -mean cell volume -mean corpuscular hemoglobin concentration -mean platelet volume -platelets -red cell count -red cell distribution  -white cell count (neutrophils, lymphocytes, monocytes,  eosinophils, and basophils) -HbA1C |
| --- | --- |

aPTT=activated partial thromboplastin time; eGFR=estimated glomerular filtration rate; FCBPs=females of childbearing potential; FSH=follicle-stimulating hormone; HBsAg=hepatitis B virus surface antigen; HbA1C=glycated hemoglobin A1c; HCV=hepatitis C virus; INR=international normalized ratio; pH=potential of hydrogen; PT=prothrombin time; THC=Tetrahydrocannabinol

The estimated total volume of blood to be drawn is approximately 200 mL: 24 samples for PK analyses (4.0 mL per sample), 13 samples for serum chemistry tests (6 mL per sample), and 13 samples for hematology tests (2 mL per sample).

* + 1. Suicidal Ideation and Behavior Risk Monitoring
  1. Unscheduled Visits

Unscheduled visits and assessments may be telephone calls or in-person visits and should be performed if clinically indicated in the opinion of the Investigator. At a minimum, the following assessments are to be performed at any unscheduled visit, whether conducted by telephone call or in-person:

* Review of AEs
* Review of concomitant medications
* C‑SSRS Since Last Visit

Other assessments (e.g., vital signs, abbreviated physical examination, 12‑lead ECGs, clinical laboratory tests, and urine pregnancy test for FCBP) may need to be completed at an in-person unscheduled visit, at the discretion of the Investigator. The reason for the visit should be documented.

1. Safety Monitoring and Reporting

Investigators are responsible for the detection and documentation of events that meet the definition of an AE, SAE, suspected adverse reaction, serious suspected adverse reaction, or unanticipated problem, as provided in this protocol.

Investigators must review the relevant IB to be knowledgeable about the study drug and aware of its safety profile.

* 1. Definition of Safety Parameters
     1. Definition of an Adverse Event

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not it is considered drug related.

An AE may be any unfavorable or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a study drug, whether or not considered causally associated with the use of the study drug. Any abnormal physical examination finding, laboratory value, vital sign result, or ECG finding that is deemed clinically significant by the Investigator, regardless of causal relationship, must be reported as an AE. A clinical diagnosis, rather than the changes in laboratory analyte or other assessment, should be recorded (e.g., anemia rather than low hemoglobin value).

Examples of AEs include:

* Significant or unexpected worsening or exacerbation of the condition or indication under study
* Exacerbation of a chronic or intermittent pre-existing condition, including either an increase in frequency or intensity of the condition (e.g. abnormal physical examination finding related to the condition)
* Signs, symptoms, or clinical sequelae of a suspected overdose of the study drug or a concurrent medication (overdose per se should not be reported as an AE or SAE, unless nonserious or serious sequelae occur)
* A diagnosis related to any clinically significant abnormal laboratory test result
* Any laboratory abnormality not associated with a diagnosis or symptom requiring further diagnostic investigation

The following examples would not be considered AEs:

* Medical or surgical procedure (e.g., endoscopy, appendectomy), although the condition that leads to the procedure would be considered an AE
* Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) (including laboratory values) present or detected at the start of the study that do not worsen during the study
* The disease or disorder being studied or expected progression, signs, or symptoms of the disease or disorder being studied, unless they become more severe or occur with a greater frequency than expected for the participant’s condition
  + 1. Definition of a Serious Adverse Event

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

* Death
* A life-threatening AE (i.e., presented an immediate risk of death from the event as it occurred; this criterion is not intended to include an AE that, had it occurred in a more severe form, might have caused death)
* Inpatient hospitalization or prolongation of existing hospitalization
* A persistent or significant incapacity or substantial disruption of the ability to conduct normal activities of daily living
* A congenital anomaly/birth defect
* Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include: allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse

The following events do not meet the definition of an SAE:

* Hospitalization for elective treatment of a pre-existing condition that does not worsen from baseline
* Hospitalization for a standard procedure for study drug administration and routine monitoring of the studied indication not associated with any deterioration in condition
* Social or convenience admission to a hospital
* Prolongation of hospitalization for social or convenience reasons not associated with the occurrence of an AE
* Hospitalization or an emergency room visit that lasts <24 hours that does not meet the criteria of an important medical or a life‑threatening event
  + 1. Definition of a Suspected Adverse Reaction

A suspected adverse reaction is defined as any AE for which there is a reasonable possibility that the AE was caused by the study drug.

* + 1. Definition of a Serious Suspected Adverse Reaction

A serious suspected adverse reaction is any suspected adverse reaction that is determined to be serious, based on the definition of an SAE described in Section 9.1.2.

* + 1. Definition of Unanticipated Problems

Unanticipated problems are incidents, experiences, or outcomes that meet all of the following criteria:

* Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the research protocol and informed consent document approved by the EC (includes IRBs and IECs) and (b) the characteristics of the participant population being studied
* Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research)
* Suggest that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized
  1. Classification of Adverse Events
     1. Severity of Adverse Events

Investigators will assess the severity of each AE based on their clinical judgment using one of the following categories:

* **Mild:** Usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
* **Moderate:** Usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the participant.
* **Severe:** Interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.
  + 1. Relationship to Study Drug

Investigators will assess the relationship (i.e. causality) of each AE to study drug based on clinical judgment. An Investigator’s assessment of the relationship of an AE to study drug is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported. All AEs must have their relationship to study drug assessed. The Sponsor’s assessment of relationship may differ from an Investigator’s assessment.

Relationship to study drug will be assessed according to the following guidelines:

* **Not related:** There is not a temporal relationship to study drug administration, or the AE is clearly and incontrovertibly due only to progress of the underlying disease or to extraneous causes.
* **Unlikely related:** There is little or no chance that the study drug caused the reported AE; the event is most likely because of another competing cause, including concomitant illnesses, progression or expression of the disease state, or a reaction to a concomitant medication.
* **Possibly related:** The association of the AE with study drug is unknown; however, the AE is not reasonably attributed to any other condition.
* **Probably related:** A reasonable temporal association exists between the AE and study drug, and based on the Investigator’s clinical experience, there is no other obvious competing cause. The event responds to withdrawal of the study drug (positive dechallenge) and rechallenge with administration of the study medication is ambiguous or not done.
* **Definitely related:** There is a reasonable causal relationship between study drug and the AE; the event responds to withdrawal of the study drug (positive dechallenge) and recurs with rechallenge by administration of the study drug (positive rechallenge).

For initial reporting of SAEs, even in situations in which minimal information is available, it is important that for every event Investigators provide an assessment of causality. The causality assessment is one of the criteria used when determining regulatory reporting requirements. Investigators may change their opinion of causality based on follow-up information and amend the SAE information accordingly in the eCRF or the SAE reporting form, as applicable.

* 1. Time Period and Frequency for Adverse Event Assessment and Follow-up
     1. Adverse Event and Serious Adverse Event Monitoring

All AEs, regardless of causality or seriousness, will be collected from the time a participant provides written informed consent through 30 days after their final dose of study drug.

* + 1. Follow-up of Events

After the occurrence of an AE or SAE, an Investigator is required to follow each participant proactively and provide further information on the participant’s condition. All AEs and SAEs documented at a previous visit or contact and designated as ongoing will be reviewed at subsequent visits or contacts.

All AEs and SAEs will be followed after the last scheduled study visit until the event resolves, the condition stabilizes, or the event is otherwise explained or judged by the Investigator to be no longer clinically significant (unless the participant is lost to follow-up, or the participant withdraws consent).

Investigators will assess the outcome of each AE using the following categories:

* **Recovered/Resolved:** The event resolved, or the participant recovered without sequelae. An event (either serious or nonserious) occurred and had an endpoint, and the participant experienced no restrictions. Examples include stent placement for coronary artery disease (a device implanted is not a sequela), an appendectomy (a scar is not a sequela), a postoperative wound infection, or an upper respiratory tract infection.
* **Recovered/Resolved with sequelae:** The event has at least 1 secondary outcome that may result in permanent disability, functional limitation, or both. Examples include hip replacement resulting in foot drop (foot drop is not the intended outcome but is a risk of surgery), stroke resulting in paralysis, or emboli formation after a bacterial infection resulting in a renal infarct and loss of renal function.
* **Recovering/Resolving:** The event is improving.
* **Not recovered/Not resolved:** At the end of the study, an event either has not changed in intensity or may not have recovered to Baseline values, and the outcome is unknown. Examples include headache, low-grade fever, or nausea.
* **Unknown:** The participant is lost to follow‑up, and the status of the event is unknown.
* **Death**
  1. Reporting Procedures
     1. Reporting Serious Adverse Events to the Sponsor

During this study, if an Investigator determines that an event meets the protocol definition of an SAE, regardless of relationship to study drug, they must notify the Sponsor as soon as possible but no later than **24 hours after becoming aware of the SAE**. An SAE is reported to the Sponsor via EDC entry within the Et available, a paper SAE report form (completed with all available information) must be sent to the Sponsor via email or fax as soon as possible, but no later than within 24 hours of the Investigator becoming aware of the SAE. The Investigator must be diligent in providing additional information as needed. The Investigator must also enter the SAE information in the eCRF as soon as possible thereafter.

In an initial report, Investigators must provide to the Sponsor the following information:

* AE record
* Medical history
* Prior and concomitant medications

Any laboratory test results, diagnostic test results, or medical reports relevant to the SAE should be provided; however, certain participant identifying information (i.e., name, address, and other identifying information not collected in a participant’s eCRF) is to be redacted from copies of the participant’s medical records.

In rare circumstances, and in the absence of access to email or fax and if EDC is not available, a copy of the SAE report form may be sent to the Sponsor by overnight mail. Initial notification of the event via telephone, email, fax, or overnight mail does not replace the need for Investigators to complete the appropriate SAE form in EDC within 24 hours of becoming aware of the SAE. The initial AE/SAE information for the event must be entered in the eCRF.

If an Investigator does not have all the information regarding an SAE, they must not wait to receive additional information before notifying the Sponsor of the event. The SAE report form must be updated when additional information is received. Follow-up information received on all SAEs must be entered into EDC using the same 24‑hour timeline as for an initial report.

In the event of death, every effort should be made to obtain a death certificate and if possible, an autopsy report. Death is considered an outcome of an event; however, if the event that resulted in death is unknown, death will be recorded as the event.

* + 1. Reporting Unanticipated Problems to the Sponsor

If an Investigator determines that an event meets the protocol definition of an unanticipated problem, they must notify the Sponsor **within 24 hours of becoming aware of the problem**.

The following information should be included with unanticipated problem reporting:

* Protocol identifying information: protocol title, protocol number, and Investigator’s name
* A detailed description of the event, incident, experience, or outcome
* An explanation of the basis for determining that the event, incident, experience, or outcome represents an unanticipated problem

It is an Investigator’s responsibility to report unanticipated problems to the Sponsor and the IRB/IEC, as required by local regulations.

* + 1. Regulatory Reporting Requirements

Investigators must promptly report all SAEs to the Sponsor in accordance with the procedures detailed in Section 9.4.1. The Sponsor has a legal responsibility to notify, as appropriate, both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. Prompt notification of SAEs by Investigators to the appropriate project contact for SAE receipt is essential so that serious suspected adverse reactions that are either unexpected or observed with increasing occurrence can be reported and legal obligations and ethical responsibilities regarding the safety of other participants are met.

Investigator letters are prepared according to Sponsor policy and are forwarded to Investigators as necessary. An Investigator letter is prepared for any suspected adverse reaction that is both serious and unexpected. The purpose of an Investigator letter is to fulfill specific regulatory and GCP requirements regarding the product under investigation.

An Investigator, or responsible person according to local requirements, must comply with requirements related to the reporting of SAEs to the IRB/IEC.

The Sponsor is responsible for informing IRBs/IECs, Investigators, and regulatory authorities of any finding that could adversely affect the safety of participants or affect the conduct of the study. Events will be reported to regulatory authorities in accordance with expedited reporting requirements.

* + 1. Pregnancy Reporting

Pregnancy is not considered an SAE; however, it is documented and followed in the same manner as an SAE. A participant who becomes pregnant during the study must be withdrawn from the study immediately. Participants who become pregnant within 30 days after receiving their final dose of study drug should also notify their Investigator. The Investigator must attempt to follow the pregnancy to term or termination. If a male study participant impregnates a female, the Investigator will attempt to collect information from the female upon consent from both the male and pregnant female. All live births will be followed for 12 months.

The Investigator must notify the Sponsor of any pregnancy by completing a pregnancy formand relaying it to the Sponsor **within 24 hours of becoming aware of the pregnancy** using the same procedures as outlined for SAE reporting.

Statistical Considerations

The SAP will be finalized prior to the database lock and will include a more detailed description of the statistical analyses described in this section.

This section is a summary of the planned statistical analyses for the endpoints.

If the analyses described in the SAP and protocol differ, the analyses in the SAP will be used for presentation in the CSR. Substantive changes from the analyses originally specified in the protocol will be described in the SAP and in the CSR.

* 1. Estimands
  2. Missing Data
  3. Determination of Sample Size
  4. Analysis Populations
  5. Statistical Analysis Methods
     1. Disposition and Demographics

The number of participants screened and enrolled will be summarized. The number and percentage of participants completing study, discontinuing study drug, and withdrawing early from the study will be summarized.

Demographic characteristics will be summarized and listed.

* + 1. Pharmacokinetic Analysis
    2. Safety Analysis

All safety data will be summarized and listed. No formal statistical analyses will be performed for the safety data.

Safety will be assessed by monitoring and recording of all AEs from signing of the ICF through 30 days after the final dose of study drug. Adverse events that occur between the time of signing of the ICF and the start of study drug administration will be considered pretreatment AEs.

A TEAE is:

* Any AE reported after the first dose of study drug and up to 30 days after the date of the final dose of study drug, or
* Any worsening of a pre-existing condition reported after the first dose of study drug and up to 30 days after the date of the final dose of study drug.

All TEAEs will be coded and tabulated by SOC and PT. Incidence of TEAEs will be summarized by TEAE category. Adverse events will be summarized with counts and percentages.

Adverse Events are assessed by the Investigator as being “not related”, “unlikely related”, “possibly related”, “probably related”, or “definitely related” to study treatment in the CRF. Study drug‑related AEs are those with a relationship to study treatment of “possibly related”, “probably related”, or “definitely related". Adverse Events that are missing an Investigator assessment of relatedness will be categorized as treatment-related for the purposes of summary tables. Treatment‑related TEAEs and treatment‑related serious TEAEs will be summarized by SOC and PT.

Laboratory parameters will be summarized using descriptive statistics. For each laboratory test, individual participant values will be listed and values outside of the normal ranges provided by the central laboratory will be flagged.

The change from Baseline (defined as the last pretreatment value) to each visit for vital sign variables will be summarized using descriptive statistics. Abnormal vital sign values will be flagged and listed. Changes from Baseline for ECG results will be summarized. Categorical summaries will be provided to show changes from Baseline in QTcF.

Results of the C-SSRS and pregnancy testing will be listed.

