Tranexamic Acid To Reduce Bleeding in Patients Treated with New Oral Anticoagulants Undergoing Dental Extraction (EXTRACT-NOAC)

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Sponsor:

University Hospitals Leuven, Herestraat 49, 3000 Leuven

Principal Investigator:

Peter Verhamme

UZ Leuven Gasthuisberg

Cardiovascular Medicine

Herestraat 49

3000 Leuven

peter.verhamme@uzleuven.be

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LIST OF ABBREVIATIONS

AE	Adverse Event
CRF	Case Report Form
FDA	Food and Drug Administration
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
LMWH	Low Molecular Weight Heparin
NOAC	New Oral Anticoagulant
NSAID	Non-steroidal anti-inflammatory drug
SAE	Serious Adverse Event
SAP	Statistical and Analytical Plan
TXA	Tranexamic Acid
VAS	Visual Analogue Scale
VKA	Vitamin K Antagonist

STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with Good Clinical Practice (GCP, ICH E6). The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants.

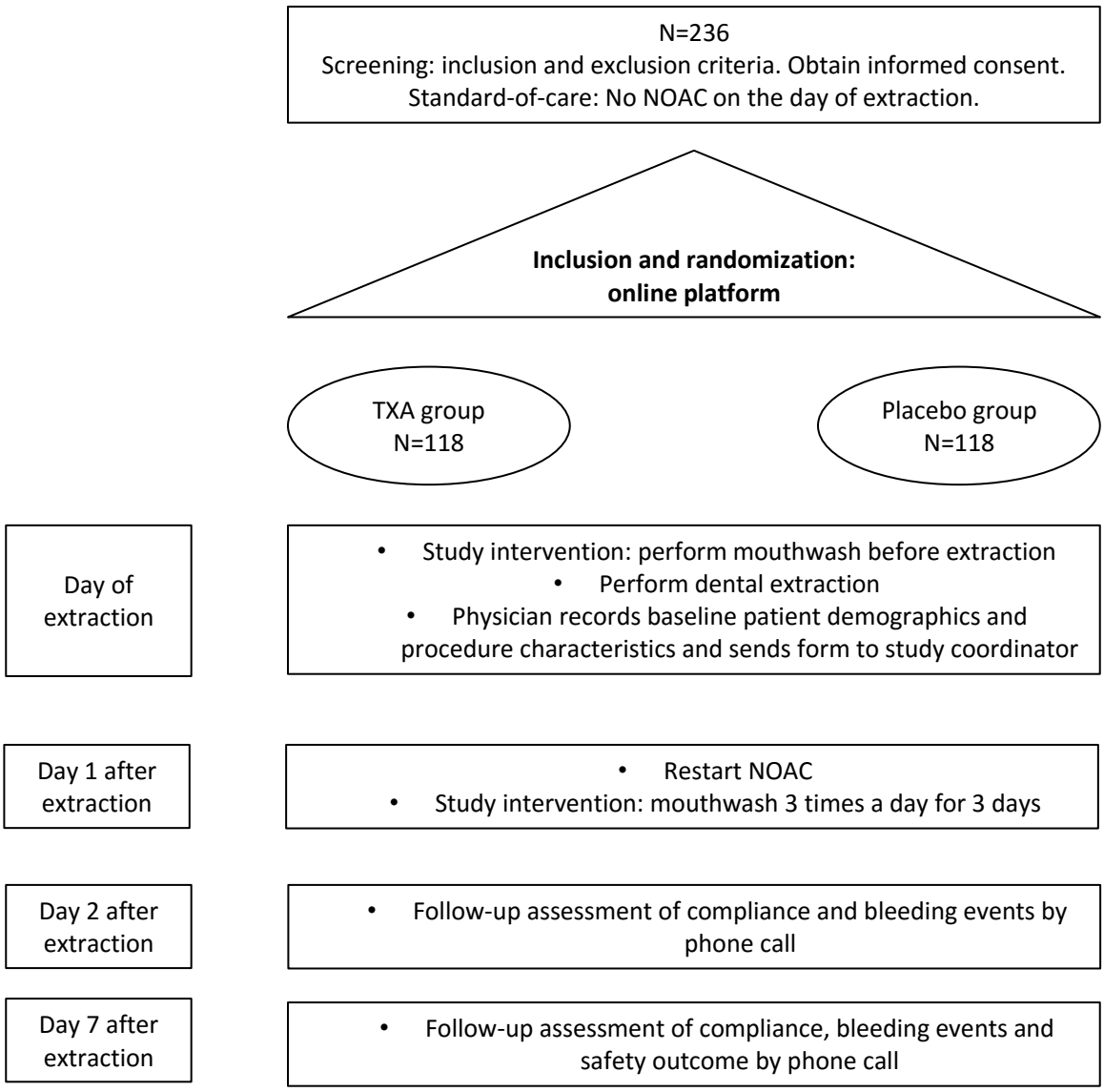
Principal Investigator: Prof. Dr. Peter Verhamme

