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HSY244

Clinical Trial Protocol CHSY244X2201

ClinicalTrials.gov Identifier: NCT04582409

A randomized, placebo-controlled, investigator- and participant-blinded study to evaluate the efficacy, safety, tolerability, and pharmacokinetics of HSY244 in participants with atrial fibrillation

Document type:	Amended Clinical Trial Protocol
EUDRACT number:	2020-004327-17
Version number:	v04 (Clean)
Clinical Trial Phase:	II
Release date:	07-Feb-2022

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List of abbreviations

AE	Adverse Event
AERP	Atrial effective refractory period
AF	Atrial fibrillation
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area under the curve
AV	Atrioventricular
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CK	Creatine Kinase
Cmax	Maximum concentration
CMO&PS	Chief Medical Office and Patient Safety
CNS	Central nervous system
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CSR	Clinical study report
DBP	Diastolic Blood Pressure
EC90	90% Effective concentration
ECG	Electrocardiogram
EDC	Electronic Data Capture
EMA	European Medicines Agency
EOS	End of Study
FIH	First-in-human
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GCS	Global Clinical Supply
GGT	Gamma-glutamyl transferase
GLDH	Glutamate Dehydrogenase
GLP	Good Laboratory Practices
h	Hour
HBcAg	Hepatitis B core antigen
HBsAg	Hepatitis B virus surface antigen
HCV	Hepatitis C Virus
HF	Heart failure
HIV	Human immunodeficiency virus
i.v.	Intravenous
IB	Investigator’s Brochure
ICF	Informed Consent Form

ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IN	Investigator Notification
INR	International Normalized Ratio
IRB	Institutional Review Board
IUD	Intrauterine device
IUS	Intrauterine system
LDH	lactate dehydrogenase
LFT	Liver function test
LLOQ	lower limit of quantification
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
mL	milliliter(s)
NIRT	Novartis Interactive Response Technology
NOAC	Novel oral anticoagulant
P-gp	P-glycoprotein
PACU	Post-anesthesia care unit
PCR	Protein-creatinine ratio
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PoC	Proof of Concept
PT	prothrombin time
QMS	Quality Management System
QTcF	QT interval corrected by Fridericia's formula
SA	Sinoatrial
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
sCR	serum creatinine
SD	standard deviation
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SMQ	Standardized MedDRA Query
SUSAR	Suspected Unexpected Serious Adverse Reaction
TdP	Torsades de Pointes
TIA	Transient ischemic attack
ULN	upper limit of normal
UTI	Urinary Tract Infection
WHO	World Health Organization
WPW	Wolff-Parkinson-White

Glossary of terms

Additional treatment	Medicinal products that may be used during the clinical trial as described in the protocol, but not as an investigational medicinal product (e.g. any background therapy)
Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study participant
Coded data	Personal Data which has been de-identified by the investigative center team by replacing personal identifiers with a code.
Cohort	A specific group of participants fulfilling certain criteria and generally treated at the same time
Control drug	A study drug (active or placebo) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Discontinuation from study treatment	Point/time when the participant permanently stops receiving the study treatment for any reason (prior to the planned completion of study drug administration, if any). Participant agrees to the other protocol required assessments including follow-up. No specific request is made to stop the use of their samples or data.
Dosage	Dose of the study treatment given to the participant in a time unit (e.g., 100 mg once a day, 75 mg twice a day)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from source data/documents used at the point of care
End of the clinical trial	The end of the clinical trial is defined as the last visit of the last participant.
Enrollment	Point/time of participant entry into the study at which informed consent must be obtained. The action of enrolling one or more participants.
Healthy volunteer	A person with no known significant health problems who volunteers to be a study participant
Intercurrent events	Events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest.
Investigational drug/ treatment	The drug whose properties are being tested in the study
Medication number	A unique identifier on the label of medication kits
Mis-randomized participants	Mis-randomized participants are those who were not qualified for randomization and who did not take study treatment, but have been inadvertently randomized into the study
Other treatment	Treatment that may be needed/allowed during the conduct of the study (i.e. concomitant or rescue therapy)
Participant	A trial participant (can be a healthy volunteer or a patient). “Participant” terminology is used in the protocol whereas term “Subject” is used in data collection.

Participant number	A unique number assigned to each participant upon signing the informed consent. This number is the definitive, unique identifier for the participant and should be used to identify the participant throughout the study for all data collected, sample labels, etc.
Period	The subdivisions of the trial design (e.g. Screening, Treatment, Follow-up) which are described in the Protocol. Periods define the study phases and will be used in clinical trial database setup and eventually in analysis
Personal data	Participant information collected by the Investigator that is coded and transferred to Novartis for the purpose of the clinical trial. This data includes participant identifier information, study information and biological samples.
Premature participant withdrawal	Point/time when the participant exits from the study prior to the planned completion of all study drug administration and/or assessments; at this time all study drug administration is discontinued and no further assessments are planned
Randomization	The process of assigning trial participants to investigational drug or control/comparator drug using an element of chance to determine the assignments in order to reduce bias.
Randomization number	A unique identifier assigned to each randomized participant
Re-screening	If a participant fails the initial screening and is considered as a Screen Failure, he/she can be invited once for a new Screening visit after medical judgment and as specified by the protocol.
Screen Failure	A participant who did not meet one or more criteria that were required for participation in the study
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource
Start of the clinical trial	The start of the clinical trial is defined as the signature of the informed consent by the first participant
Study treatment	Any drug or combination of drugs or intervention administered to the study participants as part of the required study procedures; includes investigational drug(s), control(s) or background therapy
Study treatment discontinuation	When the participant permanently stops taking any of the study drug(s) prior to the defined study treatment completion date (if any) for any reason; may or may not also be the point/time of study discontinuation
Treatment arm/group	A treatment arm/group defines the dose and regimen or the combination, and may consist of 1 or more cohorts.
Variable (or endpoint)	The variable (or endpoint) to be obtained for each participant that is required to address the clinical question. The specification of the variable might include whether the participant experiences an intercurrent event.

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Protocol summary

Protocol number	CHSY244X2201
Full Title	A randomized, placebo-controlled, investigator- and participant-blinded study to evaluate the efficacy, safety, tolerability, and pharmacokinetics of HSY244 in participants with atrial fibrillation
Brief title	A study to evaluate the efficacy, safety, tolerability, and pharmacokinetics of HSY244 in participants with atrial fibrillation
Sponsor and Clinical Phase	Novartis Institutes for BioMedical Research Phase II
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this study is to evaluate the efficacy, safety, tolerability, and pharmacokinetics of HSY244 in participants with atrial fibrillation (AF). HSY244 is a potent inhibitor of GIRK1/4 channels, which are believed to play an important role in AF. GIRK1/4 inhibition is expected to restore sinus rhythm without undesirable effects on ventricular repolarization and hence, may offer superior properties for pharmacologic cardioversion of AF. HSY244 is planned to be developed as an intravenous (i.v.) infusion for the acute cardioversion of AF to sinus rhythm.
Primary Objective(s)	The primary objective of this study is to evaluate the efficacy of HSY244 to restore sinus rhythm in participants with AF.
Secondary Objectives	To evaluate the safety and tolerability of HSY244 in participants with AF To evaluate the pharmacokinetics of HSY244 in participants with AF
Study design	This is a randomized, placebo-controlled, investigator- and participant-blinded study to evaluate the efficacy, safety, tolerability, and pharmacokinetics of HSY244 in participants with AF. An initial cohort (Cohort 1) of approximately 29 participants (approximately 20 participants receiving HSY244) is planned to be enrolled to evaluate a single 150 mg i.v. dose of HSY244 for AF cardioversion to sinus rhythm. Commercially Confidential Information Participants with AF that meet clinical criteria for direct current cardioversion will be screened, and on Day 1, after eligibility is confirmed, administration of a 15 minute i.v. infusion of HSY244 or placebo will occur. Participants will then be monitored for cardioversion to sinus rhythm. For those remaining in AF after 90 minutes, direct current cardioversion can be performed. Participants will be monitored for at least 3 hours, although overnight observation will be available. Participants will be evaluated for safety and pharmacokinetic assessments during end of study assessments, which are to occur on Day 5 (96 hours post dose) ± 24 hours. An interim analysis in Cohort 1 is planned after approximately 10 participants have received HSY244 and completed end of study assessments. Commercially Confidential Information

Study population	The study population will include hemodynamically stable men and women between 18 and 80 years of age with a clinical indication for direct current cardioversion of AF, with the current AF episode lasting between 6 hours and 60 days. In Cohort 1, a total of approximately 20 participants will receive HSY244 and a total of approximately 29 participants with AF will be randomized. The randomization ratio will be a 5:1 ratio of HSY244 and placebo. Commercially Confidential Information
Key Inclusion criteria	• Hemodynamically stable men and women between 18 and 80 years of age with a clinical indication for direct current cardioversion of AF • Current episode of AF has been ongoing for ≥6 hours and ≤60 days • Successful initiation and achievement of therapeutic levels of national guideline and institution-specific anticoagulation therapy as appropriate for the duration of the AF episode and risk for the participant • Completion of national guideline and institution-specific imaging evaluation for left atrial thrombi as appropriate for the duration of AF episode and risk for the participant • Participants must weigh at least 60 kg to participate in the study, and must have a body mass index (BMI) within the range of 18 - 45 kg/m^2. BMI = Body weight (kg) / [Height $(m)^2$] • Written informed consent must be obtained before any assessment is performed and only participants able to provide written informed consent themselves will be included in this study
Key Exclusion criteria	• Use of any class I or III anti-arrhythmic medication, or other prohibited medications, within 5 half-lives before randomization, including use of amiodarone within 3 months before randomization • History or current diagnosis of electrocardiogram (ECG) abnormalities or cardiac rhythm disorders indicating significant risk of safety for participant as determined by the Investigator's interpretation of the ECG findings • Attempted or unsuccessful cardioversion within 2 weeks prior to randomization • Presence of known severe mitral regurgitation and/or known severely dilated left atrium • Pre-existing or tachycardia-induced moderate to severe cardiac dysfunction (New York Heart Association class III or IV) • History within the preceding 3 months prior to randomization of either a: myocardial infarction, unstable angina, cardiac surgery, or a percutaneous coronary intervention • History of confirmed stroke or transient ischemic attack (TIA) • History or current diagnosis of any seizure disorder or major neurological disorder or major psychiatric disorder • Sexually active males, including those post-vasectomy, must use a condom during sexual intercourse for at least 96 hours after dosing to prevent delivery of the drug via seminal fluid and should not father a child during this period • Women must be either of non-childbearing potential or child-bearing potential using highly effective non-hormonal contraception
Study treatment	HSY244 or placebo
Efficacy assessments	Digital Holter (continuous ECG) monitor

Pharmacokinetic assessments	PK profile as measured by Cmax, Tmax, and AUClast from the plasma concentration-time data
Key safety assessments	Adverse event monitoring, vital signs, physical examinations, monitoring of laboratory markers in blood and urine, ECG parameters
Other assessments	Commercially Confidential Information
Data analysis	The rate of conversion to sinus rhythm for HSY244 and placebo will be compared using Fisher's Exact test. The difference in the conversion rates between HSY244 and placebo will be reported along with the 80% confidence limits for the difference and the p-value from Fisher's Exact test. Results may be reported for the subpopulations of participants with and without heart failure.
Key words	Atrial fibrillation, Arrhythmia, Pharmacological cardioversion, GIRK1/4

1 Introduction

1.1 Background

Atrial fibrillation (AF) is a common cardiac arrhythmia that increases in prevalence with age. AF affects approximately 2% of people under the age of 65 and about 9% of people above the age of 65. In the US, AF accounts for more than 467,000 hospitalizations and contributes to more than 99,000 deaths a year (January et al 2014). A 2010 health survey estimated that 33 million people worldwide had AF (Chugh et al 2014). With the aging of the population, the prevalence of AF is expected to rise substantially in the future adding burden to healthcare systems. AF is highly prevalent among individuals with heart failure (HF) with an increasing frequency of AF as severity of HF increases (Trulock et al 2014). Patients with AF and HF have worse outcomes as compared to patients with HF alone, regardless of the degree of cardiac dysfunction (Olsson et al 2006).

AF can lead to symptoms such as palpitations, dyspnea, chest pain, and fatigue. AF is associated with an increased risk of stroke, congestive heart failure, and a decreased quality of life. Cardioversion of AF to sinus rhythm remains an important option for patients with AF. The most commonly utilized method of restoring sinus rhythm is direct current cardioversion in which an electric shock is delivered to the heart under sedation or anesthesia. This procedure is generally performed under the supervision of a cardiologist and an anesthesiologist. Pharmacologic cardioversion is another option, but not commonly performed even though it is less invasive and could be initiated more rapidly as it does not require sedation or anesthesia. Antiarrhythmic drugs such as flecainide, propafenone, ibutilide, dofetilide, or amiodarone have demonstrated some efficacy as AF cardioversion agents, but they are limited by poor efficacy, slow onset of action, or undesired effects on ventricular repolarization leading to a prolonged QT interval and risk of torsades de pointes. There is an unmet need for a safe and effective drug that can rapidly cardiovert AF patients to sinus rhythm.

The cardiac acetylcholine-sensitive inwardly rectifying K+ current (I_{KACh}), is mediated by a channel with two subunits, GIRK1 and GIRK4, assembled as heterotetramers (Voigt et al 2014). In the heart, I_{KACh} channels are primarily expressed in the sinoatrial (SA) node, atrioventricular (AV) node, and atrial myocytes. I_{KACh} is believed to have a physiologic role in the regulation of sinus node automaticity and in the repolarization of atrial myocytes. As GIRK1/4 expression is largely absent in the ventricles, inhibition of GIRK1/4 is believed to represent an attractive antiarrhythmic drug target since such a blocker would be expected to have little to no effects on ventricular repolarization and thus be devoid of pro-arrhythmic ventricular side effects.

Increased activation of I_{KACh} channels has been proposed to contribute to AF by leading to a shortening of the atrial action potential duration. Activation of I_{KACh} has been observed in experimental models of AF induced by tachypacing, and constitutive I_{KACh} activity has been observed in atrial myocytes from patients with chronic AF (Dobrev et al 2005). Mechanistically, by shortening the atrial action potential duration and decreasing the atrial effective refractory period (AERP), I_{KACh} activity is assumed to increase vulnerability to electrical reentry promoting the propagation of AF. Indeed, several antiarrhythmic drugs such as amiodarone, flecainide, and verapamil have been shown to possess I_{KACh} blocking effects, and tertiapin, a bee venom peptide that selectively blocks I_{KACh}, has been shown to terminate AF in both dog and guinea pig models without affecting PR, QRS, and QT intervals (Voigt et al 2014). These

data suggest that a selective pharmacologic inhibitor of GIRK channels has potential as a novel antiarrhythmic drug for the cardioversion of patients with AF.

HSY244 is a potent inhibitor of GIRK channels. Novartis is developing HSY244 as an intravenous (i.v.) infusion for the acute cardioversion of patients with AF.

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The most relevant data for the present study are summarized in the sections below. For detailed information, please refer to the Investigator's Brochure.

1.2 Purpose

The purpose of this study is to evaluate the efficacy, safety, tolerability, and pharmacokinetics of HSY244 in participants with AF, with and without HF. HSY244 is a potent inhibitor of GIRK1/4 channels, which are believed to play an important role in AF.

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2 Objectives and endpoints

Table 2-1 Objectives and related endpoints

Objective(s)	**Endpoint(s)**
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To evaluate the efficacy of HSY244 to restore sinus rhythm in participants with AF	• Conversion to sinus rhythm for at least 1 minute within 90 minutes from the start of study drug administration
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To evaluate the safety and tolerability of HSY244 in participants with AF	• Results of safety assessments including adverse events, vital signs, ECG parameters, and laboratory assessments of blood and urine.
• To evaluate the pharmacokinetics of HSY244 in participants with AF	• HSY244 plasma AUClast, Cmax, and Tmax after i.v. administration
Exploratory objective(s)	**Endpoint(s) for exploratory objective(s)**

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3 Study design

This is a randomized, placebo-controlled, investigator- and participant-blinded study to evaluate the efficacy, safety, tolerability, and pharmacokinetics (PK) of HSY244 in participants with AF, with and without HF. An initial cohort (Cohort 1) evaluating a 150 mg i.v. dose of HSY244, administered over a 15-minute infusion, is planned to be enrolled.

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Figure 3-1 Study Design

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For Cohort 1 CCI the following will occur:

A screening period of up to 3 days (72 hours) will be used to assess eligibility. After eligibility is confirmed, participants will be randomized to either HSY244 or placebo. Prior to study drug administration, pre-dose assessments will be completed (refer to Section 8 for complete details). Standard clinical care practices should be followed per Investigator's discretion, including but not limited to bedside telemetry and application of defibrillator pads. A study 12-lead Holter (continuous ECG) monitor will be applied for continuous heart rate and rhythm monitoring for 24 hours and will also allow for single-timepoint ECG tracings to be captured. After the participant's ongoing AF episode is confirmed, study drug administration of a 15 minute i.v. infusion of HSY244 or placebo will begin; this is time '0' as related to all post-dose assessments. After the start of study drug administration, the participant will be monitored for cardioversion to sinus rhythm. If a participant is still in AF at 90 minutes after the start of study drug administration, direct current cardioversion may be applied at a time deemed appropriate by the investigator. Standard clinical care approaches should be followed for direct current

cardioversion but alternatives should be considered for the medications on the prohibited medication list (Table 6-2) until the EOS visit has occurred.

For the first 120 minutes (2 hours) after study drug administration, the participant should be resting in the supine or semi-recumbent position with minimal disturbances to allow for assessments of heart rate CCI If direct current cardioversion is applied at 90 minutes, there should be an additional 30 minutes afterward during which the participant should be resting in the supine or semi-recumbent position with minimal disturbances to allow for assessments of heart rate CCI

The participant should be monitored for at least 180 minutes (3 hours), after study drug administration for safety and blood sampling; this monitoring period can be extended through 24 hours if deemed necessary or appropriate by the Investigator and/or for convenience for the participant. The participant can be transferred to other locations within the study site (i.e., to a post-anesthesia care unit [PACU], hospital ward, or clinical trials unit given site staff is appropriately trained) during the 3 hour monitoring period (or for 24 hours if observation period is extended), at the discretion of the Investigator, as long as the participant can remain undisturbed (i.e., remain in supine/semi-recumbant position for the first 2 hours), and the study protocol requirements, assessments and appropriate standard clinical care practices are possible.

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If the participant remains on-site overnight, Day 2 (24 hours post-dose) assessments should be completed before the participant's release from the study site. If the participant does not remain at the site overnight, the site will call the participant on Day 2 (24 hours post dose ±4 hours) to check on AEs, as well as to guide the participant for the removal of the Holter device. The participant should remain resting in a supine or semi-recumbent position for at least 15 minutes prior to the removal of the Holter (continuous ECG) monitor to allow for the assessment of resting heart rate CCI . The participant is required to return to the study site within ±24 hours of Day 5 (96 hours post dose) for end of study (EOS) assessments.

A total of approximately 29 participants are planned to be randomized in Cohort 1, of which approximately 20 will receive HSY244. Participants will be randomized in a 5:1 HSY244-to-placebo ratio.

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4 Rationale

4.1 Rationale for study design

Table 4-1 Rationale for study design

Study Design Aspect	Rationale
Overall	This is a randomized, placebo-controlled, investigator- and participant-blinded study to evaluate the efficacy, safety, tolerability, and pharmacokinetics of HSY244 in participants with AF, with or without HF. The study design was chosen to minimize bias. An initial cohort (Cohort 1) evaluating a 150 mg i.v. dose of HSY244 or placebo given over a 15-minute infusion is planned to determine if this dose will restore sinus rhythm to participants with AF. Commercially Confidential Information
Randomization (strata, allocation ratio)	Randomizing participants 5:1 to receive HSY244 or placebo will maintain the blind and enable detection of possible differences in each group.
Participant and investigator blinding	Blinding of participants and the investigator allows for an unbiased assessment of study endpoints, particularly for subjective readouts, such as adverse events. Limited unblinding of the Sponsor as detailed in Table 6-3 will improve the accuracy of safety-related decisions.
Duration of study	The study duration minimizes the burden to the participants and allows the Sponsor to collect the data required for efficacy, safety, tolerability, and PK readouts.
Placebo comparator	The use of placebo as a comparator is to provide a comparison group for an unbiased collection and assessment of efficacy, safety and tolerability.
Observation period	This allows for close observation of safety and tolerability during the time of the highest exposure to HSY244. At 180 minutes (3 hours), the time of planned discharge, exposure is predicted to be below the threshold for physiological effect for both Cohort 1 Commercially Confidential Information The observation period can be increased if deemed necessary or appropriate by the Investigator and/or for the convenience for the participant.

4.2 Rationale for dose/regimen and duration of treatment

In Cohort 1, a single 150 mg dose of HSY244 will be administered via a 15-minute i.v. infusion.
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4.3 Rationale for choice of control drugs (comparator/placebo) or combination drugs

The use of placebo as a comparator is to provide a comparison group for an unbiased collection and assessment of efficacy, safety and tolerability.

A placebo and not an active arm comparator will be used as a control for this study because marketed drugs that are used for pharmacological cardioversion are either contraindicated in patients with AF and HF (e.g., dofetilide) or induce cardioversion much slower than 90 minutes (e.g., amiodarone).
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Due to the lack of appropriate drugs for cardioversion, in particular among patients with AF and HF, direct current cardioversion is the standard of care and may be applied at 90 minutes (or later) after HSY244 or placebo administration if sinus rhythm has not already been restored, unless deemed inappropriate by the Investigator.

4.4 Purpose and timing of interim analyses

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4.5 Risks and benefits

Participants will receive either HSY244 or placebo in the current study. Participants receiving HSY244 may benefit from cardioversion to sinus rhythm without the need for direct current cardioversion and concomitant sedation.

Risks to participants in this trial will be minimized by adherence to the eligibility criteria, close clinical monitoring, and study stopping rules.

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4.5.1 Effects on the central nervous system

GIRK1/4 is closely related to GIRK1/2, which is predominantly expressed in the brain but not the heart. Mice engineered with a knockout of the GIRK2 gene have been reported to be susceptible to stress induced seizures (Signorini et al 1997). Furthermore, at high doses of BMS 914392, an oral inhibitor of GIRK1/4, subjects reported reversible symptoms of euphoria, ataxia and impaired motor skills (Podd et al 2016).

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4.5.2 Effects on the cardiovascular system

I_{KACh} is primarily found in the SA node, atrioventricular (AV) node, and atria. I_{KACh} is believed to play an important role in the regulation of sinus node automaticity, in particular, parasympathetically mediated changes in beat-to-beat heart rate and heart rate variability. Compared to control mice, mice that are deficient in the gene for GIRK4 have slightly higher resting heart rates and exhibit a delayed heart rate recovery after sympathetic stimulation via exercise or injection of the beta-agonist isoproterenol (Mesirca et al 2013, Wickman et al 1998).

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4.5.7 Potential risk associated with the COVID-19 pandemic

Novartis is committed to supporting the safety and well-being of our study participants, investigators, and site staff. All local regulations and site requirements are being applied in the countries that are affected by the COVID-19 pandemic, including COVID-19 testing of participants if applicable. The Novartis clinical trial team will review the situation in each participating country and work with investigators to continue to ensure the safety of participants during the conduct of the trial. A benefit/risk assessment has been made and has been determined to be positive for the participants to be enrolled. As the COVID-19 situation evolves, investigators must use their best judgement to minimize risk to participants during the conduct of the study.

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4.6 Rationale for Public Health Emergency mitigation procedures

During a Public Health emergency as declared by Local or Regional authorities, i.e., pandemic, epidemic or natural disaster, mitigation procedures to ensure participant safety and trial integrity are listed in relevant sections. Notification of the Public Health emergency should be discussed with Novartis prior to implementation of mitigation procedures, and permitted/approved by Local or Regional Health authorities and Ethics Committees as appropriate.

5 Study Population

The study population will include hemodynamically stable men and women between 18 and 80 years of age with a clinical indication for direct current cardioversion of AF, with the current AF episode lasting between 6 hours and 60 days. In Cohort 1, a total of approximately 29 participants with AF will be randomized, of which approximately 20 will receive HSY244.

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Replacement participants will be allowed for those participants who discontinue study drug administration before completion if those participants have not discontinued due to adverse drug reactions or adverse events from study procedures. A maximum of 4 replacement participants will be allowed per Cohort. Please refer to Section 9.2 for additional details. Rescreening of screen failures will be allowed. Please refer to Section 8.1 for additional details.

5.1 Inclusion criteria

Participants must meet ALL of the following criteria for inclusion in this study:

1. At screening, written informed consent must be obtained before any assessment is performed. Only participants able to provide written informed consent themselves will be included in this study.
2. Hemodynamically stable men and women (either of non-child-bearing potential or child-bearing potential with highly effective contraception) between 18 and 80 years of age (inclusive) at screening with a clinical indication for direct current cardioversion of AF.
3. At screening, current episode of AF has been ongoing for ≥6 hours and ≤60 days
4. Successful initiation and achievement of therapeutic levels of national guideline and institution-specific anticoagulation therapy as appropriate for the duration of the AF episode and risk for the participant.
5. Completion of national guideline and institution-specific imaging evaluation for left atrial thrombi as appropriate for the duration of AF episode and risk for the participant.
6. At screening, participants must weigh at least 60 kg to participate in the study, and must have a body mass index (BMI) within the range of 18 - 45 kg/m^2. BMI = Body weight (kg) / [Height (m)]^2
7. At screening, vital signs (systolic blood pressure and pulse rate) will be assessed in the sitting position. Sitting vital signs should be within the following ranges (exclusive):
   - systolic blood pressure between 100-160 mmHg and diastolic blood pressure 60-100 mmHg
   - pulse rate (ventricular rate) between 60-120 bpm

   If vital signs are outside these ranges, the Investigator may obtain up to two additional readings, so that up to three consecutive assessments are made.

   At least the last set of readings must be within the ranges provided above in order for the participant to qualify.

   The investigator should consider whether to not enroll participants with a known history of symptomatic postural hypotension.
8. Able to communicate well with the investigator, to understand and comply with the requirements of the study.

5.2 Exclusion criteria

Participants meeting any of the following criteria are not eligible for inclusion in this study:

1. Use of other investigational drugs within 5 half-lives of randomization or within 30 days, whichever is longer; or longer if required by local regulations.
2. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 4 days after stopping of investigational drug. *Highly effective contraception methods include:*
   - Total abstinence from heterosexual intercourse (when this is in line with the preferred and usual lifestyle of the participant). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
   - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or bilateral tubal ligation at least six weeks before taking investigational drug. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
   - Male sterilization (at least 6 months prior to screening). For female participants in the study, the vasectomized male partner should be the sole partner for that participant.
   - Placement of non-hormonal intrauterine device (IUD) or intrauterine system (IUS)

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     If local regulations deviate from the contraception methods listed above and require more extensive measures to prevent pregnancy, local regulations apply and will be described in the ICF.

     Women are considered post-menopausal if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age appropriate, history of vasomotor symptoms). Women are considered not of childbearing potential if they are post-menopausal or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or bilateral tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of childbearing potential. Refer to Section 8.4.3 (Pregnancy and Assessments of Fertility).
3. Pregnant or nursing (lactating) women.
4. Sexually active males unwilling to use a condom during intercourse while taking investigational drug and for 96 hours after study drug administration. A condom is required for all sexually active male participants to prevent them from fathering a child AND to prevent delivery of the investigational drug via seminal fluid to their partner. In addition, male participants should not donate sperm for the time period specified above.
5. History of hypersensitivity to HSY244 or excipients of the formulation (CCI CCI) or to drugs of similar chemical classes.

6. Use of any anti-arrhythmic class I or III drug (including Ranolazine [Ranexa]) within 5 half-lives before randomization; including use of amiodarone within 3 months before randomization.
7. Use of a QT prolonging drug (as reported on crediblemeds.org in the "known risk" of QT prolongation category or other reliable source) within 5 half-lives before randomization.
8. Commercially Confidential Information
9. Use of drugs that are known to substantially affect GIRK channels (inhaled volatile anesthetics: desflurane, sevoflurane, isoflurane)
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10. At screening, history or current diagnosis of ECG abnormalities or cardiac rhythm disorders as determined by the Investigator's interpretation of the ECG findings indicating a significant safety risk for participating in the study such as:
    - History of Torsades de Pointes (TdP), any other polymorphic ventricular tachycardia, sustained monomorphic ventricular tachycardia, long QT syndrome, or Brugada syndrome
    - Wolff-Parkinson-White (WPW) syndrome
    - In the absence of a complete bundle branch block, a resting QTcF > 460 msec for men and > 470 msec for women (mean of ≥ 5 consecutive QT intervals)
    - In the presence of a complete bundle branch block, a prolonged QTcF or JTc that in the opinion of the Investigator may pose a risk to patient safety
    - Third-degree (complete) heart block, or second-degree Mobitz type II heart block
11. (This exclusion criterion was intentionally removed in amendment 04)
12. Attempted or unsuccessful cardioversion within 2 weeks prior to randomization
13. (This exclusion criterion was intentionally removed in amendment 04)
14. Presence of a left atrial thrombus that may pose a risk of embolization with cardioversion
15. Presence of known severe mitral regurgitation and/or known severely dilated left atrium.
16. Pre-existing or tachycardia-induced moderate to severe cardiac dysfunction (New York Heart Association Class III and IV).
17. History within the preceding 3 months prior to randomization of: myocardial infarction, unstable angina, cardiac surgery, or a percutaneous coronary intervention.
18. History of a confirmed stroke or transient ischemic attack (TIA).
19. History or current diagnosis of any seizure disorder, epilepsy, significant head trauma, or other disorders increasing the risk for seizures.
20. History or current diagnosis of a major neurologic or psychiatric disorder that in the opinion of the Investigator poses a risk to patient safety to participate.
21. At screening, moderately or greater impaired renal function as indicated by an eGFR <60 mL/min or abnormalities that in the opinion of the Investigator pose a risk to patient safety to participate.

22. At screening, liver disease or liver injury as indicated by abnormal liver function tests. ALT (SGPT), AST (SGOT), GGT, alkaline phosphatase must not exceed 2 x upper limit of normal (ULN) and serum bilirubin must not exceed 1.5 x ULN
23. Donation or loss of 450 mL or more of blood within eight weeks prior to randomization, or longer if required by local regulation.
24. Have any other conditions, which, in the opinion of the Investigator, would make the patient unsuitable for inclusion or could interfere with the patient participating in or completing the study including any surgical or medical condition which might significantly alter the metabolism or excretion of drugs, or which may jeopardize the participant in case of participation in the study. The Investigator should make this determination in consideration of the participant's medical history and/or clinical or laboratory evidence of any of the following:
    - At screening, anemia (hemoglobin concentration < 9 g/dL)
    - At screening, evidence of urinary obstruction or difficulty in voiding at screening
    - At screening, hypo- or hyperkalemia as indicated by a potassium <3.5 or >5.2 mmol/L
    - At screening, pancreatic injury or pancreatitis
25. Significant illness and/or infection, which has not resolved within two (2) weeks prior to randomization
26. Known difficult venous access, in which it would be difficult to obtain venous access in a large vein (i.e., antecubital) for study drug administration.

6 Treatment

6.1 Study treatment

Details on the requirements for storage and management of study treatment, and instructions to be followed for participant numbering, prescribing/dispensing, and administering study treatment are outlined in the Pharmacy Manual.

6.1.1 Investigational and control drugs

Table 6-1 Investigational and control drug

Investigational/ Control Drug (Name and Strength)	Pharmaceutical Dosage Form	Route of Administration	Supply Type	Sponsor (global or local)
HSY244 80 mg/2mL	Concentrate solution for injection	Intravenous use	Open label bulk supply	Global
HSY244 0mg/2mL	Concentrate solution for injection	Intravenous use	Open label bulk supply	Global

The investigational drug, HSY244 active and placebo, will be prepared by Novartis and supplied to the Investigator as an open labeled bulk supply to be dispensed by the unblinded pharmacist at the Investigator site according to the randomization scheme. HSY244 active and placebo is provided as a concentrate for solution for injection. HSY244 active and placebo are packed in a glass vial with stopper and seal and should be stored at 2C to 8C (35.6-46.4F), protected from light. Please refer to the Pharmacy Manual for additional information.

6.1.2 Additional study treatments

No other treatment beyond investigational drug and control drug are included in this trial.

6.1.3 Treatment arms/group

Participants will be assigned at Day 1 (Visit 101) to one of the following 2 treatment arms/groups in a ratio of 5:1.

Cohort 1:

- HSY244 150 mg i.v. infusion over 15 minutes
- Placebo

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6.2 Other treatment(s)

6.2.1 Concomitant therapy

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6.2.3 Rescue medication

In the case that a participant should still be in AF at 90 minutes after study drug administration, direct current cardioversion may be applied unless deemed inappropriate by the Investigator.

If the participant develops a new clinically or hemodynamically significant arrhythmia, medically appropriate direct current cardioversion, defibrillation, or anti-arrhythmic pharmacotherapy should be initiated at the Investigator's discretion. Alternatives should be considered for the medications on the prohibited medication list (Table 6-2) within the study treatment period.

If the participant develops a seizure or other neurological symptom, medically appropriate therapy should be initiated at the Investigator's discretion. Alternatives should be considered for the medications on the prohibited medication list (Table 6-2) within the study treatment period

6.2.4 Restriction for study participants

For the duration of the study, participants should be informed and reminded of the restrictions outlined in this section.

6.2.4.1 Dietary restrictions and smoking

1. No alcohol from randomization through EOS visit.
2. No cannabis use from randomization through EOS visit.
3. No cigarettes/use of nicotine products from randomization through EOS visit.
4. Intake of xanthine (e.g., caffeine) containing food or beverages should be discontinued upon enrollment until at least 180 minutes (3 hours) post-dose. If a deviation occurs, it

must be noted. After 3 hours post dose through the EOS visit, caffeinated beverages will be restricted to no more than 4 cups/day.

6.2.4.2 Other restrictions

- No strenuous physical exercise (e.g., weight training, aerobics, football) from screening until after EOS visit.

6.3 Participant numbering, treatment assignment, randomization

6.3.1 Participant numbering

Each participant is identified in the study by a Participant Number (Participant No.), that is assigned when the participant is enrolled for screening and is retained for the participant throughout his/her participation in the trial. A new Participant No. will be assigned at every subsequent enrollment if the participant is re-screened. The Participant No. consists of the Center Number (Center No.) (as assigned by Novartis Institutes for BioMedical Research to the investigative site) with a sequential participant number suffixed to it, so that each participant's participation is numbered uniquely across the entire database. Upon signing the informed consent form, the participant is assigned to the next sequential Participant No. available.

A new ICF will need to be signed if the investigator chooses to re-screen the participant after a participant has screen failed, and the participant will be assigned a new Participant No.

6.3.2 Treatment assignment, randomization

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from participants and investigator staff.

A participant randomization list will be produced by the Novartis Interactive Response Technology (NIRT) provider, or by a delegate under Novartis supervision, using a validated system that automates the random assignment of participant numbers to randomization numbers. These randomization numbers are linked to the different treatment arms.

The randomization scheme for participants will be reviewed and approved by a member of the Randomization Office.

6.4 Treatment blinding

This is a participant and investigator-blinded study. Participants and investigators will remain blinded to study treatment throughout the study, except where indicated below.

The identity of the treatments will be concealed by the use of study drugs that are all identical in packaging, labeling, schedule of administration, appearance, and odor.

Site staff

With the exception of any unblinded site staff identified below, all site staff (including study investigator and study nurse) will be blinded to study treatment throughout the study.

Unblinding a single participant at site for safety reasons (necessary for participant management) will occur via an emergency system in place at the site.

Drug product will be supplied in bulk, so an unblinded pharmacist who is independent of the study team will be required in order to maintain the blind. Treatment will be assigned via the NIRT system. Appropriate measures must be taken by the unblinded pharmacist to ensure that the treatment assignments are concealed from the rest of the site staff.

Sponsor staff or delegate

The following unblinded sponsor roles are required for this study:

- Unblinded field monitor(s)
- Unblinded clinical staff managing drug re-supply to site
- Unblinded sample analyst(s) (PK)

The unblinded field monitors are required to review drug accountability and allocation at site. The unblinded monitors are not provided with a randomization list directly but will be unblinded through review of source documentation compiled by the unblinded pharmacist, which details treatment allocation to individual participants.

Sponsor clinical staff are required to assist in the management and re-supply of investigational drug product. These individuals are not provided with randomization lists directly, but may be unblinded through communication of drug re-supply needs via the unblinded site pharmacists.

The sample analysts will receive a copy of the randomization schedule (via request to the Randomization Office), to facilitate analysis of the samples. The sample analysts will provide the sample data to the study team under blinded conditions unless otherwise allowed.

The study statistician will be able to access the randomization list for interim analyses and is allowed to share unblinded information with the rest of the clinical team as appropriate for internal decision purposes, as outlined in Table 6-3. For example, unblinded summaries and unblinded individual data can be shared with the team for interim analyses.

Study programmers and other personnel involved in study data analysis (e.g., biomarker expert) are allowed to access treatment assignment information for the purpose of conducting interim analyses.

The clinical trial team, unblinded at the time of analysis, is allowed to share unblinded results with other sponsor staff (e.g., decision boards) as required for internal decision making on the study or the project at the time of interim analyses while the study is ongoing.

All unblinded personnel will otherwise keep randomization lists and data or information that could unblind other study team members confidential and secure except as described above.

Following final database lock all roles may be considered unblinded.

Table 6-3 Blinding levels

Role	Time or Event			
	Randomization list generated	Treatment allocation & dosing	Safety event (single subject unblinded)	Interim Analysis
Subjects/Patients	B	B	UI	CCI
Site staff	B	B	UI	

Role	Time or Event			
Unblinded site staff (see text for details)	B	UI	UI	CCI
Drug Supply and Randomization Office	UI	UI	UI	
Unblinded sponsor staff (see text for details)	B	UI	UI	
Statistician/statistical programmer/data analysts	B	B	UI	
Independent committees used for assessing interim results	B	UI	UI	
All other sponsor staff not identified above	B	B	UI	

B Remains blinded

UI Allowed to be unblinded on individual patient level

6.5 Dose escalation and dose modification

Not applicable

6.6 Additional treatment guidance

6.6.1 Treatment compliance

Pharmacokinetic parameters (measures of treatment exposure) will be determined in all participants treated with HSY244, as detailed in pharmacokinetics section (Section 8.5.1).

6.6.2 Recommended treatment of adverse events

If a participant experiences mild injection site discomfort, the Investigator may attempt applying an arm massage or a cold compress.

If a participant develops a new clinically or hemodynamically significant arrhythmia, medically appropriate electrical cardioversion, defibrillation, or anti-arrhythmic pharmacotherapy should be initiated at the Investigator's discretion. Alternatives should be considered for medications on the prohibited medication list (Table 6-2) within the study treatment period.

If the participant develops a seizure or other neurological symptom, medically appropriate therapy should be initiated at the Investigator's discretion. Alternatives should be considered for the medications on the prohibited medication list (Table 6-2) within the study treatment period.

In the case of a development of an AE, which requires additional monitoring, the minimum 3 hour observation period can be extended at the discretion of the Investigator.

Medication used to treat adverse events (AEs) must be recorded on the appropriate CRF.

6.6.3 Emergency breaking of assigned treatment code

Emergency code breaks must only be undertaken when it is required to in order to treat the participant safely. Most often, discontinuation from study treatment and knowledge of the possible treatment assignments are sufficient to treat a study participant who presents with an

emergency condition. Emergency treatment code breaks are performed using the NIRT. When the investigator contacts the system to break a treatment code for a participant, he/she must provide the requested participant identifying information and confirm the necessity to break the treatment code for the participant. The investigator will then receive details of the investigational drug treatment for the specified participant and a fax or email confirming this information. The system will automatically inform the Novartis monitor for the site and the study team that the code has been broken.

It is the investigator's responsibility to ensure that there is a dependable procedure in place to allow access to the NIRT at any time in case of emergency. The investigator will provide:

- protocol number
- participant number

In addition, oral and written information to the participant must be provided on how to contact his/her backup in cases of emergency, or when he/she is unavailable, to ensure that un-blinding can be performed at any time.

6.7 Preparation and dispensation

Each study site will be supplied with study drug in packaging as described under investigational and control drugs section (Section 6.1.1). Please refer to the Pharmacy Manual for detailed instructions.

A unique medication number is printed on the study medication label.

Investigator staff will identify the treatment to dispense to the participant by contacting NIRT and obtaining the randomization number and treatment assignment. As per the treatment assigned to the participant, investigator staff will select the study treatment to dispense to the participant and record the batch number on the accountability logs accordingly.

6.7.1 Handling of study treatment and additional treatment

6.7.1.1 Handling of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels.

Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis Institutes for BioMedical Research CO Quality Assurance.

Study treatment must be prepared by an unblinded pharmacist to ensure treatment masking. Please refer to the Pharmacy Manual for complete preparation instructions.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the study treatment but no information about the participant.

The investigator must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial.

At the conclusion of the study, and as appropriate during the course of the study, the investigator will return all unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis Institutes for BioMedical Research monitor or to the Novartis Institutes for BioMedical Research address provided in the investigator folder at each site.

6.7.2 Instruction for prescribing and taking study treatment

HSY244 or placebo will be administered to the participant via i.v. injection route of administration for a 15-minute infusion at the study site. Please refer to the Pharmacy Manual for detailed instructions.

7 Informed consent procedures

Eligible participants may only be included in the study after providing, IRB/IEC-approved informed consent.

Informed consent must be obtained before conducting any study-specific procedures (e.g., all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the participant source documents. Only participants able to provide written informed consent themselves will be included in this study.

Novartis Institutes for BioMedical Research will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guidelines and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed by Novartis Institutes for BioMedical Research before submission to the IRB/IEC.

Information about common side effects already known about the investigational drug can be found in the Investigator's Brochure (IB). This information will be included in the participant informed consent and should be discussed with the participant during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an investigator notification or an aggregate safety finding. New information might require an update to the informed consent and then must be discussed with the participant.

The following informed consents are included in this study:

- Main study consent, which also included:
  - A subsection that requires a separate signature for the ‘Optional Consent for Additional Research’ to allow future research on data/samples collected during this study
- As applicable, Pregnancy Outcomes Reporting Consent for female participants or the female partners of any male participants who took study treatment

Women of child-bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirements.

Male participants are required to agree to not father a child, donate sperm, and wear a condom from time of randomization through 96 hours after treatment. Male participants must be informed that if a female partner becomes pregnant while he is enrolled in the study, contact with the female partner will be attempted to request her consent to collect pregnancy outcome information.

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A copy of the approved version of all consent forms must be provided to Novartis Institutes for BioMedical Research after IRB/IEC approval.

8 Visit schedule and assessments

The Assessment Schedule (Table 8-1) lists all of the assessments when they are performed. All data obtained from these assessments must be supported in the participant's source documentation.

Participants should be seen for all visits/assessments as outlined in the assessment schedule (Table 8-1) or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation. Participants who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit will be performed as indicated in the Assessment Schedule. At this final visit, any adverse events and concomitant medications not previously reported must be recorded on the eCRF.

The "X" in the table denotes the assessments to be recorded in the clinical database or received electronically from a vendor. The "S" in the table denotes the assessments that are only in the participant's source documentation and do not need to be recorded in the clinical database.

When the following assessments are scheduled to be performed at the same time point, the recommended order of priority will be as follows:

- For Day 1, 0 min: 1) assess concomitant medications and therapies, 2) assess pre-existing injection/infusion site reaction (i.e., bruising from i.v. placement), 3) attach pads and leads for study Holter monitor, and for any standard clinical care devices and practices, 4) assess vital signs, 5) short physical exam, 6) blood draw per assessment schedule, 7) obtain ECG tracing, 8) after confirmation of AF episode, initiate study drug administration, and 9) monitor for adverse events and AF conversion to sinus rhythm.

- For Day 1, 30 min: 1) assess injection/infusion site, 2) assess vital signs, 3) short physical exam, 4) blood draw per assessment schedule, 5) obtain ECG tracing, and 6) monitor for adverse events and AF conversion to sinus rhythm.
- For Day 1, 90 min: 1) assess injection/infusion site, 2) assess vital signs, 3) short physical exam, 4) blood draw per assessment schedule, 5) obtain ECG tracing, and 6) after confirmation of persistent AF, initiate direct current cardioversion under appropriate sedation/anesthesia, unless deemed inappropriate by the Investigator. Alternatives to medications listed in the prohibited medication list (Table 6-2) should be used for sedation/anesthesia, as deemed appropriate by the Investigator.
- For Day 1, 180 min: 1) assess injection/infusion site, 2) assess vital signs, 3) short physical exam, 4) blood draw per assessment schedule, 5) obtain ECG tracing, 6) CCI 7) monitor for adverse events. At this point, the participant can leave the study site to return for assessments at the EOS visit.The observation period can be extended through 24 hours if deemed necessary or appropriate by the Investigator and/or for the convenience of the participant.
- For assessments during other Day 1 time points: 1) assess concomitant medications and therapies, 2) assess injection/infusion site reaction, 3) assess vital signs, 4) blood draw per assessment schedule, and 5) monitor for adverse events.

Blood draws should be obtained at the protocol specified time and within the assessment window as specified in Table 8-1. Every effort should be made for the other assessments (e.g., ECG, vital signs, etc.) to be obtained at the specified assessment time either before or after the blood draw, as described by the order of assessments above.

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities, i.e., pandemic, epidemic or natural disaster that limits or prevents on-site study visits, alternative methods of providing continuing care may be implemented by the investigator as the situation dictates. If allowable by a local Health Authority and depending on operational capabilities, phone calls, virtual contacts (e.g., tele consult) or visits by site staff/home nursing staff to the participant's home, can replace on-site study visits, for the duration of the disruption until it is safe for the participant to visit the site again.

Table 8-1 Assessment Schedule

Epoch	**Screening**	**Treatment**										
Visit Name	**Screening[2]**	**Day 1**								**Day 2[10]**	**End of Study**	**Post Study Safety Contact**
Visit Numbers[1]	**1**	**101**								**102**	**199**	
Days	**-3 to 1**	**1**								**2**	**5**	**Last treatment +30**
Time (post-dose)	**-**	**0min**	**5min**	**10min**	**15min ±5[9]**	**30min ±5[9]**	**60min ±5[9]**	**90min ±5[3,9]**	**180min ±5[9]**	**24h ±4**	**96h ±24**	**-**
Informed consent	X											

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Inclusion / Exclusion criteria	S	S										
Medical history/current medical conditions	X											
Study drug administration		X										
Injection/Infusion site reaction		X	X	X	X	X	X	X	X	X	X	
Demography	X											
Vital Signs	X	X[4]	X	X	X	X	X	X	X		X	
Body Height	X											
Body Weight	X										X	
Physical Examination	S[5]	S				S		S	S		S[5]	

Epoch	**Screening**	**Treatment**										
Visit Name	**Screening**[2]	**Day 1**								**Day 2**[10]	**End of Study**	**Post Study Safety Contact**
Visit Numbers[1]	**1**	**101**								**102**	**199**	
Days	**-3 to 1**	**1**								**2**	**5**	**Last treatment +30**
Time (post-dose)	**-**	**0min**	**5min**	**10min**	**15min ±5**[9]	**30min ±5**[9]	**60min ±5**[9]	**90min ±5**[3,9]	**180min ±5**[9]	**24h ±4**	**96h ±24**	**-**
Hepatitis screen	S											
HIV screen	S											
Alcohol Test and Drug Screen	S											
Pregnancy and assessments of fertility[6]	S[6]										S[6]	
Hematology	X	X[4]									X	
Clinical Chemistry	X	X[4]									X	
Urinalysis	X										X	
PK blood collection		X[4]			X[7]	X	X	X	X		X	
Electrocardiogram (ECG)	X	X[4]				X		X	X		X	
Continuous digital 12-lead Holter		X[4]										

Epoch	**Screening**	**Treatment**										
Visit Name	**Screening**[2]	**Day 1**								**Day 2**[10]	**End of Study**	**Post Study Safety Contact**
Visit Numbers[1]	**1**	**101**								**102**	**199**	
Days	**-3 to 1**	**1**								**2**	**5**	**Last treatment +30**
Time (post-dose)	**-**	**0min**	**5min**	**10min**	**15min ±5**[9]	**30min ±5**[9]	**60min ±5**[9]	**90min ±5**[3,9]	**180min ±5**[9]	**24h ±4**	**96h ±24**	**-**

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Adverse Events		X	
Concomitant medications		X	
Concomitant therapies		X	

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Study completion information											X	
Safety Follow up Call												S

[X] Assessment to be recorded in the clinical database or received electronically from a vendor
[S] Assessment to be recorded in the source documentation only
[1] Visit structure given for internal programming purpose only
[2] Allowed screening period is 72 hours; Screening and Day 1 activities are allowed to occur on the same day
[3] All assessments should be completed prior to direct current cardioversion (if deemed necessary by the Investigator)
[4] Assessment to be done pre-dose
[5] Complete physical examination to be done
[6] All pre-menopausal women who are not surgically sterile will have pregnancy testing
[7] Sample drawn at end of infusion
[8] Commercially Confidential Information
[9] Assessment windows as specified apply only to blood draw assessments
[10] Can occur on site or via phone call

8.1 Screening

Screening

It is permissible to re-screen a participant if s/he fails the initial screening; however, each case must be discussed and agreed with the Sponsor on a case-by-case basis.

In the case where a safety laboratory assessment at screening is outside of the range specified in the exclusion criteria, the assessment may be repeated once prior to randomization. If the repeat value remains outside of the specified ranges, the participant must be excluded from the study.

8.1.1 Eligibility screening

8.1.1.1 Hepatitis screen, HIV screen

All participants will be screened for Hepatitis B surface antigen (HBsAg) and, if standard local practice, Hepatitis B core antigen (HBcAg). Screening for Hepatitis C will be based in HCV antibodies and if positive, HCV RNA levels should be determined.

Evaluation for HIV seropositivity will be performed, and, if positive, confirmation by a second technique available at the laboratory site, e.g., Western blot. Appropriate counseling will be made available by the Investigator in the event of a positive confirmatory test. Notification of state and federal authorities, as required by law, will be the responsibility of the Investigator.

Hepatitis and HIV results will not be required to determine eligibility.

8.1.1.2 Alcohol test and Drug screen

Participants will be tested for substances of abuse (e.g., alcohol, amphetamines, barbituates, benzodiazepines, cannabinoids, cocaine and opiates).

8.1.2 Information to be collected on screening failures

Participants who sign an informed consent form and subsequently found to be ineligible prior to randomization will be considered a screen failure. The reason for screen failure should be recorded on the appropriate Case Report Form. The demographic information and informed consent must also be completed for screen failure participants. No other data will be entered into the clinical database for participants who are screen failures, unless the participant experienced a serious adverse event during the screening phase (see Section 10.1.3 for reporting details). If the participant fails to be randomized, NIRT should be notified within 2 days of the screen fail that the participant was not randomized.

Participants who are randomized and fail to start treatment, e.g., participants randomized in error, will be considered an early terminator. The reason for early termination should be recorded on the appropriate Case Report Form.

8.2 Participant demographics/other baseline characteristics

Participant demographics: date or year of birth, sex, race, predominant ethnicity (if permitted) and relevant medical history/current medical conditions, including heart failure disease status, (until date of signature of informed consent) will be recorded in the eCRF. If available, the most recent echocardiogram results should be provided as part of medical history. Where possible, the diagnosis and not symptoms should be recorded. Participant race and ethnicity are collected and analyzed to identify variations in safety or efficacy due to these factors as well as to assess the diversity of the study population as required by Health Authorities.

All prescription medications, over-the-counter drugs and significant non-drug therapies prior to the start of the study must be documented. See Section 6.2.1 for further details on what information must be recorded on the appropriate page of the eCRF.

8.3 Efficacy

The primary efficacy measure is defined as conversion from AF to sinus rhythm, sustained for at least 1 minute during the 90 minutes after the start of the study drug administration, as assessed on the study Holter monitor. After 90 minutes, all participants may undergo direct current cardioversion if they remain in persistent AF, unless deemed inappropriate by the Investigator.

The Investigator should record periods in AF or sinus rhythm during the first 90 minutes after study drug administration, CCI and time of direct current cardioversion (if occurs, unless deemed inappropriate by the Investigator).

Blood and urine samples will be collected at the time points defined in the Assessment Schedule (Table 8-1). Follow instructions outlined in the manual provided by the designated CRO regarding collection, numbering, and processing.

Results need to remain blinded during the study.

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8.3.1 Continuous digital 12-lead Holter

All study Holter monitor data will be collected using a standard continuous 12-lead ECG digital recorder (e.g., the Global Instrumentation [Manlius, NY, USA] M12R). The continuous 12-lead digital ECG data will be stored on SD memory cards. AF detection by both automated algorithms and manual confirmation by trained technicians will be employed to evaluate cardioversion to sinus rhythm and burden of AF with central reading by a designated CRO. Please refer to the device's Instruction Manual for additional details.

In addition to continuous monitoring, the device can also obtain and output single time point 12-lead ECG tracings. Details regarding the single time point 12-lead ECGs are provided in Section 8.4.2.

8.3.2 Appropriateness of efficacy assessments

Assessment of an individual's heart rhythm by a Holter monitor is standard practice in clinical care (January et al 2014). AF detection by both automated algorithms and manual confirmation by trained technicians will be employed.

8.4 Safety

Safety assessments are specified below with the assessment schedule detailing when each assessment is to be performed.

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities, i.e., pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, regular phone or virtual calls can occur for safety monitoring and discussion of the participant's health status until it is safe for the participant to return to the site again.

For details on AE collection and reporting, refer to AE section (Section 10.1.1).

Assessment	Specification
Physical examination	At Screening and EOS, a complete physical examination will include the examination of the participant's general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, and neurological system (including assessment of euphoria symptoms and seizure-related adverse events). A short physical exam will include the examination of the participant's general appearance, vital signs (blood pressure [SBP and DBP] and pulse), and a limited neurologic exam. The abbreviated neurological exam should include, but is not limited to, a brief assessment of: 1) mental status (level of alertness, orientation, and euphoria symptoms), 2) motor exam (observe for tremors/twitches/involuntary muscle movements), and 3) coordination (finger-nose-finger test, heel-shin test). Any abnormalities or concerns can warrant a full physical examination at the discretion of the Site Investigator. The short physical exam will be completed at designated time points, as outlined in Table 8-1. Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent must be recorded on the appropriate eCRF that captures medical history. Significant findings made after signing informed consent which meet the definition of an Adverse Event must be recorded as an adverse event. Seizure-related AEs must be reported to the Sponsor within 24 hours.
Vital signs	Vital signs will include the collection of body temperature (recorded in °C), blood pressure (BP) and pulse measurements. For screening, systolic and diastolic blood pressure and pulse rate will be assessed after the participant has been sitting for 3 minutes, with back supported and both feet placed on the floor. An automated validated device, with an appropriately sized arm cuff will be used, and in case the cuff sizes available are not large enough for the participant's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used.

Assessment	Specification
	If vital signs are out-of-range at screening, two additional readings can be obtained, so that a total three consecutive assessments are made, with the participant seated quietly for approximately five minutes preceding each repeat assessment. The last reading must be within the ranges provided in the eligibility criteria in order for the participant to qualify. In case of repeated vital assessments, the eCRF should contain the qualifying results. Starting on Day 1, systolic and diastolic BP will be measured using an automated validated device, e.g., OMRON with an appropriately sized cuff used on the arm, which does not have the i.v. line placed. In case the cuff sizes available are not large enough for the subject's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used. Vital signs may be repeated if unexpected results arise, as clinically appropriate.
Height and weight	Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes) will be measured as specified in Table 8-1. Body mass index (BMI) will be calculated using the following formula: • BMI = Body weight (kg) / [Height (m)]^2 Rounding should be done to the nearest whole number.
Phone call on Day 2	If the participant does not remain at the site overnight from Day 1 to Day 2, the participant will be called on Day 2 (24 hours post dose ±4 hours) to perform the assessments as defined in the assessment schedule. The participant will also be instructed how to remove, and store the Holter device. The Holter device should be returned by the time of the EOS visit.

8.4.1 Laboratory evaluations

All safety laboratory evaluations will be evaluated locally.

In the case where a laboratory range is not specified by the protocol, but a value is outside the reference range for the laboratory at screening, a decision regarding whether the result is of clinical significance or not shall be made by the Investigator (in consultation with the sponsor as needed) and shall be based, in part, upon the nature and degree of the observed abnormality. If needed, the assessment may be repeated once prior to randomization.

In all cases, the Investigator must document in the source documents, the clinical considerations (i.e., result was/was not clinically significant and/or medically relevant) in allowing or disallowing the participant to continue in the study.

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities, i.e., pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, if participants cannot visit the site for protocol-specified safety lab assessments, an alternative local lab collection site may be used.

Urinalysis

A midstream urine sample (approx. 30 mL) will be obtained, in order to avoid contamination with epithelial cells and sediments, and allow proper assessments.

All abnormal lab results must be evaluated for criteria defining an adverse event and reported as such if the criteria are met. For those lab adverse events, repeated evaluations are mandatory until normalization of the result(s) or until the result is no longer considered to be clinically significant.

Test Category	Test Name
Hematology	Hemoglobin, Platelets, White blood cells, Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, Other)
Chemistry	Albumin, Alkaline phosphatase, ALT , AST, GGT, Lactate dehydrogenase (LDH), Bicarbonate, Calcium, Chloride, Magnesium, Phosphorus, Sodium, Potassium, Creatinine, Direct Bilirubin, Total Bilirubin, Blood Urea Nitrogen (BUN) or Urea, Uric Acid, Amylase, Lipase, Glucose (non-fasting)
Urinalysis	Macroscopic Panel (Dipstick) (Color, Bilirubin, Blood, Glucose, Ketones, Leukocytes esterase, Nitrite, pH, Protein, Specific Gravity, Urobilinogen)
Pregnancy Test	Serum / Urine pregnancy test (refer to Section 8.4.3 'Pregnancy and assessments of fertility' section)

8.4.2 Electrocardiogram (ECG)

ECGs must be recorded after a few minutes rest in the supine or semi-recumbent position to ensure a stable baseline. In addition to any ECGs obtained for clinical care, single time point 12-lead ECG tracings will be captured using the same 12-lead Holter monitor that captures the continuous recording. These safety assessment ECGs should be interpreted by a qualified physician to ensure participant safety. Clinically significant abnormalities must be reported on the AE eCRF.

ECGs to be used in the analyses will be selected by pre-determined time points as defined in Table 8-1 and may be read centrally in addition to local interpretation by the Investigator.

If ECGs are read centrally, the following principals will be followed at the designated CRO:

1. ECG analysts are blinded to the participant, visit and treatment allocation
2. Baseline and on-treatment ECGs for a particular participant will be over-read on the same lead and will be analyzed by the same reader.
3. The primary analysis lead is lead II. If lead II is not analyzable, then primary lead of analysis will be changed to another lead for the entire participant data set.

The Fridericia QT correction formula (QTcF) must be used for clinical decisions.

Unless auto-calculated by the ECG machine, the Investigator must calculate QTcF at the Screening visit (as applicable) to assess eligibility according to the following formula:

$$QTcF = \frac{QT}{\sqrt[3]{RR}}$$

Each ECG tracing must be labeled with study number, participant initials, participant number, date and time, and filed in the study site source documents. Investigator should document clinical evaluation in source. For any ECGs with participant safety concerns, two additional ECGs must be performed to confirm the safety finding. Clinically significant ECG findings that pose a risk to participant safety at Day 1 Time 0 must be discussed with the sponsor before administration of study treatment.

Clinically significant abnormalities must be recorded on the relevant section of the medical history/Current medical conditions/AE eCRF as appropriate.

8.4.3 Pregnancy and assessments of fertility

A condom is required for all sexually active male participants to prevent them from fathering a child AND to prevent delivery of study treatment via seminal fluid to their partner. In addition, male participants should not donate sperm for 96 hours after study drug administration.

Pregnancy Test

All pre-menopausal women who are not surgically sterile will have pregnancy testing. Additional pregnancy testing might be performed if requested by local requirements.

If participants cannot visit the site to have local serum pregnancy tests during a Public Health emergency as declared by Local or Regional authorities, i.e., pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, urine pregnancy test kits may be used, if and where permitted by the local regulations and agreed with the local Health Authorities (in Germany only serum pregnancy tests are permitted at screening and EOS visits). Relevant participants can perform the urine pregnancy test at home and report the result to the site. A communication process should be established with the participant so that the site is informed and can verify the pregnancy test result (e.g., following country specific measures).

Assessments of fertility

Medical documentation of oophorectomy, hysterectomy, or tubal ligation must be retained as source documents. Subsequent hormone level assessment to confirm the woman is not of childbearing potential must also be available as source documentation in the following cases:

1. Surgical bilateral oophorectomy without a hysterectomy
2. Reported 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile.

In the absence of the above medical documentation, FSH testing is required of any female participant regardless of reported reproductive/menopausal status at screening.

8.4.4 Appropriateness of safety measurements

The safety assessments selected are standard for this indication/participant population.

8.4.5 Injection/Infusion site reaction

Any local tolerability symptoms/signs related to injection will be reported as adverse events and followed until resolution.

8.5 Additional assessments

8.5.1 Pharmacokinetics

PK samples will be collected at the visits defined in the Assessment Schedule (Table 8-1). Follow instructions outlined in the laboratory manual regarding sample collection, numbering, processing and shipment. See Section 8.5.2.1 regarding the potential use of residual samples for more information.

If participants cannot visit the site for lab assessments conducted through central labs, local lab collection may be used during a Public Health emergency as declared by Local or Regional authorities, i.e., pandemic, epidemic or natural disaster, that limits or prevents on-site study visits.

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For standard pharmacokinetic abbreviations and definitions see the list provided at the beginning of this protocol.

The following pharmacokinetic parameters will be determined using the actual recorded sampling times and non-compartmental method(s) with Phoenix WinNonlin (Version 6.4 or higher): Cmax, Tmax, AUClast from the plasma concentration-time data. Additional parameters may be estimated as relevant.

The linear trapezoidal rule will be used for AUC calculation.

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9 Study discontinuation and completion

9.1 Discontinuation and completion

9.1.1 Study treatment discontinuation and study discontinuation

The Investigator must discontinue study treatment for a given participant if, he/she believes that continuation would negatively impact the participant's well-being.

Study drug administration must be discontinued under the following circumstances:

- Participant withdraws consent
- Development of new complete bundle branch block (QRS duration >120ms) for a participant with a normal QRS duration at baseline as determined by the Investigator's interpretation of the ECG findings or an increase in QRS duration that in the opinion of the Investigator may be a risk to participant safety
- QTcF >500 ms for those individuals with a normal QTcF at baseline as determined by the Investigator's interpretation of the ECG findings, or an increase in QTcF that in the opinion of the Investigator may be a risk to participant safety
- A change in atrioventricular conduction that in the opinion of the Investigator may be a risk to participant safety
- An increase in the resting heart rate to >130 beats per minute sustained for >2 minutes as determined by the Investigator, unless there is an obvious alternative explanation other than administration of study drug
- Hypotension, defined as >20 mmHg systolic blood pressure drop (repeat measurement) that is (a) symptomatic or (b) sustained to the point requiring medical intervention
- Any moderate or higher CNS-related AE that in the opinion of the Investigator is suspected to be related to the study drug
- A seizure
- A severe or serious adverse event
- Hypersensitivity reactions and/or injection site reactions of moderate severity or greater

If discontinuation of study drug administration occurs, the investigator should make a reasonable effort to understand the primary reason for the participant’s premature discontinuation of study drug administration and record this information.

Participants who discontinue study drug administration or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see 'Withdrawal of Informed Consent' Section 9.2).

Where possible, they should return for the assessments indicated in the Assessment Schedule (Table 8-1). If they fail to return for these assessments for unknown reasons, every effort (e.g., telephone, e-mail, letter) should be made to contact the participant/pre-designated contact as specified in the lost to follow-up section (Section 9.2.1). This contact should preferably be done according to the study visit schedule.

If the participant cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the participant, or with a person pre-designated by the participant. This telephone contact should preferably be done according to the study visit schedule.

After study drug administration discontinuation, at a minimum, in abbreviated visits, the following data should be collected at clinic visits or via telephone/email contact:

- New / concomitant treatments
- Adverse Events / Serious Adverse Events

The Investigator must also contact NIRT to register the participant's discontinuation from study treatment.

If discontinuation occurs because treatment code has been broken, please refer to Emergency breaking of treatment code section (Section 6.6.3).

9.1.2 Replacement policy

Participants who discontinue study drug administration before completion will be replaced except for those participants who discontinued due to adverse drug reactions or adverse events from study procedures.

9.2 Withdrawal of informed consent

Participants may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a participant:

- Does not want to participate in the study anymore

and

- Does not want any further visits or assessments

and

- Does not want any further study related contacts

In this situation, the investigator should make a reasonable effort (e.g., telephone, e-mail, letter) to understand the primary reason for the participant’s decision to withdraw their consent and record this information.

Where consent to the use of Personal and Coded Data is not required, the participant therefore cannot withdraw consent. However, they still retain the right to object to the further use of their Personal Data.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the participant are not allowed unless safety findings require communicating or follow-up.

All efforts should be made to complete the assessments prior to study discontinuation. If the participant agrees, a final evaluation at the time of the participant's study discontinuation should be made as detailed in the Assessment Schedule (Table 8-1).

Novartis Institutes for BioMedical Research will continue to retain and use all research results (data) that have already been collected for the study evaluation.

9.2.1 Lost to follow-up

For participants whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the participant, e.g., dates of telephone calls, registered letters, etc. A participant should not be considered as lost to follow-up until due diligence has been completed or until the end of the study.

9.2.2 Study stopping rules

The study will be stopped, and no further dosing will be performed pending a full safety review, if any of the following criteria are met:

- 1 or more study treatment related serious adverse events (SAEs) are reported
- At least 3 participants experience a similar AE which is assessed as either moderate or severe in intensity, and is related to study treatment
- Any moderate adverse event that in the opinion of the investigator is indicative of a nervous system process of major clinical significance (such as stroke, seizure, acute psychosis or delirium) and is related to study drug administration
- 3 or more participants experience symptomatic sinus tachycardia with a resting heart rate >120 bpm that is sustained for >90 minutes during the observation period following study drug administration, unless there is an obvious alternative explanation other than administration of study drug
- The Sponsor considers that the number and/or severity of AEs suggest that there is a significant safety concern.

If one of the above stopping rules is met, the Competent Authorities and IRB/IECs will be informed of the temporary halt of study conduct according to local regulations. In addition, PIs will be informed of the temporary halt and based on the outcome of the safety review, participants will be notified and given appropriate guidance should any safety concern be identified. The study may resume following the safety review, if the Investigator and Sponsor agree it is safe to proceed and after approval to restart the study is obtained from the Competent Authorities and IRB/IECs.

9.2.3 Early study termination by the sponsor

The study can be terminated by Novartis Institutes for BioMedical Research at any time.

Reasons for early termination include:

- Unexpected, significant, or unacceptable safety risk to participants enrolled in the study
- Decision based on recommendations from applicable board(s) after review of safety and efficacy data

- Discontinuation of study drug development

In taking the decision to terminate, Novartis Institutes for BioMedical Research will always consider participant welfare and safety. Should early termination be necessary, participants must be seen as soon as possible and treated as a prematurely withdrawn participant as outlined in Section 9.1.1. The Investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the participant's interests. The Investigator or Sponsor depending on local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

9.3 Study completion and post-study treatment

Study completion is defined as when the last participant finishes their Study Completion visit and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator or, in the event of an early study termination decision, the date of that decision. Each participant will be required to complete the study in its entirety and thereafter no further study treatment will be made available to them.

All randomized and/or treated participants should have a safety follow-up call conducted 30 days after administration of study treatment. The information collected is kept as source documentation. All SAEs reported during this time period must be reported as described in Section 10.1.3. Documentation of attempts to contact the participant should be recorded in the source documentation.

10 Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a clinical investigation participant after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

The Investigator has the responsibility for managing the safety of individual participant and identifying adverse events.

Novartis Institutes for BioMedical Research qualified medical personnel will be readily available to advise on trial related medical questions or problems.

The occurrence of adverse events must be sought by non-directive questioning of the participant at each visit during the study. Adverse events also may be detected when they are volunteered by the participant during or between visits or through physical examination findings, laboratory test findings, or other assessments.

Adverse events must be recorded under the signs, symptoms, or diagnosis associated with them, accompanied by the following information (as far as possible) (if the event is serious refer to Section 10.1.2):

1. The severity grade
- mild: usually transient in nature and generally not interfering with normal activities
- moderate: sufficiently discomforting to interfere with normal activities
- severe: prevents normal activities
2. Its relationship to the study treatment. If the event is due to lack of efficacy or progression of underlying illness (i.e., progression of the study indication) the assessment of causality will usually be 'Not suspected.' The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single participant
3. Its duration (start and end dates or ongoing) and the outcome must be reported
4. Whether it constitutes a SAE (see Section 10.1.2 for definition of SAE) and which seriousness criteria have been met
5. Action taken regarding with study treatment.
6. All adverse events must be treated appropriately. Treatment may include one or more of the following:
- Dose not changed
- Dose reduced
- Drug interrupted/withdrawn
7. Its outcome

Conditions that were already present at the time of informed consent should be recorded in medical history of the participant.

Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms.

Adverse event monitoring should be continued for at least 30 days following the study drug administration.

Once an adverse event is detected, it must be followed until its resolution or until it is judged to be permanent (e.g., continuing at the end of the study), and assessment must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the interventions required to treat it, and the outcome.

Information about adverse drug reactions for the investigational drug can be found in the Investigator's Brochure (IB).

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:
- they induce clinical signs or symptoms
- they are considered clinically significant
- they require therapy

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from

baseline or the previous visit, or values which are considered to be non-typical in participant with the underlying disease.

10.1.1.1 AEs of special interest

Any seizure-related AEs, regardless of causality and severity, occurring after the participant has provided informed consent and until 30 days after study drug administration must be reported to the Sponsor within 24 hours of learning of its occurrence.

Participants should be informed that the site should be contacted immediately if any seizure-related AEs occur after EOS but before the 30-day safety follow-up phone contact.

10.1.2 Serious adverse events

A serious adverse event (SAE) is defined as any adverse event [appearance of (or worsening of any pre-existing)] undesirable sign(s), symptom(s), or medical conditions(s) which meets any one of the following criteria:

- fatal
- life-threatening

Life-threatening in the context of a SAE refers to a reaction in which the participant was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to the ICH-E2D Guidelines).

- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition of AF
    - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
    - social reasons and respite care in the absence of any deterioration in the participant's general condition
    - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- is medically significant, e.g. defined as an event that jeopardizes the participant or may require medical or surgical intervention to prevent one of the outcomes listed above

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the participant or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as "medically significant." Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization or development of dependency or abuse (please refer to the ICH-E2D Guidelines).

All new malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

All reports of intentional misuse and abuse of the product are also considered serious adverse event irrespective if a clinical event has occurred.

10.1.3 SAE reporting

To ensure participant safety, every SAE, regardless of causality, occurring after the participant has provided informed consent and until 30 days following the administration of study treatment must be reported to Novartis Institutes for BioMedical Research safety immediately, without undue delay, but under no circumstances later than within 24 hours of obtaining knowledge of the events (Note: If more stringent, local regulations regarding reporting timelines prevail).. Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site. Information about all SAEs is collected and recorded on the paper Serious Adverse Event Report form; all applicable sections of the form must be completed in order to provide a clinically thorough report.

SAEs occurring after the participant has provided informed consent until the time the participant is deemed a Screen Failure must be reported to Novartis Institutes for BioMedical Research.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode immediately, without undue delay, but under no circumstances later than within 24 hours of the investigator receiving the follow-up information (Note: If more stringent, local regulations regarding reporting timelines prevail). A SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment, a CMO & PS Department associate may urgently require further information from the investigator for health authority reporting. Novartis Institutes for BioMedical Research may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study treatment that this SAE has been reported.

Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

Any SAEs experienced after the 30 day period following the administration of study treatment should only be reported to Novartis Institutes for BioMedical Research Safety if the Investigator suspects a causal relationship to study treatment, unless otherwise specified by local law/regulations.

10.1.4 Pregnancy reporting

If a female trial participant becomes pregnant, the study treatment should be stopped, and the pregnancy consent form should be presented to the trial participant. The participant must be given adequate time to read, review, and sign the pregnancy consent form. This consent form is necessary to allow the Investigator to collect and report information regarding the pregnancy. To ensure participant safety, each pregnancy occurring after signing the informed consent must be reported to Novartis Institutes for BioMedical Research within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded and reported by the Investigator to the Novartis Institutes for BioMedical Research Chief Medical Office and Patient Safety (CMO&PS). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment any pregnancy outcome. Any SAE experienced during pregnancy must be reported.

If a female partner of a male trial participant who took study treatment in this study becomes pregnant, pregnancy outcomes should be collected. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

After consent is provided, the pregnancy reporting will occur up to one year after the estimated date of delivery.

10.1.5 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, participant or consumer (EMA definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Study treatment errors and uses outside of what is foreseen in the protocol will be recorded on the appropriate CRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE within 24 hours of Investigator's awareness.

Table 10-1 Guidance for capturing the study treatment errors including misuse/abuse

Treatment error type	Document in Dosing CRF (Yes/No)	Document in AE eCRF	Complete SAE form
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes	Yes, even if not associated with a SAE

For more information on AE and SAE definition and reporting requirements, please see the respective sections (Section 10.1.1 and Section 10.1.2).

10.2 Additional Safety Monitoring

10.2.1 Liver safety monitoring

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

Please refer to Table 16-1 in Appendix 1 for complete definitions of liver laboratory triggers.

Once a participant is exposed to study treatment, every liver event defined in Table 16-1- should be followed up by the Investigator or designated personnel at the trial site, as summarized below. Additional details on actions required in case of liver events are outlined in Table 16-2 and Table 16-3. Repeat liver chemistry tests (i.e. ALT, AST, TBL, PT/INR, ALP and G-GT) to confirm elevation.

- These liver chemistry repeats should be performed using the local laboratory used by the site. Repeated laboratory test results must be reported as appropriate.
- If the initial elevation is confirmed, close observation of the participant will be initiated, including consideration of treatment interruption if deemed appropriate.
- Hospitalization of the participant if appropriate
- Causality assessment of the liver event
- Thorough follow-up of the liver event should include
    - These investigations can include based on investigator's discretion: serology tests, imaging and pathology assessments, hepatologist's consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease

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

10.2.2 Renal safety monitoring

Once a participant is exposed to study treatment, the following two categories of abnormal renal laboratory alert values should be assessed during the study period:

- Serum creatinine increase ≥ 25% compared to baseline during normal hydration status
- Any one of the following:
    - Urine protein-creatinine ratio (PCR) ≥1g/g or ≥100 mg/mmol, OR
    - New onset dipstick proteinuria ≥ 3+, OR
    - New onset dipstick hematuria ≥ 3+ (after excluding menstruation, UTI, extreme exercise, or trauma)

Abnormal renal event findings must be confirmed within 24-48 hours after the first assessment

Once a participant is exposed to study treatment, renal laboratory alerts or renal safety events should be monitored and followed up by the Investigator or designated trial staff as summarized in Table 16-4 in Appendix 2.

Every renal laboratory trigger or renal event as defined in Table 16-4 in Appendix 2 should be followed up by the Investigator or designated personnel at the trial site as summarized in Table 16-5 in Appendix 2.

11 Data Collection and Database management

11.1 Data collection

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs, allow modification and/or verification of the entered data by the investigator staff.

The Investigator/designee is responsible for assuring that the data (recorded on CRFs) (entered into eCRF) is complete, accurate, and that entry and updates are performed in a timely manner. The Investigator must certify that the data entered are complete and accurate.

After final database lock, the Investigator will receive copies of the participant data for archiving at the investigational site.

Laboratory samples will be processed at the designated lab (locally or centrally) and the results will be sent electronically to Novartis (or a designated CRO).

ECG tracings will be processed locally and may be read centrally and the results will be sent electronically to Novartis (or a designated CRO).

Holter monitor data will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

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All data should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.

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11.2 Database management and quality control

Novartis Institutes for BioMedical Research personnel (or designated CRO) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the World Health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

Dates of screenings, randomizations, screen failures and study completion, as well as randomization codes will be tracked using NIRT. The system will be supplied by a vendor, who will also manage the database. The data will be sent electronically to Novartis (or a designated CRO) at specific timelines.

Each occurrence of a code break via NIRT will be reported to the clinical team and monitor. The code break functionality will remain available until study shut down or upon request of Novartis.

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked **and the treatment codes will be unblinded** and made available for data analysis/moved to restricted area to be accessed by independent programmer and statistician. Any changes to the database after that time can only be made after written agreement by Novartis Institutes for BioMedical Research development management.

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis Institutes for BioMedical Research representative will review the protocol and data capture requirements (i.e., eSource DDE or eCRFs) with the Investigators and their staff. During the study, Novartis Institutes for BioMedical Research employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of participant records, the accuracy of data capture / data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis CRA organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis Institutes for BioMedical Research clinical teams to assist with trial oversight.

The Investigator must maintain source documents for each participant in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the participant's file. The investigator must also keep the original informed consent form signed by the participant (a signed copy is given to the participant).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Novartis Institutes for BioMedical Research monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the

CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the participants will be disclosed.

12 Data analysis and statistical methods

Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

12.1 Analysis sets

For all analysis sets, participants will be analyzed according to the study treatment(s) received.

The safety analysis set will include all participants that received any investigational product.

The PK analysis set will include all participants with at least one available valid PK concentration measurement, who received any investigational product and with no protocol deviations that impact on PK data.

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12.2 Participant demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics will be listed and summarized descriptively by treatment group and cohort for the safety analysis set.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented.

Relevant medical histories and current medical conditions at baseline will be summarized by system organ class and preferred term by treatment group and cohort.

12.3 Treatments

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed and summarized according to the Anatomical Therapeutic Chemical (ATC) classification system by treatment group and cohort.

12.4 Analysis of the primary endpoint(s)/estimand(s)

12.4.1 Definition of primary endpoint(s)/estimand(s)

The primary endpoint will be conversion to sinus rhythm for at least one minute within 90 minutes after the start of study drug administration (yes or no).

12.4.2 Statistical model, hypothesis, and method of analysis

The conversion rates between HSY244 and placebo will be compared using Fisher's Exact test. This will test a null hypothesis that the conversion rate is the same for HSY244 and placebo. The difference in the conversion rates between HSY244 and placebo will be reported along with the 80% confidence limits for the difference, as well as the odds ratio, the 80% CI for the odds ratio, and the associated p-value.

Results will be displayed tabular and graphically, where the conversion rate (80% CI) for each treatment will be displayed in dot plots and a forest plot.

The impact of duration of current atrial fibrillation episode (< 48 hours, 48 hours - 7 days, 7 - 14 days, 14 - 30 days, and 30 - 60 days) on conversion rate will be investigated in a supporting analysis.. Commercially Confidential Information

Only participants who complete study treatment will be included in the primary analysis.

12.4.3 Handling of remaining intercurrent events of primary estimand

Not applicable.

12.4.4 Handling of missing values not related to intercurrent event

Given the short treatment duration in this study, missing data impacting the primary endpoint is expected to be minimal. All participants who complete Day 1 assessments will be included in the primary analysis.

12.4.5 Sensitivity analyses for primary endpoint/estimand

Not applicable.

12.4.6 Not applicable Supplementary analysis

As a supplementary analysis, the conversion rates between HSY244 and placebo will again be compared using a Fisher's Exact test. All participants that received any study drug will be included in this analysis (the safety analysis set).

12.5 Analysis of secondary endpoints/estimands

12.5.1 Safety endpoints

For all safety analyses, the safety set will be used. All listings and tables will be presented by treatment group and cohort.

Safety summaries (tables, figures) include only data from the on-treatment period with the exception of baseline data, which will also be summarized where appropriate (e.g., change from baseline summaries). In particular, tables for adverse events (AEs) will summarize only on-treatment events, with a start date during the on-treatment period (treatment-emergent AEs). The on-treatment period lasts from the date of administration of study treatment to EOS visit.

Adverse events

All information obtained on adverse events will be displayed by treatment group, cohort and participant.

The number (and percentage) of participants with treatment emergent adverse events (events started after the first dose of study medication or events present prior to start of double-blind

treatment but increased in severity based on preferred term) will be summarized in the following ways:

- by treatment, primary system organ class and preferred term.
- by treatment, primary system organ class, preferred term and maximum severity.
- by treatment, Standardized MedDRA Query (SMQ) and preferred term.

A participant with multiple adverse events within a primary system organ class is only counted once towards the total of the primary system organ class.

Vital signs

All vital signs data will be listed by treatment group, cohort, participant, and visit/time and if ranges are available, abnormalities (and relevant orthostatic changes) will be flagged. Summary statistics will be provided by treatment, cohort and visit/time.

ECG

1. PR, QRS, QT, QTcF, and RR intervals will be obtained from 12-lead ECGs for each participant during the study. ECG data will be read and interpreted locally for safety. In addition, 12-lead ECGs may be read centrally.
2. Categorical Analysis of QT/QTc interval data based on the number of participants meeting or exceeding predefined limits in terms of absolute QT/QTc intervals or changes from baseline will be presented. In addition, a listing of these participants will be produced (by treatment group).

QTcF and QRS duration will be examined separately between individuals with and without a complete bundle branch block.

All ECG data will be listed by treatment group, cohort, participant, and visit/time, and abnormalities will be flagged. Summary statistics will be provided by treatment, cohort and visit/time.

Clinical laboratory evaluations

All laboratory data will be listed by treatment group, cohort, participant, and visit/time and if normal ranges are available abnormalities will be flagged. Summary statistics will be provided by treatment, cohort and visit/time. Shift tables using the low/normal/high/ (low and high) classification will be used to compare baseline to the worst on-treatment value.

12.5.2 Pharmacokinetics

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Table 12-1 Non-compartmental pharmacokinetic parameters

AUClast	The AUC from time zero to the last measurable concentration sampling time (tlast) (mass x time x volume-1)
Cmax	The maximum (peak) observed plasma drug concentration after single dose administration (mass x volume-1)
Tmax	The time to reach maximum (peak) plasma drug concentration after single dose administration (time)

12.5.3 PK/PD relationships

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12.6 Analysis of exploratory endpoints

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12.7 Interim analyses

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12.8 Sample size calculation

12.8.1 Primary endpoint(s)

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13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US CFR 21), and with the ethical principles laid down in the Declaration of Helsinki.

13.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the Investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, participant recruitment procedures (e.g., advertisements) and any other written information to be provided to participants. Prior to study start, the Investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis Institutes for BioMedical Research monitors, auditors, Novartis Institutes for BioMedical Research Quality Assurance representatives, designated agents of Novartis Institutes for BioMedical Research, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the Investigator must inform Novartis Institutes for BioMedical Research immediately that this request has been made.

13.3 Publication of study protocol and results

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in EudraCT. In addition, after study completion (defined as last patient last visit) and finalization of the study report the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the Novartis clinical trial results website and all required Health Authority websites (e.g., Clinicaltrials.gov, EudraCT etc.).

For details on the Novartis Institutes for BioMedical Research publication policy including authorship criteria, please refer to the Novartis Institutes for BioMedical Research publication policy training materials.

13.4 Quality Control and Quality Assurance

Novartis Institutes for BioMedical Research maintains a robust Quality Management System (QMS) that includes all activities involved in quality assurance and quality control, to ensure compliance with written Standard Operating Procedures as well as applicable global/local GCP regulations and ICH Guidelines.

Audits of investigator sites, vendors, and Novartis Institutes for BioMedical Research systems are performed by auditors, independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal SOPs, and are performed according to written Novartis Institutes for BioMedical Research processes.

13.5 Participant Engagement

The following participant engagement initiatives are included in this study and will be provided, as available, for distribution to study participants at the timepoints indicated. If compliance is impacted by cultural norms or local laws and regulations, sites may discuss modifications to these requirements with Novartis.

- Thank You letter – at beginning and end of study participation
- Plain language trial summary – after CSR publication
- Individual treatment information – after CSR publication

14 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of participants should be administered as deemed necessary on a case by case basis. Under no circumstances including incidental collection is an Investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction prohibition, data, information, observation would be incidentally collected, the investigator shall immediately disclose it to Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an Investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis Institutes for BioMedical Research and approved by the IRB/IEC and Health Authorities, where required, it cannot be implemented.

14.1 Protocol amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis Institutes for BioMedical Research, health authorities where required, and the IRB/IEC prior to implementation.

Only amendments that are required for participant safety may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the Investigator is expected to take any immediate action required for the safety of any participant included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

15 References

References are available upon request

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16 Appendices

16.1 Appendix 1: Liver event and laboratory trigger definitions & follow-up requirements

Table 16-1 Liver event and laboratory trigger definitions

	Definition/ threshold
Liver laboratory triggers If ALT, AST and total bilirubin normal at baseline:	• ALT or AST > 5 × ULN • ALP > 2 × ULN (in the absence of known bone pathology) • Total bilirubin > 3 × ULN (in the absence of known Gilbert syndrome) • ALT or AST > 3 × ULN and INR > 1.5 • Potential Hy's Law cases (defined as ALT or AST > 3 × ULN and Total bilirubin > 2 × ULN [mainly conjugated fraction] without notable increase in ALP to > 2 × ULN) • Any clinical event of jaundice (or equivalent term) • ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia • Any adverse event potentially indicative of a liver toxicity*
If ALT or AST abnormal at baseline:	• ALT or AST > 2x baseline or > 300 U/L (whichever occurs first)

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

Table 16-2 Follow up requirements for liver laboratory triggers with liver symptoms

	ALT	TBL	Liver Symptoms	Action
ALT increase without bilirubin increase:				
	If normal at baseline: ALT > 3 x ULN **If elevated at baseline:** ALT > 2 x baseline or > 300 U/L (whichever occurs first)	Normal For patients with Gilbert's syndrome: No change in baseline TBL	None	• **No change to study treatment** • Measure ALT, AST, ALP, GGT, TBIL, INR, albumin, CK, and GLDH in 48-72 hours. • Follow-up for symptoms.
	If normal at baseline: ALT > 5 x ULN for more than two weeks **If elevated at baseline:** ALT > 3 x baseline or > 300 U/L (whichever occurs first) for more than two weeks	Normal For patients with Gilbert's syndrome: No change in baseline TBL	None	• **Interrupt study drug** • Measure ALT, AST, ALP, GGT, TBIL, INR, albumin, CK, and GLDH in 48-72 hours. • Follow-up for symptoms. • Initiate close monitoring and workup for competing etiologies.
	If normal at baseline: ALT > 8 x ULN	Normal	None	

<table>
<tr><th></th><th>ALT</th><th>TBL</th><th>Liver Symptoms</th><th>Action</th></tr>
<tr><td colspan="4">ALT increase with bilirubin increase:</td><td rowspan="3">• Study drug can be restarted only if another etiology is identified and liver enzymes return to baseline.</td></tr>
<tr><td rowspan="2"></td><td>If normal at baseline:
ALT > 3 x ULN</td><td rowspan="2">TBL > 2 x ULN (or INR > 1.5)
For patients with Gilbert’s syndrome: Doubling of direct bilirubin</td><td rowspan="2">None</td></tr>
<tr><td>If elevated at baseline:
ALT > 2 x baseline
or > 300 U/L (whichever occurs first)</td></tr>
<tr><td rowspan="2"></td><td>If normal at baseline:
ALT > 3 x ULN</td><td rowspan="2">Normal or elevated</td><td rowspan="2">Severe fatigue, nausea, vomiting, right upper quadrant pain</td></tr>
<tr><td>If elevated at baseline:
ALT > 2 x baseline
or > 300 U/L (whichever occurs first)</td></tr>
</table>

Table 16-3 Follow up requirements for liver laboratory triggers

Criteria	Actions required	Follow-up monitoring
Total Biliruin (isolated)		
>1.5 – 3.0 ULN	• Maintain treatment • Repeat LFTs within 48-72 hours	Monitor LFTs weekly until resolution[c] to ≤ Grade 1 or to baseline
> 3 - 10 × ULN (in the absence of known Gilbert syndrome)	• Interrupt treatment • Repeat LFT within 48-72 hours • Hospitalize if clinically appropriate • Establish causality • Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate CRF	Monitor LFTs weekly until resolution[c] to ≤ Grade 1 or to baseline (ALT, AST, total bilirubin, Alb, PT/INR, ALP and GGT) Test for hemolysis (e.g. reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 10 x ULN	• Discontinue the study treatment immediately • Hospitalize the participant • Establish causality • Record the AE and contributing factors(e.g. conmeds, med hx, lab)in the appropriate CRF	ALT, AST, total bilirubin, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
Any AE potentially indicative of a liver toxicity*	• Consider study treatment interruption or discontinuation • Hospitalization if clinically appropriate • Establish causality • Record the AE and contributing factors(e.g., conmeds, med hx, lab)in the appropriate CRF	Investigator discretion

[a]Elevated ALT/AST > 3 × ULN and TBL > 2 × ULN but without notable increase in ALP to > 2 × ULN

[b](General) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia

[c]Resolution is defined as an outcome of one of the following: (1) return to baseline values, (2) stable values at three subsequent monitoring visits at least 2 weeks apart, (3) remain at elevated level after a maximum of 6 months, (4) liver transplantation, and (5) death.

Based on Investigator's discretion investigation(s) for contributing factors for the liver event can include: Serology tests, imaging and pathology assessments, hepatologist's consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease.

16.2 Appendix 2: Specific Renal Alert Criteria and Actions and Event Follow-up

Table 16-4 Specific Renal Alert Criteria and Actions

Renal Event	Actions
Confirmed serum creatinine increase 25-49%	• Consider causes and possible interventions • Follow up within 2-5 days
Serum creatinine increase ≥50%	• Consider causes and possible interventions • Repeat assessment within 24-48 h if possible • Consider drug interruption or discontinuation unless other causes are diagnosed and corrected • Consider patient hospitalization and specialized treatment
New onset dipstick proteinuria ≥3+ OR Protein-creatinine **ratio** (PCR) ≥1g/g Cr (or mg/mmol equivalent as converted by the measuring laboratory)	• Consider causes and possible interventions • Assess serum albumin & serum total protein • Repeat assessment to confirm • Consider drug interruption or discontinuation unless other causes are diagnosed and corrected
New onset hematuria ≥3+ on urine dipstick	Assess & document: • Repeat assessment to confirm • Distinguish hemoglobinuria from hematuria • Urine sediment microscopy • Assess sCr • Exclude infection, trauma, bleeding from the distal urinary tract/bladder, menstruation • Consider bleeding disorder

Table 16-5 Renal Event Follow Up

Follow-up of Renal Events
Assess, document, and record in eCRF: • Urine dipstick and sediment microscopy evidence of DIN: crystals, red blood cells (dysmorphic/glomerular vs. non-dsymophic/non-glomerular), white blood cells, tubular epithelial cells • Blood pressure and body weight • Serum creatinine, BUN, electrolytes (sodium, potassium, phosphate, calcium), bicarbonate, and uric acid • Urine output
Review and record possible contributing factors to the renal event (co-medications, other co-morbid conditions) and additional diagnostic procedures (MRI etc.) in the eCRF
Monitor patient regularly (frequency at investigator's discretion) until: • Event resolution (sCr within 10% of baseline or PCR <1g/g Cr, or ACR <300 mg/g Cr) or • Event stablization: sCr level with ±10% variability over last 6 months or protein-creatinine ratio stabilization at a new level with ±50% variability over the last 6 months. • Analysis of urine markers in samples collected over the course of the DIN event