* + 1. Interim Analysis

Supporting Documentation and Regulatory and Operational Considerations

* 1. Regulatory and Ethical Considerations
* This study will be conducted in accordance with the protocol and with:
  + Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS International Ethical Guidelines.
  + Applicable ICH GCP Guidelines.
  + Applicable laws and regulations.
* The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) will be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
* Any protocol amendments 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.
* The Sponsor will obtain approval to conduct the study from the appropriate regulatory agency in accordance with any applicable country specific regulatory requirements before any site may initiate the study in that country.
* An Investigator will be responsible for:
  + Providing written summaries of the status of the study to their IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by their IRB/IEC.
  + Notifying their 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 ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.
  1. Financial Disclosure

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

* 1. Data Protection
* Participants will be assigned a unique ID by the Sponsor. Any records or datasets transferred to the Sponsor will contain the ID only; any information that would make the participant identifiable will not be transferred.
* Participants must be informed that personal study‑related data will be used by the Sponsor in accordance with local data protection laws. The level of disclosure must also be explained to participants who will be required to give permission for personal data to be used as described in the ICF.
* Participants must be informed that 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 regulatory authorities.
* The contracts between the Sponsor and study sites specify responsibilities of the parties related to data protection, including handling of data security breaches and respective communication and cooperation of the parties.
* Information technology systems used to collect, process, and store study‑related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.
  1. Data Quality Assurance
* All participant data relating to the study will be recorded on an eCRF unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). Investigators are responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
* Guidance on completion of eCRFs will be provided in the study‑specific eCRF completion guidelines.
* Investigators must permit study‑related monitoring, audits by the Sponsor and their partners, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
* Monitoring details describing strategy (e.g., 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 onsite monitoring) are provided in the Monitoring Plan.
* The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
* The Sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).
* The trial master file and records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by Investigators for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified, unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period. No records may be transferred to another location or party without written notification to and approval from the Sponsor.
  1. Source Documents
* Source documents provide evidence for the existence of participants and substantiate the integrity of the data collected. Source documents are filed at an Investigator’s site.
* Data entered in the eCRF transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. Investigators may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
* Definition of what constitutes source data is provided in study‑specific documentation.
* Investigators must maintain accurate documentation (source data) that supports the information entered in the eCRF.
* Study monitors will perform ongoing source data verification to confirm that data entered in 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.
  1. Study and Site Start and Closure
     1. Study/Site Start

The study start date is the date on which the first participant is enrolled. For the purposes of this study, date of enrollment refers to the date that the participant agrees to participate in the study as indicated by signing the appropriate ICF.

* + 1. Study/Site Closure

The Sponsor or 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, destroyed, or accounted for, and a study site closure visit has been performed.

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

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

For study termination:

* Discontinuation of further study drug development

For site termination:

* Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
* Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the Investigator
* Total number of participants enrolled earlier than expected

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform Investigators, IRBs/IECs, regulatory authorities, and any Contract Research Organization(s) used in the study of the reason for termination or suspension, in accordance with applicable regulatory requirements. Investigators must promptly inform participants and should ensure appropriate participant therapy and/or follow-up.

* 1. Publication Policy

All information provided by the Sponsor and all data and information generated by the site as part of the study (other than a participant’s medical records) are the sole property of the Sponsor.

For clinical interventional studies in participants, Sponsor will post study results in accordance with relevant regulatory and disclosure guidelines. The Sponsor commits to submitting for publication results of its interventional clinical studies according to the prespecified plans for data analysis.

Any publication or presentation of the results of this study by an Investigator may only be made in compliance with the provisions outlined in the executed Clinical Trial Agreement. The Sponsor has developed a policy for the publication of scientific and clinical data that follows the recommendations of the International Committee of Medical Journal Editors, CONSORT, and Good Publication Practice. A copy of this policy will be made available to Investigators upon request.

When the study is completed or prematurely terminated, the Sponsor will submit a CSR in accordance with relevant regulatory guidelines.

* 1. Sponsor Contact Information

Sponsor contact information will be provided to the sites in a separate document.

* 1. Digital Health Technology

References

1. Permitted Methods of Contraception For Females Of ChildBearing Potential