Clinical trial results:
Apixaban for treatment of embolic stroke of undetermined source

Summary

EudraCT number	2014-005109-19
Trial protocol	DE
Global end of trial date	09 November 2021

Results information

Result version number	v1 (current)
This version publication date	26 May 2023
First version publication date	26 May 2023
Summary attachment (see zip file)	Atticus-Trial_ Final_Report (2022-02-28_ATTICUS_Final Report.pdf)

Trial information

Trial identification

Sponsor protocol code	ATTICUS

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	University Hospital Tübingen
Sponsor organisation address	Otfried-Müller-Strasse 10, Tübingen, Germany, 72076
Public contact	Prof. Dr. med. Tobias Geisler : Principal Investigator (PI) and Coordinating Investigator, University Hospital Tuebingen, tobias.geisler@med.uni-tuebingen.de
Scientific contact	Prof. Dr. med. Tobias Geisler : Principal Investigator (PI) and Coordinating Investigator, University Hospital Tuebingen, tobias.geisler@med.uni-tuebingen.de

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	09 December 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 November 2021
Global end of trial reached?	Yes
Global end of trial date	09 November 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary endpoint was the occurrence of at least one new ischemic lesion identified by magnetic resonance imaging (axial T2-weighted fluid attenuated inversion recovery MRI (FLAIR) and/or axial diffusion weighted MRI (DWI)) at 12 months when compared to the baseline MRI (FLAIR, DWI) obtained at the time of study drug initiation. MRI at 12 months was directly compared with the baseline MRI to assess for new ischemic lesions.

Protection of trial subjects:

The procedures set out in this trial protocol, pertaining to the conduct, evaluation, and documentation of this trial, are designed to ensure that all persons involved in the trial act according to Good Clinical Practice (GCP) and the ethical principles described in the applicable version of the Declaration of Helsinki. This is a scientific clinical study; the German Medicines Act (AMG) §40 is applicable without restrictions according to section §42.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 February 2016
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: 352
Worldwide total number of subjects	352
EEA total number of subjects	352

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)	352

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The general criteria for subject selection was adult male and female patients with ESUS.

Pre-assignment

Screening details:

Aproximately 900 patients were screened. Actually 371 patients were recruited and 353 were randomized.
Then there were 18 drop-outs and 1 patient who withdrew the consent on randomization day.

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:

N.a.

Arms

Are arms mutually exclusive?	Yes
Arm title	Apixaban

Arm description:

Apixaban was administered from randomization (depending on the severity of stroke and the individual risk for HTI (3-28 days after minor/moderate stroke and 14-28 days after major stroke) until 12 months after study drug initiation.

Arm type	Experimental
Investigational medicinal product name	Apixaban
Investigational medicinal product code	
Other name	Eliquis
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

5 mg, or reduced dose of 2.5 mg in patients who meet two of the following three criteria: 1. age ≥ 80 years, 2. body weight < 60 kg and 3. serum creatinin ≥ 1,5 mg/dl (133 Micromol/L)

Arm title	Acetylsalicylic acid (ASS)

Arm description:

Usual care (acetylsalicylic acid) were administered from study drug initiation (3-28 days after minor/moderate
stroke and 14-28 days after major stroke) until 12 months after study drug initiation.

Arm type	Active comparator
Investigational medicinal product name	Acetylsalicylic acid
Investigational medicinal product code	
Other name	ASS
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Dose: 100 mg

Number of subjects in period 1	Apixaban	Acetylsalicylic acid (ASS)
Started	178	174
Completed	178	174

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	352	352	
Age categorical			
One of the main inclusion criteria was to be ≥ 18 years at the time of signing the informed consent.			
Units: Subjects			
Adults (18-64 years)	102	102	
From 65-84 years	250	250	
Age continuous			
Units: years			
median	69		
full range (min-max)	38 to 91	-	
Gender categorical			
Units: Subjects			
Female	171	171	
Male	181	181	

End points

End points reporting groups

Reporting group title	Apixaban
Reporting group description:	
Apixaban was administered from randomization (depending on the severity of stroke and the individual risk for HTI (3-28 days after minor/moderate stroke and 14-28 days after major stroke) until 12 months after study drug initiation.	
Reporting group title	Acetylsalicylic acid (ASS)
Reporting group description:	
Usual care (acetylsalicylic acid) were administered from study drug initiation (3-28 days after minor/moderate stroke and 14-28 days after major stroke) until 12 months after study drug initiation.	

