Clinical trial results:
An Open-Label, Randomised, Active Controlled, Multi-Centre Phase 3 Study to Evaluate the Safety and Efficacy of Danaparoid vs Argatroban in Treatment of Subjects with Acute HIT (HITSOVA study)

Summary

EudraCT number	2018-002473-21
Trial protocol	DE FR CZ PL ES HR IT
Global end of trial date	10 June 2022

Results information

Result version number	v1 (current)
This version publication date	27 May 2023
First version publication date	27 May 2023

Trial information

Trial identification

Sponsor protocol code	ERGCR-18-ORGHIT-001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03809481
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Aspen Global Incorporated
Sponsor organisation address	GBS Plaza, Cur La Salette et Royal Roads,, Grand Bay, Mauritius,
Public contact	Michelle Singleton, Aspen Pharmacare Holdings Limited, MSingleton@aspenpharma.com
Scientific contact	Michelle Singleton, Aspen Pharmacare Holdings Limited, MSingleton@aspenpharma.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	04 February 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 February 2020
Global end of trial reached?	Yes
Global end of trial date	10 June 2022
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To show that for the treatment of subjects with acute heparin-induced thrombocytopenia (HIT) danaparoid use is not inferior to argatroban in terms of efficacy.

Protection of trial subjects:

due to the serious condition the subjects are under intensive care in the hospital

Background therapy:

All subjects will start a VKA after the platelet count has normalized to a stable plateau for 2 consecutive days, with at least 5 days overlap of receiving study drug, unless contraindicated, and continue taking a VKA until Day 42 in case of HIT without thrombosis and at the Investigator’s discretion in case of HIT with thrombosis but at least for 3 months.

Evidence for comparator:

The comparator, argatroban, is approved to treat HIT in several countries and was found to be safe and well-tolerated in this population.

Actual start date of recruitment	01 March 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	Bosnia and Herzegovina: 3
Country: Number of subjects enrolled	Serbia: 3
Worldwide total number of subjects	7
EEA total number of subjects	1

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)	5
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subject screening occurred in Italy, Germany, Serbia, and Bosnia Herzegovina in the period from July 2019 up to early March 2020 after that COVID resulted in a recruitment halt.

Pre-assignment

Screening details:

in total 14 subjects were screened. 7 screenfailed. One of the main reason for failing screening was a negative HIT test.

Period 1

Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Not applicable not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	danaparoid

Arm description:

Subjects received danaparoid sodium, a therapeutic infusion for at least 7 days (target plasma anti-factor Xa activity 0.4 to 0.8 units/mL) after which it was continued in preparation for the transition to Vitamin K antagonist (VKA).

Arm type	Experimental
Investigational medicinal product name	danaparoid sodium
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Infusion

Dosage and administration details:

Intravenous (IV) loading bolus injection of 2250 U (i.e. 3 ampoules) (for subjects less than 55 kg 1500 U, if over 90 kg, 3750 U) immediately followed by
2 step-down IV infusions at 400 U/h for 4 hours, followed by 300 U/h for 4 hours, and then the maintenance infusion of 200 U/h until the Day 14 (or longer if needed).

Arm title	argatroban

Arm description:

Subjects received argatroban, a therapeutic infusion for up to 14 days. Intravenous therapy was stopped in the period between 7 and 14 days.

Arm type	Active comparator
Investigational medicinal product name	argatroban monohydrate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

The initial dosage of argatroban in adult subjects without hepatic impairment in HIT was 2 microgram/kg/min, administered as a continuous infusion. Before argatroban was administered, heparin therapy was to be discontinued and a baseline aPTT value obtained
Subjects received argatroban, a therapeutic infusion for up to 14 days. Intravenous therapy was stopped in the period between 7 and 14 days.

Number of subjects in period 1	danaparoid	argatroban
Started	4	3
Completed	2	0
Not completed	2	3
Adverse event, non-fatal	1	1
Death	1	1
confirmed as non HIT	-	1

Baseline characteristics

Reporting groups

Reporting group title	overall trial

Reporting group description:

Of the 7 subjects randomized, 5 subjects (71.43%) were female, and 2 subjects (28.57%) were male. Majority of subjects (6/7) were not Hispanic or Latino. All the subjects 7/7 (100.0%) were white. Most of the subjects (57.14%) had Intensive care unit (ICU) admission.
Overall, the median age of subjects was 59.0 years (range: 4879 years), with median age 58.0 years (range: 5079 years) for danaparoid group and 61.0 years (range: 48-78 years) for argatroban group. Overall the median weight was 74.50 kg (range: 59.0106.0 kg).

Reporting group values	overall trial	Total	
Number of subjects	7	7	
Age categorical			
Overall, the median age of subjects was 59.0 years (range: 48-79 years), with median age 58.0 years (range: 50-79 years) for danaparoid group and 61.0 years (range: 48-78 years) for argatroban group.			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	5	5	
From 65-84 years	2	2	
85 years and over	0	0	
Age continuous			
Overall, the median age of subjects was 59.0 years (range: 48-79 years), with median age 58.0 years (range: 50-79 years) for danaparoid group and 61.0 years (range: 48-78 years) for argatroban group.			
Units: years			
median	59		
full range (min-max)	48 to 79	-	
Gender categorical			
Of the 7 subjects randomized, 5 subjects (71.43%) were female, and 2 subjects (28.57%) were male.			
Units: Subjects			
Female	5	5	
Male	2	2	

Subject analysis sets

Subject analysis set title	Efficacy
Subject analysis set type	Per protocol

Subject analysis set description:

all randomized subjects

Reporting group values	Efficacy		
Number of subjects	7		
Age categorical			
Overall, the median age of subjects was 59.0 years (range: 48-79 years), with median age 58.0 years (range: 50-79 years) for danaparoid group and 61.0 years (range: 48-78 years) for argatroban group.			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	5		
From 65-84 years	2		
85 years and over	0		
Age continuous			
Overall, the median age of subjects was 59.0 years (range: 48-79 years), with median age 58.0 years (range: 50-79 years) for danaparoid group and 61.0 years (range: 48-78 years) for argatroban group.			
Units: years			
median			
full range (min-max)			
Gender categorical			
Of the 7 subjects randomized, 5 subjects (71.43%) were female, and 2 subjects (28.57%) were male.			
Units: Subjects			
Female			
Male			

End points

End points reporting groups

Reporting group title	danaparoid

Reporting group description:

Subjects received danaparoid sodium, a therapeutic infusion for at least 7 days (target plasma anti-factor Xa activity 0.4 to 0.8 units/mL) after which it was continued in preparation for the transition to Vitamin K antagonist (VKA).

Reporting group title	argatroban

Reporting group description:

Subjects received argatroban, a therapeutic infusion for up to 14 days. Intravenous therapy was stopped in the period between 7 and 14 days.

Subject analysis set title	Efficacy
Subject analysis set type	Per protocol

Subject analysis set description:

all randomized subjects

Primary: efficacy

End point title	efficacy[1]

End point description:

Primary Endpoint
The proportion of treatment responders at Day 44, was to be defined as those subjects who had not experienced any of the following events:
- New or extended venous and/or arterial thrombosis, including gangrene/skin necrosis,
- All-cause mortality,
- Unplanned amputation, including ischaemic gut resection, were the primary endpoint for the comparison of efficacy between the treatment groups.

End point type	Primary

End point timeframe:

The primary efficacy endpoint (composite endpoint) is defined as treatment response at Day 44.

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: due to the limit number of patients no statistical analysis was performed.

End point values	danaparoid	argatroban	Efficacy	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	0[2]	0[3]	0[4]	
Units: events				
number (not applicable)				

Notes:

[2] - No efficacy analysis was performed due to low number of subjects

[3] - no efficacy analysis was performed due to low number of subjects

[4] - No analysis performed due to low number of subjects

Statistical analyses

No statistical analyses for this end point

Secondary: efficacy and safety

End point title	efficacy and safety

End point description:

Secondary Endpoints
The following endpoints were planned to be assessed to further evaluate the safety and efficacy of the two treatments:
- Percentage of subjects with consistent increases in platelets at Days 3, 5, and 7 (to identify early response) defined as monotonically increasing platelet counts, measured two days apart on days 3 (±1 day), 5 (±1 day) and 7 (±1 day).
- Deaths due to TE or bleeding up until Day 44
- Incidence of fatal or non-fatal major bleeding up until Day 44
- New or extended thrombosis, including gangrene/skin necrosis
- Unplanned amputation, including ischaemic gut resect
- All-cause mortality

End point type	Secondary

End point timeframe:

up until Day 44

End point values	danaparoid	argatroban		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[5]	0[6]		
Units: events				
number (not applicable)				

Notes:

[5] - due to the low number of subjects no statistical analysis was performed

[6] - due to the low number of subjects no statistical analysis was performed

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs were reported at start of IMP administration upto day 44 of the follow up period.

Adverse event reporting additional description:

To describe the safety of danaparoid in comparison to argatroban

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22

Reporting groups

Reporting group title	danaparoid

Reporting group description:

Subjects received danaparoid sodium, a therapeutic infusion for at least 7 days (target plasma anti-factor Xa activity 0.4 to 0.8 units/mL) after which it was continued in preparation for the transition to Vitamin K antagonist (VKA).

Reporting group title	argatroban

Reporting group description:

Subjects received argatroban, a therapeutic infusion for up to 14 days. Intravenous therapy was stopped in the period between 7 and 14 days.

Serious adverse events	danaparoid	argatroban	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 4 (50.00%)	2 / 3 (66.67%)	
number of deaths (all causes)	2	2	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant neoplasm progression			
subjects affected / exposed	0 / 4 (0.00%)	1 / 3 (33.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Intracardiac thrombus			
subjects affected / exposed	1 / 4 (25.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Septic shock			

subjects affected / exposed	1 / 4 (25.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 3 (33.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	danaparoid	argatroban	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 4 (75.00%)	2 / 3 (66.67%)	
Investigations			
Activated partial thromboplastin time prolonged			
subjects affected / exposed	0 / 4 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 4 (25.00%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Peripheral swelling			
subjects affected / exposed	0 / 4 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Haemorrhoids			
subjects affected / exposed	1 / 4 (25.00%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	1 / 4 (25.00%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Gangrene			

subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 3 (33.33%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 January 2019	protocol version 6; • Update of study design with Schedule of events, population, inclusion and exclusion criteria, number of subjects per treatment arm to suffice to reject the 1-sided null hypothesis. • IMP was updated with the information that use of VKA should be delayed until substantial resolution thrombocytopenia (e.g., platelets > 100 × 109/L) to avoid coumarin associated with microvascular thrombosis and venous limb gangrene. • Adjudication Committee was added to Independent Data Monitoring Committee.
10 September 2019	protocol version 7; • Update of study population by adding definition of Acute systemic reaction when heparin infusion was given, and specification that Pediatric subjects will not be included in every country in this study. The countries that allow inclusion of Pediatric patients are France, USA, Italy and Russia. • Update inclusion and exclusion criteria, and concomitant medications (Women of child-bearing age who are taking VKA should use effective contraception until one month after cessation of use). • IMP dosage was updated: https://www.medicines.ie/medicines/orgaran-750-anti-xa-units-0-6ml-solution-for-injection-33247/. In cases of impaired renal function (i.e. eGFR<30 mL/min/1.73m2) the maintenance dose should be reduced to 150 U/h. For further maintenance dose modifications. • If the subject has sustained an accidental traumatic bleed (falling out of bed etc.) then danaparoid should be transiently discontinued until the bleeding has stopped and the maintenance infusion restarted without a loading dose when it is considered safe to do so. • Thromboembolism section updated.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
01 April 2020	The study was stopped in April 2020 because of the COVID-19 pandemic. In June 2022 it was decided to close the study as due to low recruitment before the pandemic and the remaining effects of the pandemic making it difficult to complete the study.	-

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The efficacy data are not reported in this CSR as the study was stopped in April 2020 as a result of the COVID-19 pandemic and due to the low number of subjects, no efficacy results can be concluded in this clinical trial.

Notes: