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

Summary

EudraCT number	2020-004327-17
Trial protocol	DE
Global end of trial date	11 July 2022

Results information

Result version number	v1 (current)
This version publication date	23 July 2023
First version publication date	23 July 2023

Trial information

Trial identification

Sponsor protocol code	CHSY244X2201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04582409
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	Novartis Campus, Basel, Switzerland,
Public contact	Study Director , Novartis Pharmaceuticals , 41 613241111, Novartis.email@Novartis.com
Scientific contact	Study Director , Novartis Pharmaceuticals , 41 613241111, Novartis.email@Novartis.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	11 July 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	11 July 2022
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of HSY244 to restore sinus rhythm in participants with Atrial Fibrillation (AF)

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 November 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 9
Country: Number of subjects enrolled	United States: 4
Worldwide total number of subjects	13
EEA total number of subjects	9

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	10
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A screening period of up to 3 days (72 hours) was used to assess eligibility.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	HSY244

Arm description:

HSY244 150 mg concentrate solution for injection via intravenous infusion

Arm type	Experimental
Investigational medicinal product name	HSY244
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

HSY244 150 mg i.v. infusion over 15 minutes

Arm title	Placebo

Arm description:

Placebo concentrate solution for injection via intravenous infusion

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Placebo i.v. infusion over 15 minutes

Number of subjects in period 1	HSY244	Placebo
Started	7	6
Completed	7	6

Baseline characteristics

Reporting groups	
Reporting group title	HSY244
Reporting group description:	
HSY244 150 mg concentrate solution for injection via intravenous infusion	
Reporting group title	Placebo
Reporting group description:	
Placebo concentrate solution for injection via intravenous infusion	

Reporting group values	HSY244	Placebo	Total
Number of subjects	7	6	13
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	5	5	10
From 65-84 years	2	1	3
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	60.6	60.0	
standard deviation	± 9.73	± 4.05	-
Sex: Female, Male Units: participants			
Female	1	0	1
Male	6	6	12
Race/Ethnicity, Customized Units: Subjects			
White	7	5	12
Other	0	1	1

End points

End points reporting groups

Reporting group title	HSY244
Reporting group description:	
HSY244 150 mg concentrate solution for injection via intravenous infusion	
Reporting group title	Placebo
Reporting group description:	
Placebo concentrate solution for injection via intravenous infusion	

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

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

End point 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'.

End point type	Primary

End point timeframe:

90 minutes from the start of study drug administration

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The planned statistical analyses could not be completed as no primary outcome events occurred.

End point values	HSY244	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	6		
Units: Participants	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Plasma Concentration (Cmax)

End point title	Maximum Observed Plasma Concentration (Cmax)

End point 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.

End point type	Secondary

End point timeframe:

Day 1 (0 min (pre-dose), 15 min (end of infusion), 30 min , 60 min, 90 min and 180 min) and Day 5

End point values	HSY244	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	0[2]		
Units: ng/mL				
arithmetic mean (standard deviation)	4800 (± 3890)	()		

Notes:

[2] - Only participants who received the investigational product were evaluated

Statistical analyses

No statistical analyses for this end point

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

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

End point 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.

End point type	Secondary

End point timeframe:

Day 1 (0 min (pre-dose), 15 min (end of infusion), 30 min , 60 min, 90 min and 180 min) and Day 5

End point values	HSY244	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	0[3]		
Units: Hour				
median (full range (min-max))	0.28 (0.25 to 0.30)	(to)		

Notes:

[3] - Only participants who received the investigational product were evaluated

Statistical analyses

No statistical analyses for this end point

Secondary: Area under the plasma concentration-time curve (AUClast)

End point title	Area under the plasma concentration-time curve (AUClast)

End point 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.

End point type	Secondary

End point timeframe:

Day 1 (0 min (pre-dose), 15 min (end of infusion), 30 min , 60 min, 90 min and 180 min) and Day 5

End point values	HSY244	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	0[4]		
Units: h*ng/mL				
arithmetic mean (standard deviation)	2960 (± 1510)	()		

Notes:

[4] - Only participants who received the investigational product were evaluated

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 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.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	25.1

Reporting groups	
Reporting group title	HSY244 150 mg
Reporting group description: HSY244 150 mg	
Reporting group title	Total
Reporting group description: Total	
Reporting group title	Placebo
Reporting group description: Placebo	

Serious adverse events	HSY244 150 mg	Total	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 7 (14.29%)	1 / 13 (7.69%)	0 / 6 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 7 (14.29%)	1 / 13 (7.69%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	HSY244 150 mg	Total	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 7 (85.71%)	11 / 13 (84.62%)	5 / 6 (83.33%)
Investigations			
Blood pressure increased			

subjects affected / exposed	2 / 7 (28.57%)	2 / 13 (15.38%)	0 / 6 (0.00%)
occurrences (all)	2	2	0
Blood urine present			
subjects affected / exposed	1 / 7 (14.29%)	1 / 13 (7.69%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Injury, poisoning and procedural complications			
Procedural hypertension			
subjects affected / exposed	0 / 7 (0.00%)	1 / 13 (7.69%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 7 (14.29%)	2 / 13 (15.38%)	1 / 6 (16.67%)
occurrences (all)	1	2	1
Nervous system disorders			
Presyncope			
subjects affected / exposed	0 / 7 (0.00%)	1 / 13 (7.69%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Burning sensation			
subjects affected / exposed	1 / 7 (14.29%)	1 / 13 (7.69%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Paraesthesia			
subjects affected / exposed	1 / 7 (14.29%)	1 / 13 (7.69%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Tremor			
subjects affected / exposed	1 / 7 (14.29%)	1 / 13 (7.69%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
General disorders and administration site conditions			
Infusion site pain			
subjects affected / exposed	0 / 7 (0.00%)	1 / 13 (7.69%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 7 (0.00%)	1 / 13 (7.69%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Flatulence			

subjects affected / exposed	1 / 7 (14.29%)	1 / 13 (7.69%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Skin and subcutaneous tissue disorders			
Dermatitis contact			
subjects affected / exposed	1 / 7 (14.29%)	1 / 13 (7.69%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 7 (14.29%)	3 / 13 (23.08%)	2 / 6 (33.33%)
occurrences (all)	1	3	2
Limb discomfort			
subjects affected / exposed	1 / 7 (14.29%)	1 / 13 (7.69%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Muscle tightness			
subjects affected / exposed	1 / 7 (14.29%)	1 / 13 (7.69%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Musculoskeletal discomfort			
subjects affected / exposed	1 / 7 (14.29%)	1 / 13 (7.69%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Musculoskeletal stiffness			
subjects affected / exposed	1 / 7 (14.29%)	1 / 13 (7.69%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Pain in extremity			
subjects affected / exposed	1 / 7 (14.29%)	1 / 13 (7.69%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	1 / 7 (14.29%)	2 / 13 (15.38%)	1 / 6 (16.67%)
occurrences (all)	1	2	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 September 2020	The purpose of this amendment was to correct the EUDRACT number on the cover page.
12 January 2021	The primary purpose of this amendment was to address requests for protocol amendments from Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM). BfArM requests include the following: 1) to clarify the maximum number of replacement participants per cohort, and to clarify that only those participants would be replaced which have not discontinued due to adverse drug reactions or adverse events based on study procedures, 2) to clarify that a protocol amendment would be submitted to the Competent Authorities and IRB/IECs for approval to start Cohort 2 if a decision to initiate Cohort 2 was due to safety concerns from Cohort 1, 3) to clarify that Competent Authorities, IRB/IECs, and PIs would be informed if the study met a study stopping rule criteria, and approval was required by Competent Authorities and IRB/IECs to restart the study and 4) to clarify that only participants who were capable of providing informed consent themselves would be included in the study.
26 August 2021	The primary purpose of this amendment was to update the eligibility criteria. The changes to the eligibility criteria were based on sites' feedback, which facilitated better representation of the study population to that of patients with atrial fibrillation and a clinical indication for cardioversion. These updates were not expected to increase risk to patient safety or result in meaningful decreases in study drug efficacy. In addition, the protocol text was updated to clarify the study duration. The study duration is unchanged (96 hours or 4 days post-dose) with end of study (EOS) visit occurring on Day 5.
04 April 2022	The primary purposes of this amendment were to reduce participant burden, reduce site burden, expand eligibility, and expedite study completion. At the time of writing this amendment, eight participants had been enrolled in Cohort 1. Through discussions with investigators and site staff about enrollment challenges it was determined that the protocol needed to be updated to decrease burden and to better represent the patient population with atrial fibrillation (AF) meeting a clinical indication for cardioversion. With these changes, enrollment was expected to increase and expedite study completion, while not increasing the risk to participant safety during the trial.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported