NOVARTIS

Sponsor

Novartis Pharmaceuticals

Generic Drug Name

HSY244

Trial Indication(s)

Atrial fibrillation

Protocol Number

CHSY244X2201

Protocol 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

Clinical Trial Phase

Phase 2

Phase of Drug Development

Phase IIa

Study Start/End Dates

Study Start Date: November 30, 2020 (Actual)
Primary Completion Date: July 11, 2022 (Actual)
Study Completion Date: July 11, 2022 (Actual)

NOVARTIS

Reason for Termination (If applicable)

Terminated due to business decision

Study Design/Methodology

This was a randomized, placebo-controlled, investigator- and participant-blinded study to evaluate the efficacy, safety, tolerability, and pharmacokinetics (PK) of HSY244 in participants with atrial fibrillation, with and without heart failure. An initial cohort (Cohort 1) evaluating a 150 mg i.v. dose of HSY244, administered over a 15-minute infusion, was planned to be enrolled. Based on data from Cohort 1, a second cohort (Cohort 2) testing a lower dose of HSY244 could have been initiated. Cohort 2 was not enrolled due to the early termination of the study.

The Sponsor terminated the trial early on January 23, 2023 due to business decisions. The study completion date of July 11, 2022 reflects the last patient last study visit.

Centers

4 centers in 2 countries: United States(2), Germany(2)

Publication

No data identified.

NOVARTIS

Objectives:

Primary objective

- To evaluate the efficacy of HSY244 to restore sinus rhythm in participants with atrial fibrillation

Secondary objectives

- To evaluate the safety and tolerability of HSY244 in participants with atrial fibrillation
- To evaluate the pharmacokinetics of HSY244 in participants with atrial fibrillation

Test Product (s), Dose(s), and Mode(s) of Administration

HSY244 150 mg intravenous infusion
Placebo to HSY244 intravenous infusion

Statistical Methods

The conversion rates between HSY244 and placebo was planned to be compared using Fisher's Exact test. Due to the early termination of the study after enrolling 13 participants, the primary planned analysis was not performed due to no primary outcome events (cardioversion within the first 90 minutes of observation post start of study drug administration) being observed.

Study Population: Key Inclusion/Exclusion Criteria

Key Inclusion Criteria:
• At screening, written informed consent were required to be obtained before any assessment was performed and only participants able to provide written informed consent themselves were included in this study.
• 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.
• At screening, current episode of AF had 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.
• At screening, participants were required to weigh at least 60 kg to participate in the study and were required to have a body mass index (BMI) within the range of 18 - 45 kg/m^2. BMI = Body weight (kg) / [Height (m)]^2
• At screening, vital signs (systolic blood pressure and pulse rate) were assessed in the sitting position. Sitting vital signs were required to 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.

Key Exclusion Criteria:
• Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they were using highly effective methods of contraception during dosing and for 4 days after stopping of investigational drug.
• Sexually active males unwilling to use a condom during intercourse while taking investigational drug and for 96 hours after study drug administration. A condom was 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 could not donate sperm for the time period specified above.
• 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.
• At screening, history of current diagnosis of ECG abnormalities or cardiac rhythm disorders as determined by the Investigator's interpretation of the ECG findings indicating a significant 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.
- Wolfe-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
• 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 and IV).
• History within the preceding 3 months prior to randomization of: myocardial infarction, unstable angina, cardiac surgery, or a percutaneous coronary intervention.
• History of a confirmed stroke or transient ischemic attack (TIA).
• History or current diagnosis of any seizure disorder, epilepsy, significant head trauma, or other disorders increasing the risk for seizures.
• 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.

Participant Flow Table

Overall Study

	HSY244	Placebo	Total
Arm/Group Description	HSY244 150 mg concentrate solution for injection via intravenous infusion	Placebo concentrate solution for injection via intravenous infusion	
Started	7	6	13
Completed	7	6	13
Not Completed	0	0	0

NOVARTIS

Baseline Characteristics

	HSY244	Placebo	Total
Arm/Group Description	HSY244 150 mg concentrate solution for injection via intravenous infusion	Placebo concentrate solution for injection via intravenous infusion	
Number of Participants [units: participants]	7	6	13
Baseline Analysis Population Description			
Age Continuous (units: years) Analysis Population Type: Participants Mean ± Standard Deviation			
	60.6±9.73	60.0±4.05	60.3±7.36
Sex: Female, Male (units: participants) Analysis Population Type: Participants Count of Participants (Not Applicable)			
Female	1	0	1
Male	6	6	12
Race/Ethnicity, Customized (units: participants) Analysis Population Type: Participants Count of Participants (Not Applicable)			
White	7	5	12
Other	0	1	1

NOVARTIS

Summary of Efficacy

None of the participants cardioverted during the 90-minute observation period post-treatment.

