Clinical trial results:
Tranexamic Acid to reduce bleeding in patients treated with new oral anticoagulants undergoing dental extraction (EXTRACT-NOAC)

Summary

EudraCT number	2017-001426-17
Trial protocol	BE
Global end of trial date	19 March 2020

Results information

Result version number	v1 (current)
This version publication date	13 June 2021
First version publication date	13 June 2021
Summary attachment (see zip file)	EXTRACT-NOAC (2021.05_Ockerman_PlosMed_EXTRACT-NOAC.pdf)

Trial information

Trial identification

Sponsor protocol code	1M

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03413891
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University Hospitals Leuven
Sponsor organisation address	Herestraat 49, Leuven, Belgium, 3000
Public contact	Barbara Debaveye, Universitary Hospitals Leuven (Gasthuisberg), 032 16341463, barbara.debaveye@uzleuven.be
Scientific contact	Barbara Debaveye, Universitary Hospitals Leuven (Gasthuisberg), 032 16341463, barbara.debaveye@uzleuven.be

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	19 October 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 March 2020
Global end of trial reached?	Yes
Global end of trial date	19 March 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate whether TXA mouthwash reduces post-extraction bleeding in patients who undergo dental extraction and are treated with NOACs

Protection of trial subjects:

Potential risks of systemic administration of TXA, as reported by the package insert, include convulsions, blurred vision, haematuria and thrombo-embolism. However, none of these potential risks have been shown to be present in case of mouthwash as compared to systemic administration. This can be explained by the low systemic TXA levels in case of administration by mouthwash.
Therefore, the immediate potential risk of TXA mouthwash is limited to:

- Allergic reaction
- Bleeding in case of extensive or traumatic mechanical rinsing

There are no known long-term risks. Because of these limited potential risks, the potential benefit of this treatment is expected to outweigh the risks.

Background therapy:

0

Evidence for comparator:

0

Actual start date of recruitment	07 February 2018
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	Belgium: 222
Worldwide total number of subjects	222
EEA total number of subjects	222

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)	33
From 65 to 84 years	163
85 years and over	26

Subject disposition

Recruitment

Recruitment details:

First patient first visit: 7 feb 2018
Last patient last visit: 19 nov 2020
Total randomized patients: 222

Pre-assignment

Screening details:

293 patients were assessed for eligibility, of whom 71 patients were not eligible:
- 35 declined to participate
- 29 did not meet inclusion criteria
- 4 language barriers
- 3 tooth extractions annulated

Pre-assignment period milestones

Number of subjects started	222
Number of subjects completed	222

Period 1

Period 1 title	Patients Full Analysis Set (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

A computer-generated block-randomization list will be generated by an independent person for treatment allocation. Labeling of the study drug and matched placebo will occur by an independent person.

Arms

Are arms mutually exclusive?	Yes
Arm title	tranexamic acid

Arm description:

10% (1g/10mL) tranexamic acid mouthwash, 10 doses: 1 dose immediately prior to dental extraction, 3 doses per day for 3 days thereafter.

Arm type	Experimental
Investigational medicinal product name	tranexamic acid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Mouthwash
Routes of administration	Topical use

Dosage and administration details:

10 doses: 1 dose immediatly prior to dental extraction, 3 doses per day for 3 days thereafter.

Arm title	Placebo

Arm description:

cherry-flavoured water as mouthwash, 10 doses: 1 dose immediately prior to dental extraction, 3 doses per day for 3 days thereafter.

Arm type	Placebo

Investigational medicinal product name	cherry-flavoured water
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Mouthwash
Routes of administration	Topical use

Dosage and administration details:

1 dose immediately prior to dental extraction, 3 doses per day for 3 days thereafter.

Number of subjects in period 1	tranexamic acid	Placebo
Started	108	114
Completed	106	112
Not completed	2	2
Lost to follow-up	2	1
Protocol deviation	-	1

Baseline characteristics

Reporting groups	
Reporting group title	tranexamic acid
Reporting group description:	
10% (1g/10mL) tranexamic acid mouthwash, 10 doses: 1 dose immediately prior to dental extraction, 3 doses per day for 3 days thereafter.	
Reporting group title	Placebo
Reporting group description:	
cherry-flavoured water as mouthwash, 10 doses: 1 dose immediately prior to dental extraction, 3 doses per day for 3 days thereafter.	

Reporting group values	tranexamic acid	Placebo	Total
Number of subjects	108	114	222
Age categorical			
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)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Age of all patients included in the full analysis set			
Units: years			
arithmetic mean	75	73	
standard deviation	± 8.9	± 10.7	-
Gender categorical			
Gender of all patients included in the full-analysis set			
Units: Subjects			
Female	27	48	75
Male	81	66	147
NOAC type			
Patients treated with all four types of NOACs, currently available on the market, were included			
Units: Subjects			
rivaroxaban	38	42	80
apixaban	30	33	63
edoxaban	22	19	41
dabigatran	18	20	38

End points

End points reporting groups

Reporting group title	tranexamic acid
Reporting group description:	
10% (1g/10mL) tranexamic acid mouthwash, 10 doses: 1 dose immediately prior to dental extraction, 3 doses per day for 3 days thereafter.	
Reporting group title	Placebo
Reporting group description:	
cherry-flavoured water as mouthwash, 10 doses: 1 dose immediately prior to dental extraction, 3 doses per day for 3 days thereafter.	

Primary: Patients with oral bleeds until 7 days after dental extraction

End point title	Patients with oral bleeds until 7 days after dental extraction
End point description:	
End point type	Primary
End point timeframe:	
From the day of the dental extraction until 7 days thereafter.	

End point values	tranexamic acid	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	106	112[1]		
Units: whole	28	32		

Notes:

[1] - 32

Statistical analyses

Statistical analysis title	Analysis primary endpoint
Comparison groups	tranexamic acid v Placebo
Number of subjects included in analysis	218
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.72
Method	Chi-squared
Parameter estimate	Risk ratio (RR)
Point estimate	0.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.31
upper limit	1.05

Secondary: Type and number of oral bleeds until 7 days after dental extraction

End point title	Type and number of oral bleeds until 7 days after dental extraction

End point description:

Bleedings are defined as:
- Minor bleeding: any oral bleeding experienced by the patient that does not require medical contact. Eg. blood on the pillow, bleeding requiring the use of additional gauzes, clear red bleeding when spitting out the mouthwash
- Clinically relevant bleeding: any oral non-major bleeding requiring unplanned medical contact (by phone or with any health care professional (dentist, general practitioner, maxillofacial surgeon), with or without re-intervention
- Early bleeding: any oral bleeding occurring after the extraction up to and including day 1 after the extraction
- Delayed bleeding: any oral bleeding occurring between day 2 and day 7

End point type	Secondary

End point timeframe:

From the day of the dental extraction until 7 days thereafter.

End point values	tranexamic acid	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	106	112		
Units: whole				
All oral bleeds	46	85		
Clinically relevant oral bleeds	5	13		
Minor oral bleeds	41	72		
Early oral bleeds	35	49		
Delayed oral bleeds	11	36		

Statistical analyses

Statistical analysis title	Analysis secondary oral bleeding endpoints

Statistical analysis description:

The secondary outcomes were were analyzed by means of a logistic regression (for the number of patients with oral bleeds) and negative-binomial regression model (for the number of oral bleeds). The treatment effect was estimated as a rate ratio (the number of bleeds per patient during the first seven days after dental extraction).

Comparison groups	tranexamic acid v Placebo
Number of subjects included in analysis	218
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.07 [2]
Method	negative-binomial regression model
Parameter estimate	rate ratio
Point estimate	0.57

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.31
upper limit	1.05

Notes:

[2] - P-value is given for all oral bleeding events.

Secondary: Number of reinterventions for oral bleeding

End point title	Number of reinterventions for oral bleeding

End point description:

A reintervention is defined as any procedure in the oral cavity for the treatment of bleeding, performed by any dentist or maxillofacial surgeon, except for rinsing the extraction socket with saline.

End point type	Secondary

End point timeframe:

from day of dental extraction until 7 days thereafter

End point values	tranexamic acid	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	106	112		
Units: whole	7	13		

Statistical analyses

Statistical analysis title	Sec. Outcome number of reinterventions
Comparison groups	tranexamic acid v Placebo
Number of subjects included in analysis	218
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.37
Method	negative-binomial regression model
Parameter estimate	Rate Ratio
Point estimate	0.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.17
upper limit	1.91

Secondary: Number of unplanned medical contacts

End point title	Number of unplanned medical contacts

End point description:

End point type	Secondary

End point timeframe:

From the day of dental extraction until 7 days thereafter

End point values	tranexamic acid	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	106	112		
Units: whole	10	27		

Statistical analyses

Statistical analysis title	Sec. Outcome number of unplanned medical contacts
Comparison groups	tranexamic acid v Placebo
Number of subjects included in analysis	218
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.04
Method	negative-binomial regression model
Parameter estimate	Rate Ratio
Point estimate	0.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.16
upper limit	0.98

Secondary: Number of NOAC interruptions

End point title	Number of NOAC interruptions

End point description:

End point type	Secondary

End point timeframe:

From re-intake of the NOAC after dental extraction until 7 days after dental extraction

End point values	tranexamic acid	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	106	112		
Units: whole	6	9		

Statistical analyses

Statistical analysis title	Sec. Outcome number of NOAC interruptions
Comparison groups	tranexamic acid v Placebo
Number of subjects included in analysis	218
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.66
Method	Chi-squared
Parameter estimate	Risk ratio (RR)
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.26
upper limit	1.91

Secondary: Number of non-oral bleeds

End point title	Number of non-oral bleeds
End point description:	
End point type	Secondary
End point timeframe:	
From day of the dental extraction until 7 days thereafter	

End point values	tranexamic acid	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	106	112		
Units: whole	12	30		

Statistical analyses

Statistical analysis title	Sec. Outcome number of non-oral bleeds
Comparison groups	tranexamic acid v Placebo

Number of subjects included in analysis	218
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.01
Method	negative-binomial regression model
Parameter estimate	Rate Ratio
Point estimate	0.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.18
upper limit	0.78

Other pre-specified: Safety endpoint from inclusion until last visit

End point title	Safety endpoint from inclusion until last visit
End point description: thrombotic events	
End point type	Other pre-specified
End point timeframe: From inclusion until last visit	

End point values	tranexamic acid	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	106	112		
Units: whole	0	1		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

From inclusion until 7 days after dental extraction.

Assessment type	Systematic

Dictionary used

Dictionary name	short description
Dictionary version	0

Reporting groups

Reporting group title	Tranexamic acid

Reporting group description:

10% (1g/10mL) tranexamic acid mouthwash, 10 doses: 1 dose immediately prior to dental extraction, 3 doses per day for 3 days thereafter.

Reporting group title	Placebo

Reporting group description:

cherry-flavoured water as mouthwash, 10 doses: 1 dose immediately prior to dental extraction, 3 doses per day for 3 days thereafter.

Serious adverse events	Tranexamic acid	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 108 (0.00%)	0 / 114 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Tranexamic acid	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 108 (0.00%)	0 / 114 (0.00%)	

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: Adverse events (non-oral bleeds and thrombotic events) were recorded as endpoints.

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