Signed: _____ Date: _____

PROTOCOL SUMMARY

Title:	Tranexamic Acid To Reduce Bleeding in Patients Treated with New Oral Anticoagulants Undergoing Dental Extraction
Acronym:	EXTRACT-NOAC
Précis:	Two hundred thirty-six patients treated with NOACs and scheduled for dental extraction will be randomized to tranexamic acid mouthwash 10% or placebo: one administration before extraction and 3 times daily on day 1 till day 3 after extraction. Bleeding events will be evaluated on day 2 and day 7.
Objectives:	Primary objective: To evaluate whether TXA mouthwash reduces the number of oral bleeding events in patients who undergo dental extraction and are treated with NOACs .
Outcome:	Primary outcome: Any oral bleeding (early or delayed; minor or clinically relevant) from randomization till end of study follow-up)
Population:	Patients treated with a NOAC, aged 18 years or older undergoing dental extraction
Phase:	Phase IV
Number of Sites enrolling participants:	2 Site 1: University Hospitals Leuven, Belgium Site 2: Ziekenhuis Oost-Limburg, Genk, Belgium
Description of Study Agent :	Tranexamic acid mouthwash (1g in 10ml, 10%) before extraction and 3 times daily on day 1 till day 3 after extraction
Study Duration:	24 months
Participant Duration:	7 days

SCHEMATIC OF STUDY DESIGN



1 KEY ROLES

1. Principal Investigator

Name	Peter Verhamme, MD, PhD
Title	Principal investigator
Address	UZ Leuven. Cardiovascular Medicine. Herestraat 49, 3000 Leuven. Belgium.
Phone	0032 16 344235
E-mail	peter.verhamme@uzleuven.be

2. Assistant

Name	Isabel Craessaerts
Title	Assistant
Address	UZ Leuven. Bloedings- en vaatziekten. Herestraat 49, 3000 Leuven. Belgium.
Phone	0032 16 343533
E-mail	isabel.craessaerts@uzleuven.be

3. Study Coordinator

Name	Barbara Debaveye
Title	Research coordinator
Address	UZ Leuven. Studiesecretariaat BLV. Herestraat 49, 3000 Leuven. Belgium
Phone	0032 16 343474
Fax	0032 16 343493
E-mail	barbara.debaveye@uzleuven.be

4. Pharmacy

Name	Stefanie Goris
Title	Pharmacist
Address	UZ Leuven. Apotheek. Herestraat 49, 3000 Leuven. Belgium
Phone	0032 16 342835
E-mail	stefanie.1.goris@uzleuven.be

5. Manufacturing contractor (unblinded)

Name	Els Ampe
Title	Investigational Medicinal Product - Responsible
Address	Center for Clinical Pharmacology. Herestraat 49, 3000 Leuven. Belgium
Phone	0032 16 342020
E-mail	els.ampe@uzleuven.be

6. Co-principal Investigators

Name	Constantinus Politis, MD, PhD
Title	co-principal investigator
Address	UZ Leuven Sint-Rafael. Mond-Kaak en Aangezichtschirurgie. Kapucijnenvoer 33, 3000 Leuven
Phone	0032 16 332462
E-mail	stan@politis.be

Name	Isabel Miclotte, MD
Title	co-principal investigator
Address	UZ Leuven Sint-Rafael. Mond-Kaak en Aangezichtschirurgie. Kapucijnenvoer 33, 3000 Leuven
Phone	0032 16 332462
E-mail	isabel.miclotte@uzleuven.be

Name	Thomas Vanassche, MD, PhD
Title	co-principal investigator
Address	UZ Leuven. Cardiovascular Medicine. Herestraat 49, 3000 Leuven. Belgium.
Phone	0032 16 344235
E-mail	thomas.vanassche@uzleuven.be

Name	Maarten Vanhaverbeke, MD
Title	co-principal investigator
Address	UZ Leuven. Cardiovascular Medicine. Herestraat 49, 3000 Leuven. Belgium.
Phone	0032 16 344235
E-mail	maarten.vanhaverbeke@uzleuven.be

2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 BACKGROUND INFORMATION

Since the introduction of new oral anticoagulant drugs (NOACs), the number of patients treated with this class of antithrombotics is steadily increasing. For major surgical procedures, vitamin K antagonists (VKAs) are discontinued prior to the procedure and resumed thereafter. Temporary interruption of VKA treatment confers both an ischemic as well as bleeding risk. This is caused by complex pharmacokinetics during interruption, the long half-life of VKA, and concomitant bridging therapy with low molecular weight heparins (LMWH). Since there is no increased risk of major bleeding when performing minor procedures such as dental extractions on stable VKA treatment, it is current practice not to discontinue VKAs for dental extractions (1).

In contrast to VKA, little evidence is available for the periprocedural management of NOACs in dental extractions (2). The current guidelines of the European Heart Rhythm Association advise to perform dental extractions at trough level (3-6). However, in clinical practice it can be complicated to schedule the extraction at the time of the day corresponding to trough plasma levels.

We have therefore recently shown that a standardized pragmatic approach in patients who undergo dental extractions, by skipping only the dose on the morning of the extraction, regardless of timing of extraction, drug regimen or renal function, is feasible and safe (7). In a total of 52 patients, there was no difference in the procedural bleeding score or in early bleeding between NOAC patients and controls (patients without any antithrombotics). However, delayed bleeding between day 1 and day 7 occurred more frequently in anticoagulated compared to non-anticoagulated patients (7 versus none, p=0.01). Similarly, an increase in bleeding during the first postoperative week was reported in a retrospective study in patients undergoing dental extraction under uninterrupted NOAC treatment (8). The combination of peak plasma levels of the NOAC with an immature coagulum at the extraction site could trigger bleeding.

Since bleeding events can lead to unscheduled interruption of NOAC treatment and subsequent increased risk of thrombo-embolic events, an optimal strategy to minimize bleeding events after dental extractions is required. In this interventional phase IV study, we want to assess whether adding tranexamic acid (TXA) mouthwash reduces the number of bleeding events in patients treated with NOACs undergoing a dental extraction.

2.2 RATIONALE

The aim of this study is to evaluate whether adding TXA 10% mouthwash to standard-of-care (i.e. performing the extraction at trough level by skipping the NOAC on the day of the extraction) will decrease the number of bleeding events.

TXA is an antifibrinolytic agent that reversibly inhibits plasminogen, preventing plasmin from degrading fibrin. Oral administration of TXA is approved in the United States by the FDA to prevent bleeding in patients with hemophilia undergoing dental extraction. To avoid any possible prothrombogenic effects in an unselected patient population or accumulation in case of renal insufficiency, there is increased interest in topical administation of TXA. It has been shown that upon systemic administration of 1g TXA, peak plasma levels reach 7µg/mL, whithout detectable levels in saliva. However, when administering a 10ml 5% TXA mouthwash, plasma levels remained low (below 2µg/mL) while the levels in saliva remained at therapeutic level for two hours (9). TXA mouth wash is therefore the suitable route of administration, and is considered safe without evidence for prothrombotic effects (10).

Two studies have shown that TXA 5% mouthwash during 7 days after dental extraction significantly reduces the number of bleeding events in patients treated with VKA (11, 12). A third study showed no difference between a 2-day TXA regimen compared to 5 days (13). In Belgium, 10% TXA mouthwash unidoses are commercially available in packages of 10 doses. Therefore, we opt to treat patients with 10% TXA mouthwash for 3 days, 3 times a day (9 doses) starting on the day after the dental extraction. In order not to mechanically dislodge the immature coagulum, there is no post-extraction mouthwash, but one additional mouthwash is performed immediately prior to the dental procedure.

The control group will receive a water solution, which does not confer any issues. All patients older than 18 years, treated with a NOAC and scheduled for dental extraction are eligible for inclusion.

2.3 POTENTIAL RISKS AND BENEFITS

2.3.1 KNOWN POTENTIAL RISKS

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 (10). This can be explained by the low systemic TXA levels in case of administration by mouthwash (9).
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.

2.3.2 KNOWN POTENTIAL BENEFITS

Local administration of TXA is known to reduce bleeding, resulting in immediate potential benefits:

- In patients on VKA treatment, TXA 5% mouthwash reduced the number of bleeding events (11, 12).
- In patients undergoing surgery, local administration of TXA significantly reduced the number of bleeding events (10).

Since a reduction of bleeding would possibly result in less unplanned discontinuation of the NOAC, a reduction in thrombo-embolic events caused by NOAC cessation can be expected, although the current study will not be powered to evaluate this long-term benefit.

3 OBJECTIVES AND PURPOSE

Primary objective:

- To evaluate whether TXA mouthwash 10% reduces the number of oral bleeding events in patients treated with NOACs and undergoing dental extraction.

Secondary objectives:

- To evaluate whether TXA mouthwash before the extraction reduces the bleeding during the procedure.
- To evaluate whether TXA mouthwash reduces early and/or delayed bleeding events
- To evaluate whether TXA mouthwash reduces minor, clinically relevant or major bleeding events or reinterventions.
- To evaluate whether TXA mouthwash reduces the number of unplanned NOAC interruptions.
- To evaluate the safety of skipping the dose of the NOAC on the day of the extraction.

Exploratory analyses:

- To investigate the potential relationship between time of last NOAC dose administered prior to the extraction (regardless of specific NOAC type), time of resuming NOAC after the procedure, and bleeding events
- To investigate the potential benefit of TXA in subgroups of patients (molar versus non-molar extraction)

4 STUDY DESIGN AND OUTCOMES

4.1 DESCRIPTION OF THE STUDY DESIGN

This is a randomized, double-blind, placebo-controlled, multi-center phase IV clinical trial assessing the benefit of TXA mouthwash.

4.2 STUDY OUTCOMES

The procedural bleeding score is a visual analogue score (VAS) ranging from 0 (no bleeding) to 10 (unstoppable bleeding).
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.
All suspected bleeding events and reinterventions will be adjudicated by a blinded adjudicator, unaware of the assigned treatment.

Bleedings are defined as previously published (7):

- 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 non-major 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
- Major bleeding: any oral bleeding requiring blood transfusion, hospitalization or resulting in death
- 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

4.2.1 PRIMARY OUTCOME

- Any oral bleeding (early or delayed; minor or clinically relevant)

4.2.2 SECONDARY OUTCOMES

- The procedural bleeding score
- Early and delayed bleeding
- Minor, clinically relevant non-major and major bleeding
- Clinically-relevant bleeding (non-major and major)

- The number of reinterventions
- The number of unplanned NOAC interruptions

Safety outcomes:

- Any non-oral bleeding
- All thrombotic events including myocardial infarction, stroke, systemic embolism and venous thrombo-embolism up to the endo of study follow-up.

4.2.3 EXPLORATORY OUTCOMES

The following subgroup analyses are planned:

- Risk factor analysis for bleeding, eg. patient demographics and procedural characteristics
- The number of bleeding events in patients in relation to the time since stopping and resuming NOAC in relation to the dental extraction, e.g. in patients who stopped/resumed NOAC treatment within 24 hours prior/after extraction compared to more than 24 hours prior/after extraction.

5 STUDY ENROLLMENT AND WITHDRAWAL

5.1 PARTICIPANT INCLUSION CRITERIA

- Patients scheduled for dental extraction and treated with edoxaban, apixaban, rivaroxaban or dabigatran
- Not having taken the NOAC on the day of the extraction
- Provision of signed and dated informed consent form
- Stated willingness to comply with all study procedures and availability for the duration of the study
- 18 years or older

5.2 PARTICIPANT EXCLUSION CRITERIA

- Subjects with any condition that as judged by the Investigator would place the subject at increased risk of harm if he/she participated in the study.
- Pregnancy or lactation
- Known allergic reaction to TXA

5.3 STRATEGIES FOR RECRUITMENT AND RETENTION

All patients undergoing dental extraction at the outpatient clinic of the registered sites will be screened for eligibility before their dental extraction. Standard-of-care (discontinuation of the NOAC on the day of the procedure) is already implemented in the participating site. Adherence to the study protocol will be assessed by phone call on day 2 and day 7.

5.4 PARTICIPANT WITHDRAWAL OR TERMINATION

5.4.1 REASONS FOR WITHDRAWAL OR TERMINATION

Participants are free to withdraw from participation in the study at any time upon request. An investigator may terminate participation in the study if:

- Any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.

5.4.2 HANDLING OF PARTICIPANT WITHDRAWALS OR TERMINATION

When a participant is withdrawn from the study, planned follow-up by phone call will be continued, unless the patients does not provide consent to follow-up. However, all data collected prior to discontinuation from the study will be retained in the database.

5.5 PREMATURE TERMINATION OR SUSPENSION OF STUDY

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension.
Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable

Study may resume once concerns about safety, protocol compliance, data quality are addressed

6 STUDY AGENT

6.1 STUDY AGENT(S) AND CONTROL DESCRIPTION

6.1.1 ACQUISITION

Blinded 10% TXA mouthwash or placebo will be manufactured in collaboration with the Center of Clinical Pharmacology, University Hospitals Leuven

6.1.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

- Active treatment: 10 doses of 10% TXA mouthwash 10ml, blinded, in oral syringes, labeled according to randomization scheme
- Placebo: 10 doses of 10ml water with addition of white cherry flavor, in oral syringes, labeled according to randomization scheme

6.1.3 PRODUCT STORAGE AND STABILITY

Repackaged TXA 10% in 10ml oral syringes (Exacta-Med, Bayer) will be submitted for stability testing to Phasius, Stevinstraat 137, 1000 Brussels. As backup, 100ml TXA 10% in glass bottles will be tested for stability (room temperature and refrigerated). Batches of 100 syringes (equivalent of 10 patients) will be delivered to the sites.

6.1.4 PREPARATION

TXA 10% oral ampoules will be repackaged into blinded and labeled 10ml Exacta-Med oral syringes. For placebo, white cherry flavor will be added to water up to 10ml and packaged in blinded and labeled 10ml Exacta-Med oral syringes.

6.1.5 DOSING AND ADMINISTRATION

- 10ml 10% TXA mouthwash before dental extraction
- 10ml 10% TXA mouthwash from day 1 until day 3, 3 times a day (morning, noon, evening)

6.1.6 ROUTE OF ADMINISTRATION

10 ml mouthwash

6.1.7 STARTING DOSE AND DOSE ESCALATION SCHEDULE

1g TXA in 10ml (10%) mouthwash

6.1.8 DOSE ADJUSTMENTS/MODIFICATIONS/DELAYS

No dose adjustments

6.1.9 DURATION OF THERAPY

Until and including day 3 after extraction.

6.1.10 TRACKING OF DOSE

Adherence to study treatment will be assessed during the follow-up phone calls at day 2 and day 7.

6.2 STUDY AGENT ACCOUNTABILITY PROCEDURES

TXA 10% mouthwash is used on-label in this study. A service level agreement between the investigators and manufacturing contractor will be made in agreement with good clinical, pharmacological and manufacturing practice.

7 STUDY PROCEDURES AND SCHEDULE

7.1 STUDY PROCEDURES/EVALUATIONS

7.1.1 STUDY SPECIFIC PROCEDURES

- Mouthwash: patients are instructed to gently rinse the mouth with 10ml of 10% TXA or placebo for 1 minute and to spit out the mouthwash thereafter.
- Patients will be given 9 vials of 10ml 10% TXA or placebo and instructed to rinse 3 times a day for 3 days, starting the day after the procedure. Patients will be instructed to monitor and record bleeding events.
- Patients will be contacted be telephone call on day 2 and day 7, and the prespecified outcomes will be assessed.
- In case of unplanned medical contact, the prespecified outcomes will be assessed as planned by phone call, and in addition, additional relevant medical data on the type of unplanned medical contact will be identified from the medical file.

7.1.2 STANDARD OF CARE STUDY PROCEDURES

- No NOAC dose is to be taken on the day of the procedure
- Dental extraction is then performed according to the current and local standard-of-care, at the discretion of the treating physician. The use of additional hemostatic measures is permitted but will be recorded.
- Patients will be instructed to restart the NOAC the day after the extraction, according to current standard-of-care.
- Any other antithrombotic medication is to be continued

7.2 LABORATORY PROCEDURES/EVALUATIONS

Not applicable

7.3 STUDY SCHEDULE

7.3.1 SCREENING

- Review medical history and medication to determine eligibility based on inclusion/exclusion criteria (age and use of NOAC).
- Obtain informed consent of potential participant verified by signature on study informed consent form.
- Randomize patient (investigator takes next batch of pre-randomized study medication)

7.3.2 ENROLLMENT/BASELINE

- Assess patient characteristics:
    - Age
    - Sex
    - Date of birth
    - Alcohol and tobacco use
    - Phone number for follow-up calls
    - NOAC type: rivaroxaban, apixaban, dabigatran, edoxaban
    - NOAC dose and regimen
    - NOAC indication
    - Date and time of last NOAC dose
    - Serum creatinine when available (up to 12 months before inclusion)
    - Other antithrombotic drugs: aspirin (Asaflow®, Cardio-aspirine®), clopidogrel (Plavix®), ticagrelor (Brilique®), prasugrel (Efient®), dipyridamole (Aggrenox®), LMWH
    - Non-steroidal anti-inflammatory drug use (eg. ibuprofen)
    - Record full list of medication in the medical file
- Administer the study treatment
- Perform dental extraction
- Assess procedure characteristics:
    - Date and time of extraction
    - Number of extracted teeth
    - Teeth numbers
    - Stitches: yes/no
    - Persistent infection: yes/no
    - Burring: yes/no
    - Procedural bleeding score (0-10)
    - Use of additional hemostatic measures: eg. tranexamic acid gauze
    - Prophylactic antibiotics: yes/no
- Instructions to patient:
    - Supply patient with 9 vials of mouthwash
    - Supply patients with instructions to perform mouthwash starting 1 day after extraction, 3 times a day for 3 days
    - Instruct patients to restart NOAC the day after the extraction according to their normal regimen
    - Instruct patients to write down any signs of bleeding

7.3.3 FOLLOW-UP

Follow-up assessment on day 2 (phone call). In case this would be a Saturday, follow-up can be performed on Friday afternoon. In case this would be a Sunday, follow-up can be performed on Monday.

- Date and time of assessment
- Date and time of restarting NOAC
- Did patient use mouthwash day after the extraction: yes/no
- Bleeding assessment:
    - Blood on pillow, additional gauze, other: yes/no
    - Blood when brushing teeth: yes/no
    - Blood when rinsing with mouthwash: yes/no
    - Date and time of bleeding
    - Unplanned medical contact (by phone, new consultation or hospitalization) with any health care professional (dentist, general practioner, maxillofacial surgeon): yes/no
- In case of unplanned medical contact:
    - Date and time
    - Reason (adjudicated): bleeding - infection - death - other (specify)
    - Treatment: no treatment - oral antibiotics - only rinsing with saline - hemostasis with gauze - hemostasis with coagulation - removal of false coagulum - new sutures - blood transfusion - hospitalization
- Unplanned interruption of NOAC: yes/no
- AE and SAE assessment

7.3.4 FINAL STUDY VISIT

Follow-up assessment on day 7 (phone call). In case this would be a Saturday, follow-up can be performed on Friday afternoon. In case this would be a Sunday, follow-up can be performed on Monday.

- Date and time of assessment
- Number of used study drug vials
- Bleeding assessment between day 2 and day 7:
    - Blood on pillow, additional gauze, other: yes/no
    - Blood when brushing teeth: yes/no
    - Blood when rinsing with mouthwash: yes/no
    - Date and time of bleeding
    - Unplanned medical contact (by phone, new consultation or hospitalization) with any health care professional (dentist, general practioner, maxillofacial surgeon): yes/no
- In case of unplanned medical contact:
    - Date and time
    - Reason (adjudicated): bleeding - infection - death - other (specify)
    - Treatment: no treatment - oral antibiotics - only rinsing with saline - hemostasis with gauze - hemostasis with coagulation - removal of false coagulum - new sutures - blood transfusion - hospitalization
- Unplanned interruption of NOAC: yes/no
- Any signs or symptoms or established diagnosis of stroke, myocardial infarction, deep vein thrombosis or pulmonary embolism
- Any non-oral bleeding
- AE and SAE assessment

7.3.5 EARLY TERMINATION VISIT

Not applicable.

7.3.6 UNSCHEDULED VISIT

In case of unplanned medical contact, the prespecified outcomes will be assessed as planned by phone call, and in addition, additional relevant medical data on the type of unplanned medical contact will be identified from the medical file. All suspected bleeding events and reinterventions will be adjudicated by a blinded adjudicator, unaware of the assigned treatment.

7.3.7 SCHEDULE OF EVENTS TABLE

Procedures	Screening	Day 0 Baseline	Day 2 Follow-up	Day 7 Follow-up
Assess inclusion and exclusion criteria	x			
Informed consent	x			
Randomization	x			
Patient characteristics		x		
Procedure characteristics		x		
Study drug administration		x	x (up to day 3)	
Outcome assessment			x	x
Adverse events			x	x
Serious adverse events			x	x

7.4 JUSTIFICATION FOR SENSITIVE PROCEDURES

Not applicable

7.5 CONCOMITANT MEDICATIONS, TREATMENTS, AND PROCEDURES

The use of the concomitant medication will be recorded in the CRF, including:

- Other antithrombotic drugs: aspirin (Asaflow®, Cardio-aspirine®), clopidogrel (Plavix®), ticagrelor (Brilique®), prasugrel (Efient®), dipyridamole (Aggrenox®), LMWH
- Non-steroidal anti-inflammatory drug use (eg. ibuprofen)

7.6 PROHIBITED MEDICATIONS, TREATMENTS, AND PROCEDURES

In patients treated with NOACs, the use of NSAIDs should be limited according to the current standard-of-care, and is left at the discretion of the treating physician.

7.7 PROPHYLACTIC MEDICATIONS, TREATMENTS, AND PROCEDURES

Not applicable

7.8 RESCUE MEDICATIONS, TREATMENTS, AND PROCEDURES

The treatment of a bleeding event is considered standard-of-care and may include (at the discretion of the treating physician):

- Rinsing the extraction socket, applying hemostatic measures, removal of the false coagulum, stitching
- Interruption of the NOAC when necessary

7.9 PARTICIPANT ACCESS TO STUDY AGENT AT STUDY CLOSURE

TXA 10% mouthwash is commercially available.

8 ASSESSMENT OF SAFETY

8.1 SPECIFICATION OF SAFETY PARAMETERS

In this phase IV study with on-label use of TXA mouthwash, no serious adverse reactions are anticipated.

8.1.1 DEFINITION OF ADVERSE EVENTS (AE)

Any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product (ICH E2A Guideline. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, Oct 1994).

8.1.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

Any untoward medical occurrence that at any dose:

- Results in death;
- Is life-threatening;
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity;
- Is a congenital anomaly/birth defect; or
- Is an important medical event.

In addition, suspected transmission of an infectious agent, pathogenic or nonpathogenic are considered a SAE. Although pregnancy, overdose and cancer are not always serious by regulatory definition, these events are handled as SAEs. An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important.

8.1.3 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

Not applicable.

8.2 CLASSIFICATION OF AN ADVERSE EVENT

8.2.1 SEVERITY OF EVENT

The following definitions will be used to assess intensity of AEs per the NCI CTCAE criteria:

- Grade 1 Mild AE
- Grade 2 Moderate AE
- Grade 3 Severe AE
- Grade 4 Life-threatening consequences; urgent intervention indicated
- Grade 5 Death related to AE

8.2.2 RELATIONSHIP TO STUDY AGENT

Adverse events will be recorded during the follow-up visit at day 7. The relationship to the study agent will be adjudicated:

- Related – The AE is known to occur with the study agent, there is a reasonable possibility that the study agent caused the AE, or there is a temporal relationship between the study agent and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study agent and the AE.
- Not Related – There is not a reasonable possibility that the administration of the study agent caused the event, there is no temporal relationship between the study agent and event onset, or an alternate etiology has been established.

8.2.3 EXPECTEDNESS

No adverse events are expected, therefore any adverse event will be unexpected.

8.3 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

Adverse events will be assessed at day 2 and 7 follow-up.

8.4 REPORTING PROCEDURES

Following the subject's written consent to participate in the study, all AEs and SAEs, related to the study agent (tranexamic acid, IMP) will be collected.

Although no drugs other than the study agent will be provided by the sponsor to the subjects participating in this interventional study, investigators may become aware of (S)AEs in subjects possibly in relation to marketed drugs as a part of their ongoing therapies. Data on SAEs will be collected, and relatedness of these events to the use of marketed drugs associated with this study (where applicable) will be assessed by the investigator. SAEs determined to be related, including exposure during pregnancy and overdose, will be recorded and reported. A form will be completed for any event where doubt exists regarding its status of seriousness, including overdose and cancer. Reporting of SAEs of marketed drugs will follow regulatory guidelines. Pending on the marketed drug, reconciliation of SAEs cases (case level only) with the manufacturer is indicated. (E.g. for apixaban, frequency of reconciliation is planned every 3 months and

prior to the database lock or final data summary. BMS GPV&E will email, upon request from the Sponsor, the GPV&E reconciliation report. Requests for reconciliation should be sent to aepbusinessprocess@bms.com. The data elements listed on the GPV&E reconciliation report will be used for case identification purposes. If the Sponsor determines a case was not transmitted to BMS GPV&E, the case will be sent immediately to BMS. For apixaban, BMS will be contacted at Worldwide.Safety@BMS.com for SAE. Adverse Events of special interest for apixaban include potential or suspected cases of liver injury, including but not limited to liver test abnormalities, jaundice, hepatitis or cholestasis, regardless of whether the events are classified as serious or unexpected.)

8.5 STUDY HALTING RULES AND SAFETY OVERSIGHT

Interim analysis will be performed after inclusion of 100 patients to assess thrombotic events, allergic reaction and non-oral bleeding.

9 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s).

10 STATISTICAL CONSIDERATIONS

10.1 STATISTICAL AND ANALYTICAL PLANS

There is no external statistical and analytical plan.

10.2 STATISTICAL HYPOTHESES

This is a superiority study. The null hypothesis is that there is no difference in any oral bleeding between the intervention group and the control group (primary outcome).

10.3 ANALYSIS DATASETS

- The primary analysis set of interest will first be the intention-to-treat population (all randomized patients according to their randomized treatment).
- In addition, a sensitivity analysis will be done on the per-protocol population. The per-protocol population is defined as the subjects without major protocol deviations who complied to the assigned treatment for at least 80%. The per-protocol population will be finalized prior to the unblinding of the data.

10.4 DESCRIPTION OF STATISTICAL METHODS

10.4.1 GENERAL APPROACH

- Categorical and continuous data will be presented by randomized treatment group using appropriate summary statistics.
- The overall significance level for the primary endpoint of this study is set at 5% (2-sided). To account for the planned interim analysis (see section…), the methods as described by Cui, Hung & Wang (1999) will be used to preserve the overall Type I error.
- For the secondary endpoints, no adjustment will be made to the significance level to account for multiple testing.
- For all primary and secondary endpoints, an estimate of the treatment effect and associated 95% confidence interval will be presented. E.g. for the primary endpoint, the risk difference and its 95% confidence interval will be presented.

10.4.2 ANALYSIS OF THE PRIMARY EFFICACY OUTCOME(S)

The number of bleeding events up to day 7 will be analysed in terms of a risk difference between the two treatment groups, using the methods described by Cui, Hung & Want (1999).

10.4.3 ANALYSIS OF THE SECONDARY OUTCOME(S)

- The number of all different type of bleeding events, number of reinterventions and number of unplanned NOAC interruptions in the TXA group and placebo group will be compared using the Fisher Exact Test or Chi Square test, depending on the number of events. The effect of treatment will be estimated by the risk difference and presented along with its associated 95% confidence interval.

The procedural bleeding score in the TXA group and placebo group will be compared using the Student t-test of Mann-Whitney U-test, as appropriate. The effect of treatment will be estimated by the difference between treatments and presented along with its associated 95% confidence interval.

10.4.4 SAFETY ANALYSES

- The number of non-oral bleeding, allergic reactions and thrombotic complications in the TXA group and placebo group will be compared using the Fisher Exact Test or Chi Square test, depending on the number of events.

10.4.5 ADHERENCE AND RETENTION ANALYSES

No formal testing for adherence is planned, but the number of vials of the study drug will be recorded. Compliance will be calculated as the total number of vials taken divided by the required number of vials. Patients with less than 80% compliance will be excluded from the Per Protocol Set.

10.4.6 BASELINE DESCRIPTIVE STATISTICS

Baseline characteristics will be presented by randomized treatment group, using appropriate summary statistics.

10.4.7 PLANNED INTERIM ANALYSES

10.4.7.1 SAFETY REVIEW

After inclusion of 100 patients, a safety reviewed is planned to assess thrombotic events, allergic reaction and non-oral bleeding.

10.4.7.2 EFFICACY REVIEW

After 100 patients have reached their 7-day visit, an efficacy review is planned to reassess the required sample size. This will be done using the methods described by Cui, Hung & Wang (1999). The sample size re-estimation (SSR) will be based on the observed conditional power at the time of the interim analysis. The re-estimated sample size will be required to be between 150 and 300 patients. Full details for the methodology of the SSR will be provided in an Interim Statistical Analysis Plan.

10.4.8 ADDITIONAL SUB-GROUP ANALYSES

A number of exploratory subgroup analyses is planned, for which the study is not powered, including:

- The number of bleeding events in patients who resumed their NOAC treatment within 24 hours after extraction compared to later than 24 hours after extraction, stratified per treatment group.
- Risk factor analysis for bleeding, eg. patient demographics and procedural characteristics

10.4.9 MULTIPLE COMPARISON/MULTIPLICITY

A limited number of predefined subgroup analyses will be tested. No adjustment to the significance level will be made.

10.4.10 TABULATION OF INDIVIDUAL RESPONSE DATA

Individual data will be collected and stored.

10.4.11 EXPLORATORY ANALYSES

Defined under subgroup analysis.

10.5 SAMPLE SIZE

- Based on the previously cited pilot study, we estimate the rate of the primary outcome at 30% in the placebo group (7).
- We estimate to show an absolute risk reduction (ARR) of 15% This means an incidence of 15% in the tranexamic acid group.
- Confidence level is set to 95%, power is set to 80%.
- Under the above assumptions, in order to have 80% to detect a statistically significant risk difference between treatments, 118 patients per group or 236 patients in total will be required.

10.6 MEASURES TO MINIMIZE BIAS

10.6.1 ENROLLMENT/ RANDOMIZATION/ MASKING PROCEDURES

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. Sealed envelopes will contain patient number and randomization group.

10.6.2 EVALUATION OF SUCCESS OF BLINDING

Not applicable.

10.6.3 BREAKING THE STUDY BLIND/PARTICIPANT CODE

All patients can be continued to be treated based on standard-of-care irrespective of the study allocation.

11 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Each participating site will maintain appropriate medical and research records for this trial, in compliance with ICH E6 and regulatory and institutional requirements for the protection of confidentiality of participants

12 QUALITY ASSURANCE AND QUALITY CONTROL

Following written SOPs, the investigators and study coordinators will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP.

13 ETHICS/PROTECTION OF HUMAN SUBJECTS

13.1 ETHICAL STANDARD

The investigator will ensure that this study is conducted in full conformity with the Declaration of Helsinki and GCP.

13.2 INSTITUTIONAL REVIEW BOARD

The protocol, informed consent form, recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

13.3 INFORMED CONSENT PROCESS

13.3.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study agent, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study product.

13.3.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families. Consent forms will be IRB-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study

13.4 PARTICIPANT AND DATA CONFIDENTIALITY

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the principal investigator.

Participant details and research data, for follow-up, statistical analysis and scientific reporting, will be transmitted to and stored at the University Hospitals Leuven. Participant details and anonymized research data will be stored separately, the latter by using a unique study identification number. The study data entry and study management systems used by clinical sites and by the University Hospitals Leuven research staff will be secured. At the end of the study, all study databases will be archived at the University Hospitals Leuven.

13.4.1 RESEARCH USE OF STORED HUMAN SAMPLES,SPECIMENS OR DATA

Data collected under this protocol may be used for future patient-level meta-analyses, retrospective studies or other additional studies, eg. risk factor identification, after approval by the principal investigator.

14 DATA HANDLING AND RECORD KEEPING

14.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Copies of the CRF will be provided for use as source documents and maintained for recording data for each participant enrolled in the study. Data reported in the eCRF derived from source documents should be consistent with the source documents or the discrepancies should be explained and captured in a progress note and maintained in the participant's official electronic study record.

Clinical data (patient and procedure characteristics) and safety and efficacy outcome will be anonymized and entered into a clinical database. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

14.2 STUDY RECORDS RETENTION

Study documents will be retained according to local institution guidelines and GCP.

14.3 PROTOCOL DEVIATIONS

Protocol deviation is any noncompliance with the clinical trial protocol, GCP, or MOP requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.
It is the responsibility of the site to use continuous vigilance to identify and report deviations. All deviations must be addressed in study source documents, or reported to the IRB.

14.4 PUBLICATION AND DATA SHARING POLICY

Publication of the data is the responsibility of the principal investigator. The results of the study will be submitted to a peer-reviewed journal for publication.
The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a clinical trials registration policy as a condition for publication. The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Medical interventions include drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and the like. Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events. The ICMJE policy, and the Section 801 of the Food and Drug Administration Amendments Act of 2007, requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine. The ICMJE does not review specific studies to determine whether registration is necessary; instead, the committee recommends that researchers who have questions about the need to register err on the side of registration or consult the editorial office of the journal in which they wish to publish.

15 STUDY ADMINISTRATION

15.1 STUDY LEADERSHIP

The oversight of the study will be performed by the principal investigator.

16 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial.

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APPENDIX

Version	Date	Significant Revisions
0.1	6 Jan 2017	Initial version
1.0	1 Mar 2017	Updated study drug preparation and blinding, AE and SAE reporting
1.1	6 Jul 2017	Added details on interim analysis