# 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<br>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<br>Units: years | | | |
| arithmetic mean | 60.6 | 60.0 | |
| standard deviation | ± 9.73 | ± 4.05 | - |
| Sex: Female, Male<br>Units: participants | | | |
| Female | 1 | 0 | 1 |
| Male | 6 | 6 | 12 |
| Race/Ethnicity, Customized<br>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.<br>In addition, the protocol text was updated to clarify the study duration. The study duration is<br>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.<br>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