
CLINICAL TRIAL PROTOCOL

CIV-25-06-053398_Subprotocol_017

This Clinical Trial Protocol also refers to the Master Platform Protocol “Master protocol for all Positron Emission Tomography studies using the NeuroExplorer PET/CT at UZ/KU Leuven” for those study parts where the investigational device the “NeuroEXPLORER PET/CT” is used.

This Master Protocol EUDAMED_CIV-25-06-053398 and accompanying documents (in particular IB, IFU, ICF_MDR_NX) are to be seen an integral part for the conduct of this Clinical Trial Protocol.

Prospective trial of [18F]AIF-FAPI-74 for PET imaging of fibroblast activation protein in patients with endometriosis

EM-FAPI

Version number: v2.1 – **Date** <09072026>

EU CT Number: 2026-525272-25 + EUDAMED_CIV-25-06-053398

Internal ref. number: **S71544**

Sponsor

University Hospitals Leuven (UZ Leuven)

Herestraat 49, B-3000 Leuven

Coordinating Investigator

Dr. Niloefar Ahmadi Bidakhvidi

(in case of monocentric Trial, the Principal Investigator is the same as the Coordinating Investigator)

Confidentiality Statement

The information in this document is strictly confidential and is available for review to Investigators, potential Investigators and appropriate Ethics Committees, Institutional Review Boards or Competent Authorities. No disclosure should take place without written authorization from the Sponsor.

LIST OF PARTICIPATING SITES

List Of Participating Sites

University Hospitals Leuven (UZ Leuven)
Herestraat 49, 3000 Leuven

Principal Investigator

Dr. Niloefar Ahmadi Bidakhvidi

SIGNATURES

Title: Prospective trial of [18F]AIF-FAPI-74 for PET imaging of fibroblast activation protein in patients with endometriosis

Protocol: EM-FAPI

The undersigned confirm that the above referenced protocol has been acknowledged and accepted, and agree to conduct the Trial in compliance with the approved protocol, and will adhere to: the principles outlined in the requirements for the conduct of clinical trials in the EU as provided for in the EU Clinical Trial Regulation 536/2014 (CTR) and any subsequent amendments thereto, the ICH guidelines, the most recent version of the Declaration of Helsinki, the Belgian law of May 7th 2017 related to clinical trials on medicinal products for human use, the EU General Data Protection Regulation 2016/679 (GDPR), the Belgian law of July 30th 2018 on the protection of natural persons with regard to the processing of personal data, the Belgian Law of August 22nd 2002 on patient rights, and any other regulatory requirements and Standard Operating Procedures (SOPs), as applicable.

The undersigned agree not to disclose the confidential information contained in this document for any purpose other than the evaluation or conduct of the Trial, without prior written consent of the Sponsor.

The undersigned also commit to making the findings of the Trial publicly available through publication and/or other dissemination tools, in accordance with this protocol and applicable regulations, without any unnecessary delay and to provide an honest, accurate and transparent account of the Trial; and to explain any discrepancies or deviations from the approved Trial protocol.

Coordinating Investigator

Dr. Niloefar Ahmadi Bidakhvidi

9/7/2026

.....		
Name & Title	Signature	Date

Principal Investigator (Participating Site) *(in case of monocentric Trial, the Principal Investigator is the same as the Coordinating Investigator)*