Primary Outcome Result(s)

Number of participants with conversion to sinus rhythm for at least 1 minute within 90 minutes from the start of study drug administration.

Description	Conversion to sinus rhythm was monitored using a Holter monitoring device through 90 minutes after the start of study drug administration. If a participant had been monitored for at least 45 minutes and did not convert to sinus rhythm for at least one minute, the primary endpoint was defined as 'no'. If a participant converted to sinus rhythm for at least one minute at any time during the post-treatment 90 minutes observation period, regardless of the length of time monitored, the primary endpoint was to be defined as 'yes'.
Time Frame	90 minutes from the start of study drug administration
Analysis Population Description	Pharmacodynamic (PD) analysis set: Participants with available PD data and no protocol deviations with relevant impact on PD data.

	HSY244	**Placebo**
Arm/Group Description	HSY244 150 mg concentrate solution for injection via intravenous infusion	Placebo concentrate solution for injection via intravenous infusion
Number of Participants Analyzed [units: participants]	7	6
Number of participants with conversion to sinus rhythm for at least 1 minute within 90 minutes from the start of study drug administration. (units: Participants)	**Count of Participants (Not Applicable)**	**Count of Participants (Not Applicable)**
	0 (%)	0 (%)

NOVARTIS

Secondary Outcome Result(s)

Maximum Observed Plasma Concentration (Cmax)

Description	The Cmax is the maximum (peak) observed plasma drug concentration after single-dose administration. Actual recorded sampling times were taken into consideration for PK calculations.
Time Frame	Day 1 (0 min (pre-dose), 15 min (end of infusion), 30 min , 60 min, 90 min and 180 min) and Day 5
Analysis Population Description	Pharmacokinetic (PK) analysis set: Participants with at least one available valid PK concentration measurement, who received the investigational product and with no protocol deviations that impact on PK data

	HSY244	**Placebo**
Arm/Group Description	HSY244 150 mg concentrate solution for injection via intravenous infusion	Placebo concentrate solution for injection via intravenous infusion
Number of Participants Analyzed [units: participants]	7	0
Maximum Observed Plasma Concentration (Cmax) (units: ng/mL)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
	4800 ± 3890	

Time to Reach the Maximum Concentration After Drug Administration (Tmax)

Description	Tmax is the time to reach maximum (peak) plasma drug concentration after single dose administration (time). Actual recorded sampling times were taken into consideration for PK calculations.
Time Frame	Day 1 (0 min (pre-dose), 15 min (end of infusion), 30 min , 60 min, 90 min and 180 min) and Day 5
Analysis Population Description	PK analysis set: Participants with at least one available valid PK concentration measurement, who received the investigational product and with no protocol deviations that impact on PK data

	HSY244	Placebo
Arm/Group Description	HSY244 150 mg concentrate solution for injection via intravenous infusion	Placebo concentrate solution for injection via intravenous infusion
Number of Participants Analyzed [units: participants]	7	0
Time to Reach the Maximum Concentration After Drug Administration (Tmax) (units: Hour)	**Median (Full Range)**	**Median (Full Range)**
	0.28 (0.25 to 0.30)	

Area under the plasma concentration-time curve (AUClast)

Description	AUClast is the AUC from time zero to the last measurable concentration sampling time (tlast). Actual recorded sampling times were taken into consideration for PK calculations.
Time Frame	Day 1 (0 min (pre-dose), 15 min (end of infusion), 30 min , 60 min, 90 min and 180 min) and Day 5
Analysis Population Description	PK analysis set: Participants with at least one available valid PK concentration measurement, who received the investigational product and with no protocol deviations that impact on PK data. Only participants with available AUClast data were analyzed.

	HSY244	Placebo
Arm/Group Description	HSY244 150 mg concentrate solution for injection via intravenous infusion	Placebo concentrate solution for injection via intravenous infusion
Number of Participants Analyzed [units: participants]	6	0
Area under the plasma concentration-time curve (AUClast) (units: h*ng/mL)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
	2960 ± 1510	

Other Pre-Specified Outcome Result(s)

No data identified.

Post-Hoc Outcome Result(s)

No data identified.

