Interventional Research (Medicinal Product)

TITLE

Pharmacokinetics of apixaban in subjects with end-stage renal disease treated with peritoneal dialysis

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STUDY SPONSOR

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PROTOCOL VERSION HISTORY

- Initial version V03 – 24/07/2019
- Amended version V10 – 08/03/2022
  Substantial amendment: correction of a non-inclusion criterion concerning healthy volunteers
- Favorable opinion from Ethics Committee (CPP): 07/06/2019
- Authorization by ANSM: 24/05/2019

Protocol Update History

Summary of significant changes in the protocol ApiDP

Version of the protocol	Reason of modification	Date of Authorities autorisation
2019-07-24		2019-07-18
2019-09-26	Accuracy of the time of taking the tablet	2019-12-17
2019-12-12	Removal of the T0 sample, redundant with the pre-dose sample.	2020-02-24
2020-11-30	Extension of the inclusion period (COVID-19)	2021-02-17
2021-04-21	Extension of the inclusion period (COVID-19)	2021-06-14
2021-06-15	Modify the time of tablet taking in healthy volunteers to avoid hospitalization	2021-11-05
2021-12-17	SPC ELIQUIS update	2022-02-21
2022-03-08	glomerular filtration rate of healthy volunteers: decrease in the inclusion threshold	2022-05-17

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(structure preserved – translated headings available on request)

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1. GENERAL INFORMATION

1.1 Regulatory Information

- **Acronym:** API-DP
- **Title:** Pharmacokinetics of apixaban in subjects with end-stage renal disease treated with peritoneal dialysis
- **EudraCT number:** 2019-001307-20
- **CHU number:** 19-060
- **Approved protocol version:** V10 – 08/03/2022
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2. PARTICIPATING INVESTIGATORS

(table content translated faithfully; formatting can be adapted to Word/ICH template if needed)

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3. SCIENTIFIC TEAM

- **Nephrology:** Maxence Ficheux, Clémence Béchade, Thierry Lobbedez, Mélanie Hanoy
- **Pharmacology:** Danièle Debruyne, Laure Peyro Saint Paul, Joachim Alexandre, Sophie Fedrizzi, Alexandre Cesbron, Véronique Lelong-Boulouard
- **Hematology:** Marie-François Brionne

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4. INDEPENDENT DATA MONITORING COMMITTEE

The Independent Data Monitoring Committee includes:

- A nephrologist specialized in peritoneal dialysis: Dr Courivaud (CHU Besançon)
- A pharmacologist specialized in pharmacokinetics: Dr Jean-Baptiste Woillard (CHU Limoges, INSERM U850)
- A cardiologist specialized in DOACs: Dr Guillaume Duthoit (Pitié-Salpêtrière Hospital, AP-HP, Paris)

The committee will be consulted in the event of any new safety issue, particularly any serious adverse event, and will provide its opinion on the benefit–risk balance.

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5. ABBREVIATIONS

- **ESRD:** End-Stage Renal Disease
- **PD:** Peritoneal Dialysis
- **CAPD:** Continuous Ambulatory Peritoneal Dialysis
- **APD:** Automated Peritoneal Dialysis
- **DOAC:** Direct Oral Anticoagulant
- **ISPD:** International Society of Peritoneal Dialysis
- **VKA:** Vitamin K Antagonist

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6. STUDY SYNOPSIS

Study title: Pharmacokinetics of apixaban in subjects with end-stage renal disease treated with peritoneal dialysis

Study type: Phase I pharmacokinetic study

Sponsor: CHU Caen Normandie

Population:

- ESRD subjects treated with peritoneal dialysis without indication for apixaban
- Healthy subjects with normal renal function

Primary Objective

To compare pharmacokinetic parameters (Cmax, AUC, half-life, total plasma clearance) between healthy subjects and ESRD subjects treated with peritoneal dialysis, in order to propose an appropriate dosing regimen for PD patients.

Secondary Objectives

- To characterize renal and peritoneal clearance of apixaban in PD patients
- To compare pharmacodynamic parameters (anticoagulant activity)
- To assess apixaban tolerability

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7. ABSTRACT

Direct oral anticoagulants (DOACs) include dabigatran, a direct thrombin inhibitor, and apixaban and rivaroxaban, which are factor Xa inhibitors. Several large randomized controlled trials have demonstrated that these agents are non-inferior to warfarin for stroke prevention in patients with atrial fibrillation.

In dialysis patients, warfarin remains the recommended approach for stroke prevention. However, significant concerns exist regarding the use of vitamin K antagonists in peritoneal dialysis (PD) patients, including deterioration of residual renal function, vascular calcification, and the burden of INR monitoring. DOACs could represent an attractive alternative, yet they have not been studied in this population.

Apixaban pharmacokinetics in PD patients have not yet been investigated. Since apixaban is partially renally excreted and poorly dialyzable, accumulation may occur in severe renal impairment. Currently, apixaban remains contraindicated in dialysis patients in Europe due to insufficient clinical experience.

This study proposes to compare the pharmacokinetics of a single oral dose of 5 mg apixaban between 12 PD patients and 12 healthy subjects. Blood, urine (if residual diuresis), and peritoneal dialysis fluid samples will be collected over 72 hours. Coagulation parameters and anti-Xa activity will also be measured.

The ultimate goal is to establish an appropriate dosing regimen for PD patients and to support future efficacy and safety studies.

Keywords: apixaban – peritoneal dialysis – pharmacokinetics – DOACs

8. SCIENTIFIC RATIONALE AND GENERAL DESCRIPTION OF THE STUDY

Background

While antithrombotic therapy is recommended for the primary prevention of stroke in patients with atrial fibrillation (AF), all clinical trials on which these recommendations are based have excluded patients treated with peritoneal dialysis (PD).

Study Population

Patients with end-stage renal disease (ESRD) treated with PD represent approximately 6.3% of the dialysis population. They constitute a niche population that is systematically underrepresented in clinical trials. This rare and high-risk population does not represent a priority target for pharmaceutical companies developing new drugs.

In France, the National Health Insurance estimated the cost of chronic kidney disease at more than €4 billion, based on 61,000 patients receiving renal replacement therapy (dialysis and kidney transplantation), including approximately €200 million for around 3,700 patients currently treated with peritoneal dialysis. The human cost is particularly high in terms of morbidity and mortality, impact on patients' quality of life, and consequences for caregivers and families.

In patients with ESRD, atrial fibrillation has a higher prevalence than in the general population. ESRD patients treated with PD who have AF have a higher one-year mortality than those without AF and are at particularly high risk of stroke [1].

Clinical Recommendations

The most recent 2015 recommendations from the International Society for Peritoneal Dialysis (ISPD) suggest the use of warfarin for stroke prevention in these patients and do not recommend direct oral anticoagulants (DOACs), due to the lack of data in PD patients, who have been systematically excluded from clinical trials [2].

Toxicity of Vitamin K Antagonists

However, vitamin K antagonists (VKAs) may cause deterioration of renal function [3], whereas residual renal function is strongly associated with survival in PD patients. In addition, VKAs are suspected to promote vascular calcification in this population. Finally, DOACs could eliminate the need for INR monitoring in patients whose venous access is often compromised. DOACs could therefore represent an attractive alternative, which has not yet been studied in this population.

Conflicting International Data in Renal Failure

Currently, all DOACs are contraindicated in Europe in patients with a creatinine clearance <15 mL/min (dialysis or non-dialysis). However, apixaban has been approved by the U.S. Food and Drug Administration (FDA) for use in hemodialysis patients [4], based on a pharmacokinetic study comparing 8 hemodialysis patients with 8 subjects with normal renal function. In this study, the area under the plasma concentration–time curve ($AUC_{0–\infty}$) of apixaban was increased by 36%. Despite this increase, the FDA recommends the standard dose of 5 mg twice daily [5]. A second pharmacokinetic study in 7 hemodialysis patients with chronic kidney disease recommended a reduced dose of 2.5 mg twice daily, having observed supratherapeutic plasma concentrations at the FDA-recommended dose [6].

Current Knowledge in Peritoneal Dialysis

To our knowledge, no pharmacokinetic study of DOACs has been conducted in PD patients, nor has any such study been registered on ClinicalTrials.gov. Nephrologists are therefore awaiting data that would allow safe and controlled use of DOACs in this population.

Very recently, while acknowledging that stroke prophylaxis in dialysis patients with atrial fibrillation remains an area of uncertainty, an expert consensus from a KDIGO Controversies Conference (2018) suggested that if dialysis patients require oral anticoagulation for atrial fibrillation, low-dose apixaban might be preferred over VKAs, based on observational study data [7].

Study Rationale

We hypothesize that, compared with subjects with normal renal function, PD patients will exhibit altered pharmacokinetics due to the combination of reduced renal elimination and drug clearance through peritoneal dialysis, which differs from clearance by hemodialysis.

The primary objective is to compare the pharmacokinetics of a single oral dose of 5 mg apixaban between ESRD patients treated with PD and subjects with normal renal function, in order to establish an appropriate dosing regimen for PD patients.

All PD-treated subjects, whether receiving automated peritoneal dialysis (APD) or continuous ambulatory peritoneal dialysis (CAPD), will be managed exclusively with CAPD during the three-day hospitalization following apixaban administration.

The results of this study are expected to:
a) determine plasma pharmacokinetic parameters of apixaban in PD patients ($AUC_{0-\infty}$, elimination half-life [T½], total plasma clearance [Cl]);
b) determine renal and peritoneal clearance (urinary clearance, peritoneal clearance);
c) ensure safety in both study groups through the administration of a single dose, thereby limiting toxic risk;
d) predict drug accumulation in PD patients;
e) propose an appropriate dosing regimen for this specific patient population.

The results of this study would allow progression to future efficacy and safety studies in a larger population receiving a dose guided by the findings of the present study.

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9. STUDY OBJECTIVES

9.1 Primary Objective

- To compare plasma pharmacokinetic parameters (Cmax, AUC, T½, and Cl) between subjects with normal renal function and ESRD subjects treated with peritoneal dialysis.

9.2 Secondary Objectives

- To characterize residual renal clearance and peritoneal clearance in ESRD subjects treated with PD.
- To compare pharmacodynamic parameters (anticoagulant activity) between subjects with normal renal function and ESRD subjects treated with PD.
- To assess apixaban tolerability.

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10. EVALUATION CRITERIA

10.1 Primary Endpoint

- Measurement of plasma apixaban concentrations at multiple time points until complete elimination of the drug:
    - Time zero (T0): prior to administration, to verify the absence of assay interference.
    - Blood sampling at T1h, T2h, T3h, T4h, T6h, T9h, T12h, T24h, T48h, and T72h.

10.2 Secondary Endpoints

- Measurement of peritoneal and urinary apixaban concentrations at multiple time points until complete elimination:
    - 24-hour urine collection in all subjects for 3 consecutive days.
    - Dialysate samples in PD subjects, 4 times per day for 3 days (total of 12 samples).
- Plasma measurements of anti-Xa activity, prothrombin time (PT), and activated partial thromboplastin time (aPTT) at T0, T3h, T9h, and T72h.
- Safety endpoint: systematic collection of adverse events of any grade (CTCAE v5.0) from the signing of informed consent until 72 hours post-dose, and beyond for any events potentially related to apixaban administration.

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11. STUDY METHODOLOGY

The tested dose will be a single oral administration of 5 mg apixaban.

To accelerate recruitment, the study will be conducted in two regional centers: CHU Caen Normandie and CHU Rouen.

At CHU Caen Normandie

Subjects Treated with Peritoneal Dialysis

- Screening visit: patients will be recruited by a nephrologist at CHU Caen Normandie; the visit will take place at the Clinical Research Center (CRC).
- Hospitalization from Day 0 to Day 3: patients will be hospitalized at the CRC in Caen.
- End-of-study visit: patients may be seen at the Clinical Investigation Unit (CUMR).

Healthy Subjects

- Screening visit: healthy volunteers will be recruited and followed at the CRC in Caen by CRC physicians and matched by sex, age (±5 years), and body weight (±20%).
- Hospitalization on Day 0, follow-up visits for plasma sampling on Days 1, 2, and 3, and end-of-study visit at the CRC in Caen.

At CHU Rouen

Healthy Subjects

- Screening visit: healthy volunteers will be recruited and followed at the Clinical Investigation Center (CIC) in Rouen by CIC physicians and matched by sex, age (±5 years), and body weight (±20%).
- Hospitalization on Day 0, follow-up visits for plasma sampling on Days 1, 2, and 3, and end-of-study visit at the CIC in Rouen.

Study Discontinuation Rules

The study will be immediately discontinued in the event of a serious adverse event potentially related to the study. After analysis, if no risk is ultimately identified, the study may resume following authorization from the competent authority. If a risk is identified, the study will be permanently discontinued.

Criteria for Permanent Discontinuation of Subject Participation

Subjects may withdraw from the study at any time and for any reason, or participation may be discontinued at the investigator's discretion.

Reasons for premature study withdrawal may include:

- Subject refusal to continue
- Withdrawal of consent
- Protocol violation requiring study withdrawal
- Severe toxicity
- Decision of the investigator
- Decision of the sponsor
- Participant non-compliance

Follow-up Procedures for Withdrawn Subjects

All withdrawals must be documented, and the investigator must specify the reason. The case report form will be completed up to the time of study withdrawal.

In the event of premature study withdrawal, the investigative team will send the study withdrawal form to the Clinical Research Associate (ARC) of the CPRC (02 31 06 50 68).

The following must be specified:

- Criteria and procedures for premature treatment discontinuation

- Criteria and procedures for exclusion or premature withdrawal from the study
- Medical management procedures in the event of premature treatment discontinuation
- Medical management procedures in the event of exclusion from the study
- Follow-up procedures for withdrawn subjects

Consequences of Study Withdrawal

Subjects will be considered evaluable only if they have participated through T72 on Day 3 of the study.
Withdrawals occurring before T72 will be replaced.

Management of Lost-to-Follow-Up Subjects

In the event of loss to follow-up, the subject's primary care physician, the municipality of residence, and the municipality of birth will be contacted.

Description of Rules for Temporary or Permanent Discontinuation of All or Part of the Study

The study will be discontinued in the event of an unfavorable benefit–risk balance during the trial, upon sponsor decision or at the request of the competent authorities.

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12. SELECTION AND EXCLUSION OF STUDY PARTICIPANTS

Inclusion Criteria

Subjects Treated with Peritoneal Dialysis

- Male or female aged 18 to 80 years
- ESRD patient treated with peritoneal dialysis for at least three months
- Body mass index (BMI): $18 < BMI < 40$ kg/m²
- Acceptable comorbidities and medical history as assessed by the investigating nephrologist, with an estimated life expectancy >6 months
- Hemoglobin >10 g/L
- Ability to provide written informed consent
- Affiliation with the national social security system
- French-speaking subject

OR

Healthy Subjects with Normal Renal Function

- Male or female aged 18 to 80 years
- Body mass index (BMI): $18 < BMI < 40$ kg/m²

- Subject determined to be in good health by a responsible physician, based on a medical evaluation including medical history, vital signs, physical examination, and clinical laboratory tests
- Estimated glomerular filtration rate (eGFR) >90 mL/min (assessed using the CKD-EPI formula)
- Ability to provide written informed consent
- Affiliation with the national social security system
- French-speaking subject

Non-Inclusion Criteria

- Known hypersensitivity to apixaban
- History of major bleeding
- Contraindication to apixaban according to the Summary of Product Characteristics (SmPC) for Eliquis® (except for ESRD in renal failure participants)
- Contraindication to Physioneal® or Extraneal® (for renal failure participants)
- Indication for anticoagulant therapy
- Current anticoagulant treatment
- Use of NSAIDs at anti-inflammatory doses (>300 mg)
- Treatment with strong CYP3A4 and P-gp inhibitors (increased exposure): azole antifungals (ketoconazole, itraconazole, voriconazole), amiodarone, HIV protease inhibitors, diltiazem, naproxen
- Treatment with CYP3A4 and P-gp inducers (reduced exposure): rifampicin, antiepileptic drugs, St John's wort
- Moderate (Child–Pugh B) or severe (Child–Pugh C) hepatic impairment
- Current or recent (within 14 days prior to study) antibiotic treatment
- Pregnant or breastfeeding women
- Known hypersensitivity to icodextrin
- Inability to tolerate an intraperitoneal volume of 2 liters

Exclusion Criterion

- Healthy subject with an eGFR <90 mL/min (assessed using the CKD-EPI formula) after selection as a normal renal function participant.

13. TREATMENTS ADMINISTERED TO PARTICIPANTS

1. Description/Presentation of the Investigational Medicinal Product(s), Comparator(s), and Auxiliary Medicinal Products/Devices

Investigational Medicinal Product

Item	Description
International Nonproprietary Name (INN) / strength	Apixaban 5 mg
Trade name / strength	Eliquis® 5 mg

Item	Description
Pharmaceutical form	Film-coated tablet
Study dosage	5 mg as a single dose
Route/mode of administration	Oral
Storage conditions	Room temperature – no special storage precautions

Reference SmPC for ELIQUIS® 5 mg:
http://ec.europa.eu/health/documents/community-register/2018/20180531141190/anx_141190_fr.pdf

Auxiliary Medicinal Products

	Auxiliary medicinal product 1	Auxiliary medicinal product 2
INN / strength	See SmPC for solution composition	See SmPC for solution composition
Trade name / strength	Physioneal 40 glucose (1.36% or 3.86%), double-bag system with screw (Luer) connection, 2 L	Extraneal, double bags (PVC) with Luer screw connection, 2 L
Pharmaceutical form	Peritoneal dialysis solution	Peritoneal dialysis solution
Study dosage	2 L at 08:00, 12:00, and 16:00 for 3 days	From 20:00 to 08:00 for 3 days
Route/mode of administration	Intraperitoneal	Intraperitoneal
Storage conditions	Room temperature – do not store below 4°C	Room temperature – do not store below 4°C

Reference SmPCs:

- Physioneal 40 glucose 1.36% (isotonic): http://base-donnees-publique.medicaments.gouv.fr/extrait.php?specid=61274635
- Physioneal 40 glucose 3.86% (hypertonic): http://base-donnees-publique.medicaments.gouv.fr/extrait.php?specid=67998759
- Extraneal: http://agence-prd.ansm.sante.fr/php/ecodex/rcp/R0287620.htm

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2. Supply Chain of the Investigational Treatment(s) and Auxiliary Treatments/Devices

2.1 Source of the Investigational Medicinal Product and Auxiliary Treatments/Devices

Apixaban 5 mg (ELIQUIS®) required for the study will be purchased by the coordinating pharmacy of **CHU Caen Normandie** from **Bristol-Myers Squibb**. A batch release certificate and, where applicable, certificates of analysis will be required from the supplier for each batch ordered and received.

Dialysis solutions and auxiliary devices will be provided by the participating centers and reimbursed by the sponsor. They will be used according to standard clinical practice in the care unit (CRC/CIC) where participants are included and treated.

2.2 Packaging

Apixaban 5 mg (ELIQUIS®) scored tablets in pre-cut blister packs will be repackaged into unit boxes (one apixaban tablet per box) by the coordinating pharmacy of CHU Caen Normandie, which will perform final batch release after repackaging and relabeling.

2.3 Labeling

Blister packs and unit boxes of apixaban 5 mg (ELIQUIS®) will be labeled in accordance with Article R.5121-16 of the French Public Health Code, the Order of May 24, 2006 specifying medicinal product labeling content, and the recommendations of Annex 13 of the European Good Manufacturing Practices.

2.4 Supply / Resupply

Initial supply will be performed by the coordinating pharmacy of CHU Caen Normandie at site initiation.
Resupply will be carried out if necessary by participating centers using the dedicated form provided by the sponsor.

Each receipt of apixaban 5 mg (ELIQUIS®) will be recorded (quantity, batch number, and expiry date) in an appropriate accountability log under the responsibility of the investigator and pharmacist.

2.5 Storage Conditions

The investigational treatment must be stored by the pharmacy of each investigational center in its original packaging, protected from light, at room temperature, in a temperature-controlled and locked room.

2.6 Dispensing

Dispensing of the investigational treatment will be performed upon presentation of the study-specific nominative prescription provided by the sponsor or the participating center. Each dispensing will be recorded in an appropriate accountability log under the responsibility of the investigator and pharmacist. Batch numbers and expiry dates of dispensed products will be documented to ensure traceability.

2.7 Administration

The single oral dose of apixaban 5 mg (ELIQUIS®) will be administered on Day 0 (D0) with water, after at least 2 hours of fasting.

2.8 Returns and Destruction

Used or unused investigational treatments must be returned to the hospital pharmacy of the participating center. Returned quantities will be recorded on a subject-specific accountability form.
Used, unused, or expired investigational treatments will be destroyed on site after written approval from the sponsor. A destruction certificate will be issued by the pharmacist of the participating center.

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3. Management of Toxicities Related to the Investigational Medicinal Product or Its Administration (if applicable)

Any toxicities related to apixaban 5 mg administration will be managed by the investigator or co-investigator responsible for the participant.

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4. List of Authorized and Prohibited Treatments and Substances

4.1 Prohibited Treatments and Substances

Prohibited treatments include other anticoagulants, such as unfractionated heparin, low-molecular-weight heparins (enoxaparin, dalteparin, etc.), heparin derivatives (fondaparinux, etc.), and oral anticoagulants (warfarin, rivaroxaban, dabigatran, etc.).

Subjects receiving strong CYP3A4 and P-gp inhibitors (increased exposure) will not be included: azole antifungals (ketoconazole, itraconazole, voriconazole), amiodarone, HIV protease inhibitors, diltiazem, naproxen.

Subjects receiving CYP3A4 and P-gp inducers (reduced exposure) will not be included: rifampicin, antiepileptics, St John’s wort.

Smoking and grapefruit juice are prohibited during the study due to their effects on CYP3A4.

4.2 Treatments Authorized with Precautions

Precautions must be taken in subjects treated concomitantly with nonsteroidal anti-inflammatory drugs (NSAIDs), including acetylsalicylic acid. In the ApiDP study, subjects receiving NSAIDs at anti-inflammatory doses are not included.

4.3 Special Warnings and Precautions for Use

Refer to the reference SmPC for apixaban 5 mg (ELIQUIS®).

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5. Methods for Monitoring Treatment Compliance

Subject compliance will be assessed and documented during the on-site single administration of apixaban 5 mg (ELIQUIS®).

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14. PRACTICAL CONDUCT OF THE STUDY

1. Inclusion of Subjects Undergoing Peritoneal Dialysis

Screening visit (D−30 to D−5):
During this medical visit conducted by the investigator nephrologist:

1. **Informed consent**
   The investigator will inform the subject of the study objectives, constraints, and foreseeable risks, review the information sheet and consent form, and answer all questions prior to any assessment. If the subject agrees to participate, both the subject and investigator will sign and date the consent form in duplicate. One copy will be retained by the investigator for 15 years after study completion; the other will be provided to the subject.
2. **Verification of inclusion/non-inclusion criteria**
3. **Collection of medical history and concomitant treatments**

- Clinical examination including vital signs, weight, and height
- Blood tests
- Urine pregnancy test if applicable
- Verification of administrative documents required for compensation payment and national registry enrollment
- Scheduling of subsequent visits with the CRC in Caen and CIC in Rouen

4. **Registration in the VRB registry**

Day 0 (D0) = Hospitalization and Drug Administration – MONDAY (CRC or CIC)

Morning

Initiation of the standardized **continuous ambulatory peritoneal dialysis (CAPD)** protocol for the following 3 days.
The patient arrives with a full abdomen, according to their usual peritoneal dialysis care protocol.

Time	08:00	12:00	16:00	20:00
D0 (Monday)	At home	Physioneal 2 L	Physioneal 2 L	Extraneal 2 L
D1 (Tuesday)	Physioneal 2 L	Physioneal 2 L	Physioneal 2 L	Extraneal 2 L
D2 (Wednesday)	Physioneal 2 L	Physioneal 2 L	Physioneal 2 L	Extraneal 2 L
D3 (Thursday)	Physioneal 2 L	Return to standard regimen		

Note:
If the subject presents with fluid overload (assessed after the first 24 hours), the nephrologist may replace the morning dialysis bag with a hypertonic Physioneal solution to achieve ultrafiltration.

Morning – Medical Visit

Clinical examination and verification of the absence of drug–drug interactions.
A catheter will be inserted for the various blood samplings.

- Absence of contraindications according to the Eliquis SmPC (except for end-stage renal disease in participants with renal failure) and absence of contraindications to Physioneal or Extraneal (for participants with renal failure)
- **Healthy subjects:** considered healthy by the investigator based on a medical evaluation including medical history, vital signs, physical examination, and clinical laboratory tests
- **Renally impaired subjects:** presenting comorbidities and medical history deemed acceptable by the investigator (estimated life expectancy > 6 months)

Women of childbearing potential must have a negative urinary pregnancy test (β-hCG) on D0 prior to apixaban administration. Women with amenorrhea > 12 months and follicle-stimulating hormone (FSH) levels ≥ 40 IU/L are not considered of childbearing potential. For women with amenorrhea ≥ 2 years, FSH measurement is not required.

Pre-dose (before apixaban administration)

- Blood sample for apixaban pharmacokinetics
- Blood sample for anticoagulant activity (anti-Xa), PT, and aPTT
- Peritoneal dialysis fluid sample
- Urine sample for apixaban assay

12:00 (T0)

Oral administration of apixaban 5 mg at 12:00 ± 1 hour.
The apixaban tablet must be swallowed with a glass of water, 30 minutes before lunch, after drainage and at the beginning of Physioneal infusion.

- Initiation of 24-hour urine collection

Pharmacokinetic Sampling Schedule

- **T1h (±5 min):** blood sample for apixaban PK
- **T2h (±5 min):** blood sample for apixaban PK
- **T3h (±5 min):** blood sample for apixaban PK
  - plus blood sample for anti-Xa activity, PT, and aPTT
- **T4h (±5 min):** blood sample for apixaban PK
  - start of afternoon bag infusion and sampling of drained dialysis fluid
  - peritoneal dialysis fluid sample for creatinine and urea kinetics
- **T6h (±5 min):** blood sample for apixaban PK
- **T8h (±5 min):** start of evening bag infusion and sampling of drained dialysis fluid
  - peritoneal dialysis fluid sample for creatinine and urea kinetics
- **T9h (±5 min):** blood sample for apixaban PK
  - plus blood sample for anti-Xa activity, PT, and aPTT
- **T12h (±5 min) (around midnight):** blood sample for apixaban PK

Day 1 (D1) – TUESDAY

- **T20h (around 08:00):** start of morning bag infusion and sampling of drained dialysis fluid
  - peritoneal dialysis fluid sample for creatinine and urea kinetics
- **T24h (±5 min) (around noon):** blood sample for apixaban PK
  - start of midday bag infusion and sampling of drained dialysis fluid
  - measurement of 24-hour urine volume
  - urine sample for apixaban assay
  - urine + plasma + peritoneal dialysis fluid samples for creatinine and urea kinetics
  - measurement of renal urea clearance (UV/P urea) and creatinine clearance (UV/P creatinine) using blood sampling and 24-hour urine collection; estimation of renal function by averaging the two clearances (peritoneal dialysis subjects only)
  - initiation of a new 24-hour urine collection
- **T28h (±5 min) (around 16:00):** start of afternoon bag infusion and sampling of drained dialysis fluid
- **T32h (±5 min) (around 20:00):** start of evening bag infusion and sampling of drained dialysis fluid

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Day 2 (D2) – WEDNESDAY

- **T44h (around 08:00):** start of morning bag infusion and sampling of drained dialysis fluid

- **T48h (±5 min):** blood sample for apixaban PK
    - start of midday bag infusion and sampling of drained dialysis fluid
    - measurement of 24-hour urine volume and urine sampling
    - initiation of a new 24-hour urine collection
- **T52h (around 16:00):** start of afternoon bag infusion and sampling of drained dialysis fluid
- **T56h (around 20:00):** start of evening bag infusion and sampling of drained dialysis fluid

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Day 3 (D3) – THURSDAY (T72) AND DISCHARGE

- **T68h (around 08:00):** start of morning bag infusion and sampling of drained dialysis fluid
- **T72h (±5 min) (around noon):** blood sample for apixaban PK
    - measurement of 24-hour urine volume and urine sampling
    - end of urine collection
    - sampling of drained dialysis fluid and resumption of the subject's personal peritoneal dialysis regimen
    - blood sample for anti-Xa activity, PT, and aPTT

A medical visit will then be performed, followed by subject discharge.

End-of-Study Visit at 1 Month (±10 days)

Clinical examination, vital signs, collection of concomitant treatments and adverse events.

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2. Inclusion of Healthy Volunteers with Normal Renal Function (Group 2)

The CRC of Caen or the CIC of Rouen will organize the recruitment of healthy volunteers matched to peritoneal dialysis patients (respectively at CHU Caen Normandie and CHU Rouen).

Management will be identical to that of peritoneal dialysis patients, except for the absence of peritoneal dialysis fluid sampling. In addition, apixaban administration may occur as early as 08:00. Pharmacokinetic sampling times will be adjusted accordingly.

Evaluations

Evaluation	Screening (D-30 to D-5)	D0	D1	D2	D3	End-of-Study Visit
Informed consent	X					
Eligibility verification	X					
Clinical examination	X	X				X
Vital signs (BP, weight, height, BMI)	X	X				X
Pregnancy test (if applicable)	X	X				
Laboratory tests	X					
Creatinine clearance (CKD-EPI, healthy subjects)	X					
Dialysis subjects – Kt/V clearance (creatinine & urea, from 24h urine, plasma at D1, PD fluid first 24h)		X	X			
Oral apixaban 5 mg administration		X				
Standardized peritoneal dialysis protocol (3 Physioneal + 1 Extraneal/24h) – PD subjects		X	X	X	X	
Blood collection for pharmacokinetics		X	X	X	X	
Blood collection for hemostasis tests + anti-Xa activity		X				X
24-hour urine collection		X	X	X		
Urine collection for pharmacokinetics		X	X	X	X	
Dialysis fluid collection for pharmacokinetics		X	X	X	X	
Concomitant treatments	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X

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15. Sample Management

All assays will be performed in batch at the end of the study.

Day	Time	Plasma	Dialysis fluid	Urine	Kt/V Clearance
		Apixaban assay	Anti-Xa activity, PT, aPTT	Apixaban assay	Creatinine, urea
D0	Pre-dose	X	X	X	X
	1h	X			
	2h	X			
	3h	X	X		
	4h	X		X	X (PD fluid)
	6h	X			
	8h			X	X (PD fluid)
	9h	X	X		
	12h	X			

Day	Time	Plasma	Dialysis fluid	Urine	Kt/V Clearance
D1	20h			X	X (PD fluid)
	24h	X		X	X (PD fluid + urine 24h + plasma)
	28h			X	
	32h			X	
D2	44h			X	
	48h	X		X	
	52h			X	
	56h			X	
D3	68h			X	
	72h	X	X	X	X

Total samples:

- Plasma for apixaban: 11
- Plasma for anti-Xa, PT, aPTT: 4
- Dialysis fluid: 13 (PD subjects only)
- Urine: 4 (apixaban assay)
- Kt/V clearance: 4

Sample Processing

CHU Caen (CRC):

- Blood samples: centrifuge at 1900–2000 g for 11 min at 22°C, then freeze as 3 plasma aliquots for apixaban assay.
- Anti-Xa, PT, aPTT samples: 2 aliquots of 500 µL plasma after double centrifugation (2000–2500 g, 15–25°C, 11 min).
- PD fluid samples (PD subjects): 13 tubes, frozen as 3 aliquots for apixaban assay.
- Urine: 4 tubes frozen as 4 aliquots for apixaban assay; 4 tubes sent directly for creatinine and urea assay.

CHU Rouen (CIC):

- CIC performs sampling and coordinates logistics with CRB Caen for processing.

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16. Data to Be Collected

Screening Visit (D-30 to D-5):

- Date of informed consent
- Age, sex, weight, height, BMI

- Blood pressure
- Laboratory tests: CBC (including hemoglobin g/dL), electrolytes, liver function tests (AST, ALT, γ-GT, ALP)
- Creatinine clearance (CKD-EPI, healthy subjects only)
- Concomitant medications
- Pregnancy test if applicable
- Date of initiation of peritoneal dialysis
- Renal history for PD subjects, Charlson comorbidity score
- Eligibility verification

Hospitalization (D0):

- Blood pressure, weight (for PD subjects: estimated empty abdominal weight based on full abdominal weight and Monday morning drained volume)
- Start of 24-hour urine collection
- Pregnancy test if applicable
- Time of apixaban administration
- Concomitant medications

D0–D3:

- Plasma apixaban concentrations: T0, T1h, T2h, T3h, T4h, T6h, T9h, T12h, T24h, T48h, T72h
- PD fluid and urine apixaban concentrations: 24-hour urine ×3, PD fluid 4×/day ×3 days = 12 samples (PD subjects only)
- PD fluid creatinine and urea (T4h, T8h, T20h, T24h)
- Plasma anti-Xa, PT, aPTT: T0, T3h, T9h, T72h
- PD subjects: renal clearance calculations (plasma and 24h urine creatinine and urea)
- Safety: systematic recording of adverse events (any grade, CTCAE v5.0) from informed consent until 72h post-dose and beyond if possibly related to apixaban

End-of-Study Visit (1 month ± 10 days):

- Weight, blood pressure, concomitant medications, adverse events

17. STATISTICAL METHODOLOGY

This is an open-label, parallel-group study with a single oral administration.

1. Planned Number of Participants

- 12 end-stage renal disease (ESRD) patients treated with peritoneal dialysis (PD).
- 12 healthy subjects with normal renal function, serving as the control group. Each control subject will be matched to a patient by age (±5 years), weight (±20%), and sex.

Justification
Assuming a 36% difference in AUC between the two groups (based on pharmacokinetic studies in hemodialysis patients), with a standard deviation of ±25%, a two-sided alpha of 5%, and a power of 90%, 11 evaluable subjects per group are required. To account for potential

dropouts, 12 subjects per group will be included, resulting in a total of 24 subjects. One dropout per group is anticipated.

Group 1 will consist of 12 ESRD patients on PD.
Group 2 will consist of 12 healthy subjects, matched to Group 1 by age (±5 years), weight (±20%), and sex.

The body weight of PD patients will be measured as dry weight (empty abdomen).

2. Statistical Methods
This is an open-label, parallel-group, single-dose study involving 24 subjects.
Descriptive statistics will be used to summarize baseline characteristics and to present apixaban pharmacokinetic parameters. Continuous variables will be expressed as mean ± standard deviation (SD). The coefficient of variation (CV) will be calculated as SD divided by the mean and expressed as a percentage.

The Wilcoxon rank-sum test will be used to compare pharmacokinetic parameters between groups. Pharmacokinetic and pharmacodynamic modeling will be performed using nonlinear mixed-effects models (SAS v9.0).

Subjects will be considered evaluable only if they complete assessments through 72 hours post-dose (T72) on Day 3. Early withdrawals before T72 will be replaced.

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18. FEASIBILITY

The University Center for Kidney Diseases follows 60 ESRD patients treated with PD, ensuring sufficient enrollment potential, with approximately half expected to meet the inclusion criteria.
The Nephrology Department at CHU Rouen, in collaboration with ANIDER, follows 20 ESRD patients treated with PD, also ensuring adequate enrollment potential, with about half likely to meet the inclusion criteria.

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19. ELECTRONIC DATA MANAGEMENT

Data will be managed using Ennov Clinical software.

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20. RISK-BENEFIT ASSESSMENT FOR PARTICIPANTS

Benefits
No direct benefit is expected for study participants. The anticipated benefit is collective, contributing to scientific knowledge regarding apixaban pharmacokinetics in renal impairment.

Risks
The risks are related to the known adverse effects of apixaban, particularly in patients with renal impairment due to dose-dependent effects. The most common adverse events include bleeding, bruising, epistaxis, and hematoma.

The risk is minimized by administering a single 5 mg dose. In controlled studies, oral administration of apixaban to healthy subjects at doses up to 50 mg/day for 3–7 days (25 mg twice daily for 7 days or 50 mg twice daily for 3 days) did not result in clinically significant adverse effects (Eliquis® SmPC).

21. SAFETY ASSESSMENT

Description of Safety Evaluation Parameters

- **Clinical monitoring:** Adverse events (AEs) will be closely monitored during the 3-day hospitalization period. Participants will be evaluated by the investigator at Day 30.
- **Laboratory assessments:** Anticoagulant activity measured at 3 hours (T3h) and 72 hours (T72h) post-dose will be analyzed by the investigator.

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22. ADVERSE EVENT REPORTING

1. Definitions

- **Adverse Event (AE):** Any harmful occurrence in a subject participating in biomedical research, whether or not it is related to the study or investigational product.
- **Serious Adverse Event (SAE):** Any AE that:
    - Results in death,
    - Is life-threatening,
    - Requires hospitalization or prolongation of hospitalization,
    - Results in significant or persistent disability/incapacity, or a congenital anomaly,
    - Is considered serious by the investigator.

A SAE related to the study becomes a **Serious Adverse Reaction (SAR)**.

- **Unexpected Serious Adverse Reaction (USAR):** Any SAE related to the investigational medicinal product whose nature, severity, or outcome is not consistent with the Reference Safety Information (SmPC or Investigator's Brochure).
- **Expected Serious Adverse Reaction (ESAR):** Defined in the protocol, Investigator's Brochure, or study documents:
    - Any AE already listed in the most recent SmPC or Investigator's Brochure,
    - Any serious AE expected from study procedures or methods.

2. Description of ESARs
Reference safety information for **ELIQUIS 5 mg**: most recent EPAR available on the EMA website, section 4.8.
In the indication of non-valvular atrial fibrillation, the expected AEs are primarily **bleeding events**.

Other expected effects include hypersensitivity (e.g., pruritus, anaphylactic reaction, angioedema) and syncope, occurring in <1% of patients receiving Eliquis®.

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23. PROCEDURES FOR RECORDING AND REPORTING AEs

Investigator Responsibilities

Detection and recording of AEs:
All AEs must be actively sought, reported, recorded, managed, and evaluated from the date of informed consent until one month after study completion, and until resolution. AEs are collected:

- During scheduled clinical, laboratory, or other assessments and through systematic questioning by the investigator,
- Through spontaneous reporting by participants, who are instructed to contact the investigator in case of any AE.

All AEs, regardless of severity (graded per CTCAE v5.0), will be recorded on AE case report forms. Each AE will be documented individually, with severity graded as:

- Mild (Grade 1): no interference with daily activity,
- Moderate (Grade 2): moderate interference with daily activity but acceptable,
- Severe (Grade 3): significant and unacceptable interference with daily activity,
- Life-threatening (Grade 4),
- Death (Grade 5).

Reporting of SARs:
The investigator must notify the sponsor **without delay** of all serious AEs, whether related to the study or not, expected or unexpected.

- **Form:** SARs are reported to the sponsor via fax to +33 2 31 06 35 09 (Clinical Research Pharmacovigilance Fax).

Special case: healthy volunteer studies
In case of a SAE potentially related to the study, the investigator must take urgent safety measures, suspend administration to all participants, and notify the sponsor immediately.

The investigator must provide additional information regarding SAEs promptly and assess severity, intensity, and causality. All SAEs will be followed until complete resolution. Delayed AEs reasonably related to the investigational product or study must be reported without time limitation.

Reporting period:
SAEs must be reported from:

- Date of informed consent,
- Throughout the participant’s follow-up as per the study protocol,
- Up to 4 weeks after study completion,

- Beyond the follow-up period if reasonably related to the study or investigational product (e.g., delayed serious effects such as cancer or congenital anomalies).

Sponsor Responsibilities

Reporting unexpected SAEs:
The sponsor evaluates causality between the SAE and the investigational product(s) or study procedures, determines expected vs. unexpected status, and reports all unexpected SAEs to **EMA (EudraVigilance) and ANSM**.

Regulatory timelines:

- **Immediately:** fatal or life-threatening unexpected SAEs; additional relevant information must be reported within 8 days,
- **Within 15 calendar days:** other unexpected SAEs; additional information must be reported within 8 days.

For healthy volunteer studies, all SAEs are reported **immediately** to ANSM.

Reporting new safety information:
Defined as any new data that may lead to reassessment of the benefit-risk profile, modification of product use, study conduct, study documents, or suspension/modification of the protocol.
The sponsor reports new safety information **without delay** to ANSM and the Ethics Committee (CPP).

Special consideration for first-in-human studies:
For first-in-human studies or first use in healthy volunteers, any SAE constitutes new safety information.

- The sponsor suspends administration of the product pending safety measures,
- Implements urgent safety measures,
- Notifies ANSM, CPP, and ARS immediately.

Annual Safety Report:
On the anniversary of the trial authorization by ANSM, the sponsor prepares a safety report including:

- List of all SARs (expected and unexpected),
- List of all SAEs (related and unrelated),
- Concise critical analysis of subject safety.

This report is submitted to ANSM and the relevant CPP within **60 days** of the trial authorization anniversary.

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24. PARTICIPANT INVOLVEMENT

- Study procedures will occur at the **Clinical Research Center of CHU Caen** or the **Clinical Investigation Center of Rouen**.
- Pharmacokinetic and pharmacodynamic analyses will be conducted at **CHU Caen**.
- All participants must be beneficiaries of the French social security system.
- The investigator will verify participant involvement in other clinical trials to assess compatibility with the API-DP protocol.

Compensation: €900.

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25. ACCESS TO DATA AND SOURCE DOCUMENTS

Participant Information:
In accordance with French data protection laws (Loi Informatique et Libertés, Law No. 2002-303), participants have the right to access and correct their data at any time. Participation and consent procedures are documented in the participant's medical record. Participants will be informed of overall study results at study completion.

Access to source data:
Authorized personnel from the sponsor (CHU Caen) will monitor CRFs and verify against source medical records.

27. LEGAL AND ETHICAL CONSIDERATIONS

1. Participant Information and Consent:
Free, informed, and explicit consent will be obtained after the participant has been informed of the study's objectives, procedures, duration, potential benefits, risks, and constraints, as well as the nature of the investigational product and the opinion provided by the Ethics Committee (CPP), and after adequate time for reflection.

- The information sheet will be given to the participant.
- The consent form will be dated and personally signed by the participant and by an investigator authorized for the protocol **before any study-related procedures**.
- Participation in the study will be documented in the participant's medical record at the inclusion visit (date of inclusion and dates of study visits).

For minors capable of expressing their will, a separate information sheet will be provided.
Consent must be signed by both the holders of parental authority and the minor.
Genetic analyses will require a specific information sheet and consent form.

2. Ethics Committee Opinion and Regulatory Authority Submission:
This study is considered **"interventional research"** under Article L.1121-1 of the French Public Health Code (Law No. 2012-300 of March 5, 2012, and implementing Decree No. 2016-1537 of November 16, 2016). It will be submitted for review by a CPP.

The **CHU Caen Normandie**, as the sponsor, will submit the protocol to the relevant Competent Authority (AC) and obtain authorization.
The sponsor must provide insurance covering all participants and participating centers.

3. Substantial Amendments:
Any modification to the protocol or to the information and consent documents must be authorized by the CPP and ANSM.

4. End-of-Trial Notification:
The sponsor shall notify the end of the trial within:

- **90 days** after planned completion (last participant's last visit), or
- **15 days** in case of premature termination.

5. Final Study Report:
The final report summarizes the study results. It must be submitted to ANSM **within one year** after trial completion (planned or premature, except for trials stopped due to non-enrollment).

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28. PARTICIPANT INFORMATION AND CONSENT

Free, informed, and explicit consent will be obtained after providing the participant with all necessary information regarding the study objectives, procedures, duration, potential benefits, risks, constraints, the nature of the investigational product, and the CPP opinion, with sufficient time for reflection.

- Consent will be **dated and signed** by the participant and the responsible investigator **before any study-related procedures**.
- Participation will be documented in the medical record at the inclusion visit.

For minors capable of expressing their will, a separate information sheet will be provided, and consent must be signed by both parents/guardians and the minor.
Genetic analyses require a specific information sheet and consent form.

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29. ETHICS COMMITTEE REVIEW AND COMPETENT AUTHORITY NOTIFICATION

- Interventional research under Article L.1121-1 of the Public Health Code (Law No. 2012-300, March 5, 2012, and Decree No. 2016-1537, Nov 16, 2016) requires **CPP approval**.
- The **CHU Caen**, as sponsor, will submit the protocol to the relevant Competent Authority (AC).
- The CPP must approve the protocol and informed consent form.
- Any amendment to the protocol or consent form must be submitted to the CPP and AC.
- The sponsor will maintain insurance for all participants and centers.

1. Substantial Amendments:
All protocol amendments must be authorized by the CPP and ANSM.

2. End-of-Trial Notification:

- Planned completion: within 90 days of last participant visit.
- Premature termination: within 15 days.

3. Final Study Report:
The final report summarizes the study results and must be submitted **within one year** after trial completion, except for trials stopped due to non-enrollment.

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30. DATA HANDLING AND DOCUMENT RETENTION

CHU Caen Normandie will comply with **MR-001 methodology** (Deliberation No. 2018-153, May 3, 2018) for processing personal health data collected during research, in accordance with consent. Declaration No.: 2012002-V0.

This automated processing complies with the **EU General Data Protection Regulation (GDPR) of April 27, 2016**. The methodology covers all personal data processing in research.

The coordinating investigator will conduct the study according to this methodology and retain source documents for **15 years**, including:

- Ultrasound reports,
- Laboratory results,
- Clinical observations in patient medical records, etc.

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31. PUBLICATION POLICY

Authorship must comply with **ICMJE guidelines**: each author must have contributed sufficiently to take responsibility for the content. Essential contributions:

1. Study conception/methods and/or data analysis and interpretation,
2. Drafting or critical revisions of the manuscript,
3. Final approval of the published version.

Author order (coordinating investigator, methodologist, principal investigators) reflects participation in the study (number of subjects included and evaluable) and significant contributions during study conduct. Funding sources will be disclosed.

Ancillary study results may only be published with the agreement of the principal investigators and methodologist, and after publication of the main study.

The coordinating investigator will sign the final clinical study report, confirming agreement with analyses, results, and conclusions.

The study and its results are the exclusive property of **CHU Caen**, and investigators are bound by professional confidentiality. Results may be presented at conferences and published. Drafts of communications and publications will be reviewed with all participating investigators.

32. REFERENCES

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