Clinical trial results:
Ultra-early tranexamic acid after subarachnoid hemorrhage.
A prospective, randomized, multicenter study.

Summary

EudraCT number	2012-000343-26
Trial protocol	NL
Global end of trial date	20 January 2020

Results information

Result version number	v1 (current)
This version publication date	20 December 2021
First version publication date	20 December 2021

Trial information

Trial identification

Sponsor protocol code	ULTRA12

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02684812
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AmsterdamUMC
Sponsor organisation address	Meibergdreef 9, Amsterdam, Netherlands, 1105AZ
Public contact	ULTRA contact point, Academic Medical Center Amsterdam, +31 205666564, D.Verbaan@amc.uva.nl
Scientific contact	ULTRA contact point, Academic Medical Center Amsterdam, 0031 205666564, D.Verbaan@amc.uva.nl

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	01 October 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 October 2019
Global end of trial reached?	Yes
Global end of trial date	20 January 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate whether a group of patients with subarachnoid hemorrhage (SAH) treated by standard, state-of-the-art SAH management with additional ultra-early and short-term tranexamic acid (TXA) administration (TXA group) has a significantly higher percentage of patients with a favourable outcome after six months (score 0-3 on the Modified Rankin Scale) compared to a group treated by standard, state-of-the-art SAH management without additional TXA administration (control group).

Protection of trial subjects:

safety and efficacy board monitoring

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 January 2013
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	Netherlands: 955
Worldwide total number of subjects	955
EEA total number of subjects	955

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)	641
From 65 to 84 years	302
85 years and over	12

Subject disposition

Recruitment
Recruitment details: -

Pre-assignment
Screening details: no severe renal failure, no pregnancy

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

Arms	
Are arms mutually exclusive?	Yes
Arm title	Tranexamic acid
Arm description: Treatment with tranexamic acid (TXA)	
Arm type	Experimental
Investigational medicinal product name	tranexamic acid
Investigational medicinal product code	
Other name	cyclocapron
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Infusion
Dosage and administration details: 1g bolus, 1gram every 8 hours until max. 24h or until aneurysm treatment	
Arm title	Control
Arm description: Standard care	
Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 1	Tranexamic acid	Control
Started	480	475
Completed	480	475

Baseline characteristics

Reporting groups	
Reporting group title	Baseline

Reporting group description: -

Reporting group values	Baseline	Total	
Number of subjects	955	955	
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 58.4 ± 12.4	 -	
Gender categorical			
Gender			
Units: Subjects			
Female	644	644	
Male	311	311	
WFNS			
WFNS			
Units: Subjects			
Grade 1	358	358	
Grade 2	189	189	
Grade 3	40	40	
Grade 4	187	187	
Grade 5	168	168	
Missing	13	13	
Fisher			
Fisher Grade Score			
Units: Subjects			
Grade 2	56	56	
Grade 3	277	277	
Grade 4	622	622	
Missing	0	0	
Aneurysm location			
Location of ruptured aneursysm			
Units: Subjects			
Anterior circ	659	659	
Posterior circ	153	153	
None	135	135	
Unknown	8	8	
Treatment modality			
Aneurysm treatment modality			
Units: Subjects			
Endovascular	530	530	
Clipping	175	175	

None	108	108	
Not Applicable	142	142	

End points

End points reporting groups	
Reporting group title	Tranexamic acid
Reporting group description: Treatment with tranexamic acid (TXA)	
Reporting group title	Control
Reporting group description: Standard care	

Primary: mRS at 6 months	
End point title	mRS at 6 months
End point description: Clinical outcome assessed by modified Rankin Scale Score	
End point type	Primary
End point timeframe: Six months	

End point values	Tranexamic acid	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	475	470		
Units: 0-1				
Good clinical outcome (mRS 0-3)	287	300		
Poor clinical outcome (mRS 4-6)	188	170		

Attachments (see zip file)	Distrubution of mRS at 6 months in IIT/gr2.jpg

Statistical analyses	
Statistical analysis title	Primary outcome analysis
Statistical analysis description: Differences between treatment groups are listed with odds ratio (OR) and 95% CI.	
Comparison groups	Tranexamic acid v Control
Number of subjects included in analysis	945
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)

Confidence interval	
level	95 %
sides	2-sided

Secondary: All-cause mortality 30d

End point title	All-cause mortality 30d

End point description:

All-cause mortality during the first 30 days

End point type	Secondary

End point timeframe:

During first 30 days

End point values	Tranexamic acid	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	480	475		
Units: 0-1				
alive at 30 days	377	371		
diseased at 30 days	128	104		

Statistical analyses

No statistical analyses for this end point

Secondary: All-cause mortality 6 months

End point title	All-cause mortality 6 months

End point description:

End point type	Secondary

End point timeframe:

During first 6 months

End point values	Tranexamic acid	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	480	475		
Units: 0-1				
Alive at 6 mo	352	361		
Diseased at 6 mo	128	114		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: During hospital admission	
Assessment type	Non-systematic
Dictionary used	
Dictionary name	pre defined def
Dictionary version	1
Reporting groups	
Reporting group title	Tranexamic acid
Reporting group description: -	
Reporting group title	Control
Reporting group description: Standard care	

Serious adverse events	Tranexamic acid	Control	
Total subjects affected by serious adverse events			
subjects affected / exposed	386 / 480 (80.42%)	372 / 475 (78.32%)	
number of deaths (all causes)	128	114	
number of deaths resulting from adverse events			
Vascular disorders			
Subarachnoid haemorrhage	Additional description: Recurrent bleeding		
alternative assessment type: Systematic			
subjects affected / exposed	49 / 480 (10.21%)	66 / 475 (13.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ruptured cerebral aneurysm	Additional description: Recurrent bleeding confirmed by CT		
alternative assessment type: Systematic			
subjects affected / exposed	42 / 480 (8.75%)	57 / 475 (12.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage			
alternative assessment type: Systematic			
subjects affected / exposed	29 / 480 (6.04%)	34 / 475 (7.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Surgical and medical procedures			
Thrombosis	Additional description: During endovascular treatment		
subjects affected / exposed[1]	29 / 272 (10.66%)	33 / 258 (12.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ruptured cerebral aneurysm coil	Additional description: Per-Procedural rupture during coiling		
alternative assessment type: Systematic			
subjects affected / exposed[2]	16 / 272 (5.88%)	12 / 258 (4.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ruptured cerebral aneurysm clip	Additional description: Per-procedural rupture during clipping		
alternative assessment type: Systematic			
subjects affected / exposed[3]	17 / 86 (19.77%)	22 / 88 (25.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Hydrocephalus			
alternative assessment type: Systematic			
subjects affected / exposed	292 / 480 (60.83%)	262 / 475 (55.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infarction DCI	Additional description: Delayed cerebral ischemia		
alternative assessment type: Systematic			
subjects affected / exposed	108 / 480 (22.50%)	106 / 475 (22.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infarction	Additional description: Cerebral infarction related to clipping procedure		
alternative assessment type: Systematic			
subjects affected / exposed[4]	22 / 86 (25.58%)	18 / 88 (20.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			

subjects affected / exposed	59 / 480 (12.29%)	40 / 475 (8.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium			
subjects affected / exposed	65 / 480 (13.54%)	60 / 475 (12.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Thrombosis	Additional description: Deep venous thrombosis		
alternative assessment type: Systematic			
subjects affected / exposed	0 / 480 (0.00%)	2 / 475 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
alternative assessment type: Systematic			
subjects affected / exposed	6 / 480 (1.25%)	5 / 475 (1.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia	Additional description: Severe <=125mmol/L		
alternative assessment type: Systematic			
subjects affected / exposed	12 / 480 (2.50%)	9 / 475 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
General symptom	Additional description: All other SAE not pre-specified		
subjects affected / exposed	134 / 480 (27.92%)	126 / 475 (26.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Eye haemorrhage	Additional description: Terson Syndrome		
subjects affected / exposed	18 / 480 (3.75%)	18 / 475 (3.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			

Urinary tract infection			
subjects affected / exposed	44 / 480 (9.17%)	45 / 475 (9.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	63 / 480 (13.13%)	67 / 475 (14.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis			
alternative assessment type: Systematic			
subjects affected / exposed	37 / 480 (7.71%)	31 / 475 (6.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Subset of patients

[2] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Subset of patients

[3] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Subset of patients

[4] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Subset of patients

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

Non-serious adverse events	Tranexamic acid	Control	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	277 / 480 (57.71%)	254 / 475 (53.47%)	
General disorders and administration site conditions			
Other adverse events	Additional description: All not prespecified adverse events		
subjects affected / exposed	277 / 480 (57.71%)	254 / 475 (53.47%)	
occurrences (all)	0	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

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

Treatment with tranexamic acid was not masked.
Relative high proportion of patient without underlying aneurysm

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/23680226

http://www.ncbi.nlm.nih.gov/pubmed/32070395

http://www.ncbi.nlm.nih.gov/pubmed/33357465