Primary: The occurrence of at least one new ischemic lesion

End point title	The occurrence of at least one new ischemic lesion
End point description:	
The primary endpoint was the occurrence of at least one new ischemic lesion identified by magnetic resonance imaging (axial T2-weighted fluid attenuated inversion recovery MRI (FLAIR) and/or axial diffusion weighted MRI (DWI)) at 12 months when compared to the baseline MRI (FLAIR, DWI) obtained at the time of study drug initiation. MRI at 12 months was directly compared with the baseline MRI to assess for new ischemic lesions.	
End point type	Primary
End point timeframe:	
12 months	

End point values	Apixaban	Acetylsalicylic acid (ASS)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	169	156		
Units: Patients	23	25		

Statistical analyses

Statistical analysis title	Analysis of primary endpoint
Comparison groups	Apixaban v Acetylsalicylic acid (ASS)
Number of subjects included in analysis	325
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.57 [1]
Method	t-test, 2-sided
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.68
upper limit	2.37

Variability estimate	Standard deviation

Notes:

[1] - p-value = 0.57 two-sided

Secondary: Combination of recurrent ischemic stroke, hemorrhagic stroke and systemic embolism

End point title	Combination of recurrent ischemic stroke, hemorrhagic stroke and systemic embolism

End point description:

Combination of recurrent ischemic stroke, hemorrhagic stroke and systemic embolism

End point type	Secondary

End point timeframe:

12 months

End point values	Apixaban	Acetylsalicylic acid (ASS)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	169	156		
Units: Patients	14	13		

Statistical analyses

No statistical analyses for this end point

Secondary: Combination of major adverse cardiovascular events (MACE) including recurrentstroke, myocardial infarction and cardiovascular death

End point title	Combination of major adverse cardiovascular events (MACE) including recurrentstroke, myocardial infarction and cardiovascular death

End point description:

Combination of major adverse cardiovascular events (MACE) including recurrent stroke, myocardial infarction and cardiovascular death.

End point type	Secondary

End point timeframe:

12 months

End point values	Apixaban	Acetylsalicylic acid (ASS)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	169	156		
Units: Patients	18	19		

Statistical analyses

No statistical analyses for this end point

Secondary: Combination of major adverse cardiovascular events (MACE) including recurrentstroke, myocardial infarction without cardiovascular death

End point title	Combination of major adverse cardiovascular events (MACE) including recurrentstroke, myocardial infarction without cardiovascular death

End point description:

Combination of major adverse cardiovascular events (MACE) including recurrent stroke, myocardial infarction without cardiovascular deaths.

End point type	Secondary

End point timeframe:

12 months

End point values	Apixaban	Acetylsalicylic acid (ASS)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	169	156		
Units: Patients	15	15		

Statistical analyses

No statistical analyses for this end point

Secondary: Combinationof major and clinically relevant non-major bleedings

End point title	Combinationof major and clinically relevant non-major bleedings

End point description:

Combination of major and clinically relevant non-major bleedings defined according to ISTH criteria

End point type	Secondary

End point timeframe:

12 months

End point values	Apixaban	Acetylsalicylic acid (ASS)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	169	156		
Units: Patients	5	9		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

All SAEs must be collected that occur from initiation of study drug and within 30 days of discontinuing dosing.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	0

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

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: Detail on Safety Data such as Adverse Events and Serious Adverse Events can be found in the Appendix of the summary attached.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported