Clinical trial results:
Assessment of Active Thrombin-Activatable Fibrinolysis Inhibitor (TAFIa) plasma kinetics in Patients at acute stage of Ischemic Stroke: Prospective, Multicentre, Open, Non-randomised, Biomarker Study

Summary

EudraCT number	2017-002760-41
Trial protocol	ES
Global end of trial date	05 April 2018

Results information

Result version number	v1 (current)
This version publication date	13 April 2019
First version publication date	13 April 2019

Trial information

Trial identification

Sponsor protocol code	CL2-RTCCAR-001

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Institut de Recherches Internationales Servier (I.R.I.S)
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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	05 April 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 April 2018
Global end of trial reached?	Yes
Global end of trial date	05 April 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary exploratory objective of this trial was to assess the systemic plasma kinetics of the active Thrombin-Activatable Fibrinolysis Inhibitor (TAFIa) during the acute stage of ischemic stroke in patients eligible for recombinant tissue Plasminogen Activator (rtPA) thrombolysis alone or rtPA thrombolysis followed by endovascular thrombectomy (EVT).

Protection of trial subjects:

This study was conducted in accordance with Good Clinical Practice standards, ethical principles stated in the Declaration of Helsinki and applicable regulatory requirements. After the subject has ended his/her participation in the trial, the investigator provided appropriate medication and/or arrange access to appropriate care for the patient.

Background therapy:

No Investigational Medicinal Product (IMP) was provided to the patients. The patients received the standard-of-care treatment, including rtPA thrombolysis or rtPA thrombolysis and endovasular thrombectomy if indicated according to current clinical guidelines.

Evidence for comparator: -

Actual start date of recruitment	15 November 2017
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	Spain: 35
Country: Number of subjects enrolled	France: 2
Worldwide total number of subjects	37
EEA total number of subjects	37

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)	7
From 65 to 84 years	17
85 years and over	13

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Patients ≥ 18 years old within 4.5 hours after ischemic stroke symptoms onset, with imaging evidence of cerebral artery occlusion in anterior circulation, and eligible for pharmacological thrombolysis alone or followed by EVT according to current clinical guidelines.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Group A (rtPA)

Arm description:

No IMP is used in this study.
Adult patients at acute stage of ischemic stroke eligible for rtPA (i.e. thrombolysis) alone according to current clinical guidelines and investigator, and having documented cerebral artery occlusion in anterior circulation.

Arm type	rtPA alone
Investigational medicinal product name	rtPA as background treatment
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

The recommended dose of alteplase was 0.9 mg/kg over 60 minutes as indicated in the approved SmPC

Arm title	group B (rtPA+EVT)

Arm description:

No IMP is used in this study.
Adult patients at acute stage of ischemic stroke eligible for rtPA + EVT (i.e. thrombolysis + endovascular thrombectomy) according to current clinical guidelines and investigator, and having documented cerebral artery occlusion in anterior circulation.

Arm type	rtPA + Endovascular thrombectomy
Investigational medicinal product name	rtPA as background treatment
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

The recommended dose of alteplase was 0.9 mg/kg over 60 minutes as indicated in the approved SmPC

Number of subjects in period 1	Group A (rtPA)	group B (rtPA+EVT)
Started	20	17
Completed	19	17
Not completed	1	0
Adverse event, serious fatal	1	-

Baseline characteristics

Reporting groups

Reporting group title	Group A (rtPA)

Reporting group description:

No IMP is used in this study.
Adult patients at acute stage of ischemic stroke eligible for rtPA (i.e. thrombolysis) alone according to current clinical guidelines and investigator, and having documented cerebral artery occlusion in anterior circulation.

Reporting group title	group B (rtPA+EVT)

Reporting group description:

No IMP is used in this study.
Adult patients at acute stage of ischemic stroke eligible for rtPA + EVT (i.e. thrombolysis + endovascular thrombectomy) according to current clinical guidelines and investigator, and having documented cerebral artery occlusion in anterior circulation.

Reporting group values	Group A (rtPA)	group B (rtPA+EVT)	Total
Number of subjects	20	17	37
Age categorical Units: Subjects			
Adults (18-64 years)	3	4	7
From 65-84 years	8	9	17
85 years and over	9	4	13
Gender categorical Units: Subjects			
Female	7	10	17
Male	13	7	20

Subject analysis sets

Subject analysis set title	Included Set (IS)
Subject analysis set type	Full analysis

Subject analysis set description:

All enrolled patients included in the study

Subject analysis set title	Biomarker Set (BMKS)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

All enrolled patients included in the study with a rtPA full dose administered

Reporting group values	Included Set (IS)	Biomarker Set (BMKS)	
Number of subjects	37	36	
Age categorical Units: Subjects			
Adults (18-64 years)	7	6	
From 65-84 years	17	17	
85 years and over	13	13	

Gender categorical Units: Subjects			
Female	17	17	
Male	20	19	

End points

End points reporting groups

Reporting group title	Group A (rtPA)

Reporting group description:

No IMP is used in this study.
Adult patients at acute stage of ischemic stroke eligible for rtPA (i.e. thrombolysis) alone according to current clinical guidelines and investigator, and having documented cerebral artery occlusion in anterior circulation.

Reporting group title	group B (rtPA+EVT)

Reporting group description:

No IMP is used in this study.
Adult patients at acute stage of ischemic stroke eligible for rtPA + EVT (i.e. thrombolysis + endovascular thrombectomy) according to current clinical guidelines and investigator, and having documented cerebral artery occlusion in anterior circulation.

Subject analysis set title	Included Set (IS)
Subject analysis set type	Full analysis

Subject analysis set description:

All enrolled patients included in the study

Subject analysis set title	Biomarker Set (BMKS)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

All enrolled patients included in the study with a rtPA full dose administered

Primary: systemic TAFIa plasma level assessment

End point title	systemic TAFIa plasma level assessment[1]

End point description:

The primary endpoint was the systemic TAFIa plasma level

End point type	Primary

End point timeframe:

Groups A and B : intravenous blood samples at baseline and at intervals over 24h since rtPA thrombolysis start
Group B only : one arterial blood sample through the EVT catheter immediately before first pass.

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: Within group comparisons versus baseline were specified but were not relevant due to the small sample size and the large inter-individual variability in TAFIa activity.
A between group comparison on the change between baseline and T1h was specified in the statistical analysis plan but was not relevant for the same reasons.

End point values	Group A (rtPA)	group B (rtPA+EVT)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[2]	0[3]		
Units: U/L				
number (not applicable)				

Notes:

[2] - it was not possible to interpret inferential statistics due to a few number of biomarkers data

[3] - It was not possible to interpret inferential statistics due to a few number of biomarkers data

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

-from the signature of the informed consent up to the participant's last study visit for all adverse events.
-irrespective of the time of onset after the end of the study in case of serious adverse events related to
-the research.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20

Reporting groups

Reporting group title	Group rtPA

Reporting group description:

Adult patients at acute stage of ischemic stroke eligible for rtPA (i.e. thrombolysis) alone according to current clinical guidelines, and having documented cerebral artery occlusion in anterior circulation.

Reporting group title	Group rtPA + EVT

Reporting group description:

Adult patients at acute stage of ischemic stroke eligible for rtPA + EVT (i.e. thrombolysis + endovascular thrombectomy) according to current clinical guidelines, and having documented cerebral artery occlusion in anterior circulation.

Serious adverse events	Group rtPA	Group rtPA + EVT	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 20 (15.00%)	4 / 17 (23.53%)	
number of deaths (all causes)	1	1	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 20 (5.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Bradycardia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	0 / 20 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cardiac failure			
subjects affected / exposed	0 / 20 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Haemorrhagic transformation stroke			
subjects affected / exposed	1 / 20 (5.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Coma			
subjects affected / exposed	1 / 20 (5.00%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Generalised tonic-clonic seizure			
subjects affected / exposed	1 / 20 (5.00%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Syncope			
subjects affected / exposed	1 / 20 (5.00%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myoclonic epilepsy			
subjects affected / exposed	0 / 20 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Aspiration			
subjects affected / exposed	0 / 20 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Group rtPA	Group rtPA + EVT	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 20 (30.00%)	3 / 17 (17.65%)	
Investigations			
Electrocardiogram ST segment depression			
subjects affected / exposed	1 / 20 (5.00%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Electrocardiogram T wave inversion			
subjects affected / exposed	1 / 20 (5.00%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Vascular disorders			
hypertension			
subjects affected / exposed	0 / 20 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 20 (5.00%)	1 / 17 (5.88%)	
occurrences (all)	1	1	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 20 (5.00%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 20 (5.00%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	2 / 20 (10.00%)	0 / 17 (0.00%)	
occurrences (all)	2	0	
Constipation			
subjects affected / exposed	1 / 20 (5.00%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Rectal haemorrhage			
subjects affected / exposed	1 / 20 (5.00%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			

Pneumonia aspiration			
subjects affected / exposed	1 / 20 (5.00%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Aspiration			
subjects affected / exposed	0 / 20 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 20 (5.00%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Confusional state			
subjects affected / exposed	1 / 20 (5.00%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Insomnia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	3 / 20 (15.00%)	0 / 17 (0.00%)	
occurrences (all)	3	0	

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