Clinical trial results:
A pilot trial to assess the efficacy of Argatroban (Argatra®) in critically ill patients with heparin resistance

Summary

EudraCT number	2012-000487-23
Trial protocol	AT
Global end of trial date	06 April 2016

Results information

Result version number	v1 (current)
This version publication date	14 November 2021
First version publication date	14 November 2021

Trial information

Trial identification

Sponsor protocol code	ArgHeR

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01734252
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Medical University of Innsbruck
Sponsor organisation address	Anichstraße 35, Innsbruck, Austria, 6020
Public contact	Projektmanagement, Medizinische Universität Innsbruck / Univ.-Klinik für Allgemeine und Chirurgische Intensivmedizin, 0043 051250480451, mirjam.bachler@i-med.ac.at
Scientific contact	Projektmanagement, Medizinische Universität Innsbruck / Univ.-Klinik für Allgemeine und Chirurgische Intensivmedizin, 0043 051250480451, mirjam.bachler@i-med.ac.at

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	28 June 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 April 2016
Global end of trial reached?	Yes
Global end of trial date	06 April 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective is to achieve a prophylactic anticoagulation level within 7(+/-1) hours after Baseline. The parameter to define the anticoagulation level is aPTT and will be measured at 7(+/-1) hours for the Primary Objective.

Protection of trial subjects:

After the study drug was discontinued, a radiologist performed a duplex ultrasound scan of the lower extremity veins to detect clinically apparent non-apparent venous thromboembolism.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 July 2012
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	Austria: 42
Worldwide total number of subjects	42
EEA total number of subjects	42

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)	28
From 65 to 84 years	14
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

All patients with a heparin (UFH) dose of 1,200 IU/H not reaching the target aPTT of 45 seconds were included by the study investigators

Pre-assignment

Screening details:

All patients at the participating ICU with a heparin (UFH) dose of 1,200 IU/H were screened by the study investigators

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Standard Therapie

Arm description:

The standard therapy group continued to receive heparin at 1,200 IU per hour, which was increased to a maximum heparin dose of 1,500 IU per hour.

Arm type	Active comparator
Investigational medicinal product name	Unfractionated Heparin (UFH)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

A maximum dose of 1,500 IU / hour was given as continuous intravenous infusion to reach a aPTT target range of 45 to 60 seconds

Arm title	Argatroban

Arm description:

The initial dosage of argatroban was determined by the treating physician and adjusted according to aPTT.

Arm type	Experimental
Investigational medicinal product name	Argatroban
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

The initial dosage of argatroban was determined by the treating physician and adjusted according to aPTT to reach a target aPTT range of 45 to 60 seconds. Hereby the maximum dose was 10 µg/kg/min .

Number of subjects in period 1	Standard Therapie	Argatroban
Started	20	22
Completed	20	22

Baseline characteristics

Reporting groups	
Reporting group title	Standard Therapie
Reporting group description:	
The standard therapy group continued to receive heparin at 1,200 IU per hour, which was increased to a maximum heparin dose of 1,500 IU per hour.	
Reporting group title	Argatroban
Reporting group description:	
The initial dosage of argatroban was determined by the treating physician and adjusted according to aPTT.	

Reporting group values	Standard Therapie	Argatroban	Total
Number of subjects	20	22	42
Age categorical Units: Subjects			
Adults (18-64 years)	11	16	27
From 65-84 years	9	6	15
Age continuous Units: years			
median	57.5	56.5	
inter-quartile range (Q1-Q3)	46 to 68	44.2 to 64.8	-
Gender categorical Units: Subjects			
Female	2	1	3
Male	18	21	39

End points

End points reporting groups

Reporting group title	Standard Therapie

Reporting group description:

The standard therapy group continued to receive heparin at 1,200 IU per hour, which was increased to a maximum heparin dose of 1,500 IU per hour.

Reporting group title	Argatroban

Reporting group description:

The initial dosage of argatroban was determined by the treating physician and adjusted according to aPTT.

Primary: Achievement of aPTT > 45 seconds within 8 h

End point title	Achievement of aPTT > 45 seconds within 8 h

End point description:

End point type	Primary

End point timeframe:

Within 7 h (+/-1 h) after administration start of the study medication

End point values	Standard Therapie	Argatroban		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20[1]	22		
Units: Number	20	22		

Notes:

[1] - 2 discontinued study treatment due to violating inclusion criteria

Statistical analyses

Statistical analysis title	Statistical assessment of primary endpoint
Comparison groups	Standard Therapie v Argatroban
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Fisher exact

Secondary: Achievement of aPTT > 45 seconds within 24 h

End point title	Achievement of aPTT > 45 seconds within 24 h

End point description:

End point type	Secondary

End point timeframe:

Within 24 h after administration start of the study medication

End point values	Standard Therapie	Argatroban		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20[2]	22		
Units: Number				
Number of Patients	20	22		

Notes:

[2] - 2 drop outs

Statistical analyses

Statistical analysis title	Statistical assessment of secondary endpoint
Comparison groups	Standard Therapie v Argatroban
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Fisher exact

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

Adverse Events were collected/recorded from study inclusion until safety visit on day 7 was conducted.

Adverse event reporting additional description:

All subjects in this study experienced at least 1 AE. So the total number of subjects affected bei non-serious AE is 20 in the heparin group and 22 in the argatroban group.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Standard Therapie

Reporting group description:

The standard therapy group continued to receive heparin at 1,200 IU per hour, which was increased to a maximum heparin dose of 1,500 IU per hour.

Reporting group title	Argatroban

Reporting group description:

The initial dosage of argatroban was determined by the treating physician and adjusted according to aPTT.

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: All subjects in this study experienced at least 1 non-serious AE.

Serious adverse events	Standard Therapie	Argatroban	
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 20 (45.00%)	8 / 22 (36.36%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Deep vein thrombosis leg	Additional description: Classified as SAR: heparin group (switch): 1; argatroban group 1;		
subjects affected / exposed	1 / 20 (5.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Ventricular fibrillation	Additional description: Argatroban group: 1		
subjects affected / exposed	0 / 20 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Death	Additional description: Heparin group (switch): 1		

subjects affected / exposed	1 / 20 (5.00%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Respiratory arrest	Additional description: Argatroban group: 1		
subjects affected / exposed	0 / 20 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure	Additional description: Argatroban group: 1		
subjects affected / exposed	0 / 20 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural hemorrhage	Additional description: Classified as SAR: Argatroban group: 1		
subjects affected / exposed	0 / 20 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial haemorrhage	Additional description: Classified as SAR: Heparin group: 2		
subjects affected / exposed	2 / 20 (10.00%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure acute	Additional description: Argatroban group: 1		
subjects affected / exposed	0 / 20 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Aspergillus fumigatus bronchopulmonary infection	Additional description: Heparin group: 1		
subjects affected / exposed	1 / 20 (5.00%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis	Additional description: Heparin group (switch): 1		

subjects affected / exposed	1 / 20 (5.00%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock septic	Additional description: Heparin group (switch): 1; argatroban group: 1		
subjects affected / exposed	1 / 20 (5.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal sepsis	Additional description: Argatroban group: 1		
subjects affected / exposed	0 / 20 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute peritonitis	Additional description: Heparin group (switch): 1		
subjects affected / exposed	1 / 20 (5.00%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
H1N1 influenza	Additional description: Heparin group: 1		
subjects affected / exposed	1 / 20 (5.00%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Standard Therapie	Argatroban	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 20 (0.00%)	0 / 22 (0.00%)	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 November 2013	Change of recommendation for argatroban start dosing; addition of a secondary endpoint (add: correlation of laboratory parameters and Argatroban dose/level); deletion of exclusion criteria (FXII deficiency and L. anticoagulants -> these factors were evaluated at baseline since then). Addition of two sites.
16 October 2015	Prolongation of recruitment period. Deletion of two sites due to no patient recruitment. Deletion of the DSMB.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/32244368