Summary of Safety

- All the randomized participants were included in the safety analysis set (13 participants).
- Of 13 participants, 11 participants (84.6%) experienced at least 1 AE. The most common AEs by unique 'preferred term' were atrial fibrillation (23.1%) and arthralgia (23.1%).
- Of 13 participants, 1 participant (7.7%) experienced a non-treatment related serious adverse event (SAE) in the HSY244 treatment group due to a prolonged hospitalization due to recurrence of atrial fibrillation (mild severity).
- Most treatment emergent AEs were mild in severity, and no severe AEs were reported. Two moderate severity AEs were reported, 'flatulence' for a participant receiving HSY244 and 'pre-syncope' for a participant receiving placebo.
- Of 13 participants, 6 participants (46.2%) experienced at least 1 study drug-related AE. The most common AEs by 'system organ class' were musculoskeletal and connective tissue disorders (38.5%) and nervous system disorders (23.1%). Treatment-related AEs were mostly consistent with arm pain and discomfort during the study drug infusion.
- No seizure-related AEs were reported.
- No clinically relevant effects on ventricular repolarization (QTcF) were detected. No unexpected arrhythmias were detected in this population.

Safety Results

Time Frame	Adverse events were reported from first dose of study treatment until end of study treatment plus 30 days post treatment, up to a maximum duration of 31 days.

Additional Description	Any sign or symptom that occurs during the conduct of the trial and safety follow-up
Source Vocabulary for Table Default	MedDRA (25.1)
Collection Approach for Table Default	Systematic Assessment

All-Cause Mortality

	HSY244 N = 7	**Placebo N = 6**	**Total N = 13**
Arm/Group Description	HSY244 150 mg concentrate solution for injection via intravenous infusion	Placebo concentrate solution for injection via intravenous infusion	Total
Total Number Affected	0	0	0
Total Number At Risk	7	6	13

Serious Adverse Events

	HSY244 N = 7	**Placebo N = 6**	**Total N = 13**
Arm/Group Description	HSY244 150 mg concentrate solution for injection via intravenous infusion	Placebo concentrate solution for injection via intravenous infusion	Total
Total # Affected by any Serious Adverse Event	1	0	1
Total # at Risk by any Serious Adverse Event	7	6	13
Cardiac disorders			

Atrial fibrillation	1 (14.29%)	0 (0.00%)	1 (7.69%)

Other (Not Including Serious) Adverse Events

Frequent Event Reporting Threshold 0%

	HSY244 N = 7	Placebo N = 6	Total N = 13
Arm/Group Description	HSY244 150 mg concentrate solution for injection via intravenous infusion	Placebo concentrate solution for injection via intravenous infusion	Total
Total # Affected by any Other Adverse Event	6	5	11
Total # at Risk by any Other Adverse Event	7	6	13
Cardiac disorders			
Atrial fibrillation	1 (14.29%)	1 (16.67%)	2 (15.38%)
Gastrointestinal disorders			
Flatulence	1 (14.29%)	0 (0.00%)	1 (7.69%)
Nausea	0 (0.00%)	1 (16.67%)	1 (7.69%)
General disorders and administration site conditions			
Infusion site pain	0 (0.00%)	1 (16.67%)	1 (7.69%)
Injury, poisoning and procedural complications			
Procedural hypertension	0 (0.00%)	1 (16.67%)	1 (7.69%)
Investigations			

Blood pressure increased	2 (28.57%)	0 (0.00%)	2 (15.38%)
Blood urine present	1 (14.29%)	0 (0.00%)	1 (7.69%)
Metabolism and nutrition disorders			
Hypokalaemia	1 (14.29%)	1 (16.67%)	2 (15.38%)
Musculoskeletal and connective tissue disorders			
Arthralgia	1 (14.29%)	2 (33.33%)	3 (23.08%)
Limb discomfort	1 (14.29%)	0 (0.00%)	1 (7.69%)
Muscle tightness	1 (14.29%)	0 (0.00%)	1 (7.69%)
Musculoskeletal discomfort	1 (14.29%)	0 (0.00%)	1 (7.69%)
Musculoskeletal stiffness	1 (14.29%)	0 (0.00%)	1 (7.69%)
Pain in extremity	1 (14.29%)	0 (0.00%)	1 (7.69%)
Nervous system disorders			
Burning sensation	1 (14.29%)	0 (0.00%)	1 (7.69%)
Paraesthesia	1 (14.29%)	0 (0.00%)	1 (7.69%)
Presyncope	0 (0.00%)	1 (16.67%)	1 (7.69%)
Tremor	1 (14.29%)	0 (0.00%)	1 (7.69%)
Skin and subcutaneous tissue disorders			
Dermatitis contact	1 (14.29%)	0 (0.00%)	1 (7.69%)

Other Relevant Findings

Conclusion:

No participants pharmacologically cardioverted in the 90-minute observation period after the start of study drug administration. Efficacy for cardioversion could not be reliably assessed in only 13 participants in this trial terminated early (7 participants received HSY244 150 mg i.v.); however, available data suggest that HSY244 is not a highly effective cardioversion agent at the dose tested in this clinical population.

HSY244 is generally safe and well tolerated with frequent infusion-related arm pain or discomfort, as expected from preclinical and healthy volunteer data.

Date of Clinical Trial Report

9 August 2023