Dr. Niloefar Ahmadi Bidakhvidi

9/7/2026

.....		
Name & Title	Signature	Date

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LIST OF ABBREVIATIONS

Abbreviation	Definition
(e)CRF	(electronic) Case Report Form
AE	Adverse Event
AESI	Adverse Event of Special Interest
AR	Adverse Reaction
CA	Competent Authority
CAF	Cancer-associated fibroblasts
CI	Coordinating Investigator
CM	Concomitant Medication
CSR	Clinical Study Report
CT	Computed Tomography
CTP	Clinical Trial Protocol
CTIS	Clinical Trial Information System
CTR	EU Clinical Trial Regulation 536/2014
DE	Deep Infiltrating Endometriosis
DMP	Data Management Plan
DPA	Data Processing Annex
DSMB	Data Safety Monitoring Board
DSUR	Development Safety Update Report
EC	Ethics Committee
EU	European Union
ECG	Electrocardiogram
EoT	End of Trial
FAP	Fibroblast Activation Protein
FAPI	Fibroblast Activation Protein Inhibitor
FDG	Fluorodeoxyglucose
FPFV	First Patient First Visit
GCP	Good Clinical Practice (latest version of ICH E6)
GDPR	EU General Data Protection Regulation 2016/679
GnRH	Gonadotropin-Releasing Hormone
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council on Harmonisation
IHC	Immunohistochemistry
IMP	Investigational Medicinal Product
ISF	Investigator Site File
JCI	Joint Commission International
LPLV	Last Patient Last Visit
MAH	Marketing Authorisation Holder

MP	Monitoring Plan
MRI	Magnetic Resonance Imaging
NX	NeuroEXPLORER
PET	Positron Emission Tomography
PI	Principal Investigator (Participating Site)
PRO	Patient Reported Outcome
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SPE	Superficial Peritoneal Endometriosis
SUSAR	Suspected Unexpected Serious Adverse Reaction
SUV	Standardized Uptake Value
TBR	Tumor-to-Background Ratio
TMF	Trial Master File
UHR	Ultra-High Resolution
WOCBP	Women of Childbearing Potential

FUNDING AND THIRD PARTIES

Funder or service provider

UZ Leuven

Type of Support

- KOOR-FAS 30.000 euro (RTI556 FAS)
- Scientific reserve budget Nuclear Medicine P70010

Reasonable travel expenses incurred by Trial participants and directly related to participation in the Trial, will be reimbursed by the Sponsor, as follows:

- (i) At a flat rate of €35

A travel reimbursement payment log will be kept by the Investigator Site staff and made available for monitoring and verification purposes.

ROLES AND RESPONSIBILITIES

The Principal Investigator (PI) is responsible for the conduct of the Trial at his/her Participating Site, and for protecting the rights, safety and well-being of the Trial participants. As such the PI must ensure adequate supervision of the Trial conduct at the Participating Site. If any tasks are delegated, the PI will maintain a log of appropriately qualified persons to whom he/she has delegated specified Trial-related duties. The PI will ensure that adequate training is provided and documented for all Trial staff, prior to conducting assigned Trial-related activities.

It is the Coordinating Investigator's (CI's) responsibility to supervise the general conduct (e.g. Trial progress, communication, protocol training and support of the participating sites, annual reporting to the Ethics Committee (EC), end of Trial notification(s) and results reporting...) of the Trial. The CI fulfils both Investigator and Sponsor responsibilities, as outlined in latest version of the International Council on Harmonisation – Good Clinical Practice (ICH-GCP) E6 and applicable regulations.

PI and CI shall each be referred to as «Investigator(s)».

TRIAL SYNOPSIS

Title of clinical Trial («Trial»)	Prospective trial of [¹⁸ F]AIF-FAPI-74 for PET imaging of fibroblast activation protein in patients with endometriosis
Protocol Short Title Acronym	EM-FAPI
Trial Phase (I, II, III, IV)	II
Sponsor name	University Hospitals Leuven (UZ Leuven)
Coordinating Investigator	Dr. Niloefar Ahmadi Bidakhvidi
Contact Address CI	Herestraat 49, BE-3000 Leuven, Belgium
Contact Email CI	niloefar.ahmadibidakhvidi@uzleuven.be
Contact Phone CI	+3216 34 37 15
EU CT number	2026-525272-25 + EUDAMED_CIV-25-06-053398
Other public database nbr	N.A.
Medical condition or disease under investigation	Deep infiltrating endometriosis (DE), superficial peritoneal endometriosis (SPE)
Trial rationale	The aim of this project is to evaluate the diagnostic performance of non-invasive [¹⁸ F]AIF-FAPI-74 PET/CT compared to laparoscopy, which is the current standard-of-care, invasive examination to diagnose endometriosis, in patients with a suspicion of deep infiltrating endometriosis (DE) and/or superficial peritoneal endometriosis (SPE).
Primary objective	To evaluate the diagnostic performance of [¹⁸ F]AIF-FAPI-74 PET/CT for the detection of deep infiltrating endometriosis and/or superficial peritoneal endometriosis. Additional objectives related to the clinical investigational NeuroEXPLORER device: See Master Protocol EUDAMED_CIV-25-06-053398.
Trial Design	Prospective, non-randomized, single center, multi-cohort, interventional phase II trial.
Primary endpoints	Evaluation of the diagnostic performance of [¹⁸ F]AIF-FAPI-74 PET/CT as a non-invasive tool to diagnose deep infiltrating endometriosis and/or superficial peritoneal endometriosis, in comparison with intra-operative laparoscopic findings (current gold-standard) in women with suspected endometriosis. The diagnostic performance is evaluated by correlating the locations of endometriotic lesions on [¹⁸ F]AIF-FAPI-74 PET/CT and the locations of endometriotic lesions detected during laparoscopy. Additional primary endpoints related to the clinical investigational NeuroEXPLORER device: See Master Protocol EUDAMED_CIV-25-06-053398.
Secondary endpoints	I. Sensitivity, specificity, positive predictive value, negative predictive value, accuracy of [¹⁸ F]AIF-FAPI-74 PET/CT in detecting endometriotic lesions.

	2. Semi-quantitative uptake measurements (maximal standardized uptake value (SUV_{max}), average SUV (SUV_{mean}), peak SUV (SUV_{peak}) of endometriotic lesions on [^{18}F]AIF-FAPI-74 PET/CT. 3. Endometriotic lesion-to-background uptake values (SUV lesion divided by SUV background) for [^{18}F]AIF-FAPI-74 PET/CT, using following background organs: liver, lung, gluteus muscle, mediastinal bloodpool, bowel, bone marrow (L4 if no abnormal uptake). 4. Total FAP-positive endometriotic burden, defined as the sum of the volumes of all lesions deemed to be endometriotic in nature. 5. Number of additional endometriotic lesions recorded after unblinding of the surgeon during laparoscopy. 6. Diagnostic performance of MRI in detecting endometriotic lesions, in patients in which MRI is available, and comparison with [^{18}F]AIF-FAPI-74 PET/CT, laparoscopy and if available ultrasound. 7. Diagnostic performance of ultrasound in detecting endometriotic lesions, in patients in which ultrasound is available, and comparison with [^{18}F]AIF-FAPI-74 PET/CT, laparoscopy and if available MRI. 8. Impact on clinical management. 9. Psychological impact on patient of [^{18}F]AIF-FAPI-74 PET/CT procedure. 10. Intra- and interobserver reproducibility of [^{18}F]AIF-FAPI-74 PET/CT. 11. Patient safety: adverse events of [^{18}F]AIF-FAPI-74 PET/CT. 12. Correlation of [^{18}F]AIF-FAPI-74 biodistribution with FAP tissue expression as measured by immunohistochemistry (IHC). 13. Evolution of [^{18}F]AIF-FAPI-74 PET/CT scans in patients initiating GnRH-agonist or GnRH-antagonist medication and receiving 2 [^{18}F]AIF-FAPI-74 PET/CT (prior and post initiation of GnRH-agonist or GnRH-antagonist medication) : (i) number of lesion; (ii) uptake; (iii) endometriotic lesion-to-background value; (iv) correlation with laparoscopy and if available MRI and/or ultrasound. 14. Additional secondary endpoints related to the clinical investigational NeuroEXPLORER device: See Master Protocol EUDAMED_CIV-25-06-053398.
Exploratory endpoints	1. Comparison of NeuroEXPLORER PET/CT for detection and characterization of endometriotic lesions, compared with standard [^{18}F]AIF-FAPI-74 PET/CT acquisitions obtained after the same tracer injection.
Sample Size	No sample size calculation was performed for the DE and SPE cohorts given that this is a proof-of-concept, pilot study. • DE cohort: 16 participants (with possibility to add up to 16 more participants after interim analysis)

	SPE cohort: 16 participants (with possibility to add up to 16 more participants after interim analysis)
IMP, dosage and route of administration	[¹⁸ F]AIF-FAPI-74, 3.5MBq/kg, intravenous administration
Active comparator product(s)	Depending on availability from standard clinical work-up: ultrasound, CT and/or MRI.
Maximum duration of diagnostic exposure and Follow Up of a Participant	Up to 6 months
Date anticipated First Patient First Visit (FPFV)	1/9/2026
Date anticipated Last Patient Last Visit (LPLV)	31/8/2029

TRIAL FLOWCHART

Schedule of Events – Trial specific Procedures / Assessments

Procedures/ Assessment	Screening	Diagnostic period		Laparoscopy ⁶ (end of trial)	Early termination
		Visit 2	If initiation GnRH (ant)agonist ⁵ : Visit 3		
Visits / Contacts	Visit 1				
Timing		Max. 2 months after screening visit; max. 1 month before laparoscopy	Max. 5 months after screening visit; Max. 1 month before laparoscopy		
Informed consent	X ¹				
Inclusion / Exclusion criteria	X				
Demographics	X				
Medical, Surgical history	X				
Weight / Height	X				
Medical imaging (MRI, CT, echography)	X ²				
Vital signs	X ⁹	X ⁹	X ⁹		
Laboratory parameters	X ¹⁰				
Pregnancy test		X ³	X ³		
[¹⁸ F]AIF-FAPI-74 PET/CT		X ⁸	X ⁸		
Immunohistochemical staining				X ⁷	
Reason for discontinuation					X
(Serious) Adverse event (S)(AE) assessment	X ⁴	X ⁴	X ⁴	X ⁴	X ⁴

1: Informed Consent will be obtained prior to performing any other Trial-related procedures

2: Availability of medical imaging tests is not mandatory for the trial.

3: A urinary hCG pregnancy test will be conducted in all WOCBP before each administration of [¹⁸F]AIF-FAPI-74.

4: (Serious) adverse events will be assessed at every visit, the participant will also be encouraged to make contact with the study team should there be a (suspicion of) adverse event.

5: Administration of GnRH (ant)agonist is standard of care.

6: Laparoscopy is standard of care.

7: In patients who have undergone tissue removal of endometriotic lesions during their laparoscopy, we may perform additional immunohistochemical staining with a validated FAP antibody.

8: Patients may additionally undergo imaging on the NeuroEXPLORER PET/CT system using the same [¹⁸F]AIF-FAPI-74 injection administered for the standard PET/CT acquisition. This is optional and no additional radiotracer injection is required.

9: Vital signs include heart rate, blood pressure and oxygen saturation.

10: Laboratory parameters include hematology, clinical chemistry and coagulation parameters. Standard-of-care laboratory results obtained during the gynaecology consultation or pre-operative work-up may be used if available before [¹⁸F]AIF-FAPI-74 administration and considered sufficiently recent and clinically representative by the Investigator.

I Background, Rationale and Risk Assessment

Background and Rationale

At least 10% of women world-wide will be affected by **endometriosis** during their reproductive years, which is reflected by the fact that **more than 176 million women** have endometriosis worldwide [1, 2]. Despite its high prevalence, the **diagnosis** of endometriosis is typically **delayed** on average by **6-7 years** starting from symptom onset, **misdiagnosis** is common with 65% of women being initially misdiagnosed, and **delivery of effective therapy is prolonged** [2, 3]. Also, the **economic burden** is responsible for about \$70 billion in yearly health expenditures in USA alone [4].

Endometriosis is classically defined as a chronic, gynaecological disease characterised by endometrial-like tissue (endometrial epithelial and stromal cells) present outside of the uterus [2]. Endometriosis can be divided into three different types: superficial peritoneal endometriosis, deep infiltrating endometriosis and ovarian endometriosis [5]. Endometriosis lesions can grow on the outer perimetrium, fallopian tubes, ovaries, bowels, rectum, bladder or even within the thoracic cavity; leading to **debilitating symptoms** such as acute and chronic (pelvic) pain, dysmenorrhoea and infertility [4].

The question remains **why there is such a delay in diagnosis and treatment of endometriosis**, even though the disease has a high prevalence, comes with debilitating symptoms and leads to a high cost for society. There are two major factors for this problem. First, women experience difficulty that their **symptoms are inappropriately normalised** by the health care system [2]. Second, the current standard-of-care for the diagnosis of endometriosis is **diagnostic laparoscopy**, which is an invasive surgery prone to sampling and operator bias [2, 4]. Moreover, the absence of visible lesions during surgery or negative histology of the surgical specimens does not exclude the diagnosis of endometriosis given that occult endometriosis has been documented in random peritoneal biopsy specimens [2].

In an attempt to reach a quicker diagnosis of endometriosis, efforts have been made to find radiological methods with high accuracy in diagnosing endometriosis. First, **transvaginal ultrasound** is the most commonly used imaging tool, with a high accuracy for diagnosing endometriomas and it may offer improved accuracy for deep-infiltrating endometriosis, however transvaginal ultrasound is suboptimal in visualising peritoneal lesions and smaller endometriosis lesions. Second, magnetic resonance imaging (**MRI**) can be used to determine the size, location, and infiltrative stage of large lesions before surgical resection, especially in cases of deep-infiltrating endometriosis, however MRI is also suboptimal in visualising peritoneal lesions and smaller endometriosis lesions [2, 4]. Therefore, the current radiological methods can be used as a tool to aid the diagnosis, however given that diagnostic laparoscopy is still the current standard-of-care, there is a **need for novel non-invasive diagnostic procedures** to diagnose endometriosis.

Molecular imaging with positron emission tomography (**PET**) is currently an **indispensable tool** for modern oncological and inflammatory/infectious care. PET allows repetitive detection and quantitation of molecular processes within human beings in a non-invasive manner with a high spatial resolution (≈ 4 mm) [6]. The molecular information obtained is dependent on the specific radiopharmaceutical (synonym: tracer) being injected. The **most used radiopharmaceutical in clinical practice is [^{18}F]FDG**, with more than 1 million patients scanned worldwide per year and >60,000 scans/year in Belgium (Flanders: >30,000). [^{18}F]FDG, a glucose analog tracing glucose metabolism, has proven to be a very potent tracer to detect viable cancer cells and inflammatory/infectious processes. However, [^{18}F]FDG PET performs poorly in a number of cancer types or inflammatory processes with low glycolytic phenotype. A recently published systematic review by Fox et al. included 7 cohort studies including 98 patients, that have investigated [^{18}F]FDG PET in endometriosis and concluded that [^{18}F]FDG PET does not appear to consistently identify endometriosis lesions, and therefore its **reliability and usefulness in endometriosis diagnosis is limited** [3].

Recently, a novel and promising PET tracer class has emerged with a potential to replace [^{18}F]FDG as a general tracer for staging and follow-up of cancer in selected indications. The novel PET tracers are based on fibroblast activation protein α inhibitors (**FAPi**). FAP is a type II integral membrane protein and a

member of the dipeptidyl peptidase (DPP) 4 family. FAP is overexpressed in **cancer-associated fibroblasts (CAF)**, which are abundant in the tumoral stroma. One tracer, [¹⁸F]AIF-FAPI-74, is labeled with fluorine-18, similar to [¹⁸F]FDG, and can be centrally prepared in a radiopharmacy and shipped to distant PET centers. Pilot data from FAPI PET has shown better sensitivity and specificity compared to other imaging techniques, including [¹⁸F]FDG PET/CT, in a range of tumor types [7, 8].

As mentioned earlier, endometriosis is classically defined as a chronic, gynaecological disease characterised by endometrial-like tissue (endometrial epithelial and stromal cells) present outside of the uterus [2]. However, evidence has emerged in recent literature that the definition falls short due to the low representation of epithelial cells in some lesions. Moreover, endometriosis appears to be fibrotic of nature in all stages of the disease, which is leading to a redefinition of **endometriosis as a pro-fibrotic disease** [9, 10].

In a recent European patent application titled “Agents for treatment of endometriosis and other benign gynecological neoplasms”, the inventors demonstrated for the **first time** that in **endometriosis patient samples, FAP is expressed** on the surface of **ectopic endometrium as well as endometriosis associated adhesions** [10]. Depending on the sample, the proportion of FAP-positive stromal cells was 67.3% for ovarian endometriosis, 98.1% for deep infiltrating endometriosis, and 85.1% for endometriosis adhesions. In comparison, the eutopic endometrial fibroblasts expressed FAP 13.8% on average, which confirms the low expression of FAP in the healthy uterus. Given the high expression of FAP in endometriosis lesions, FAPI PET could be a novel imaging method in these types of patients. Given the novelty of the FAP PET tracer and the novelty of the confirmation of FAP expression in endometriosis lesions, **the use of FAPI PET in endometriosis has not yet been investigated**.

Furthermore, a novel breakthrough development in molecular imaging is the **next-generation ultra-high resolution PET/CT system**, the NeuroEXPLORER (NX) [11]. The NX features a long axial field-of-view (AFOV) design with a 49.5 cm axial length and advanced high-resolution PET detectors, providing both markedly increased sensitivity and strongly improved spatial resolution (~1.5 mm). This results in an approximately twenty-fold improvement in volumetric resolution compared with current standard clinical PET systems. The improved image quality and lesion detectability of the NeuroEXPLORER PET/CT may be particularly relevant for the detection of small lesions or lesions with low tracer uptake. Given the often small size and infiltrative nature of endometriotic lesions, the enhanced spatial resolution of the NeuroEXPLORER system may further improve lesion conspicuity and anatomical delineation. Although the system was designed for brain imaging, a feet-first approach allows us to scan from midfemoral to abdominal making use of a bed modification (CIV-25-06-053398 amendment 3; May 2026).

We designed this prospective, pilot trial of **[¹⁸F]AIF-FAPI-74 PET/CT in patients with endometriosis** in which its diagnostic accuracy will be compared with laparoscopy. Two patient cohorts will be investigated:

1. Clinical or diagnostic suspicion of deep infiltrating endometriosis
2. Clinical or diagnostic suspicion of superficial peritoneal endometriosis

An additional exploratory acquisition on the NeuroEXPLORER PET/CT system on the same day may be performed following the standard [¹⁸F]AIF-FAPI-74 PET/CT acquisition, using the same tracer injection and without additional radiopharmaceutical administration.

As a result of current diagnostic delays of endometriosis, the life impact is more severe than would be expected if treatment were prompt and effective. It is clear that early identification and treatment of endometriosis is essential and facilitated by a shift towards an earlier clinical/imaging-based diagnosis instead of relying on surgical diagnosis alone [2]. Therefore, we believe this prospective, pilot trial will be of great importance for the large amount of women dealing with endometriosis.

Risk assessment

The potential risks associated with participation in this trial are mainly related to exposure to ionising radiation, intravenous administration of the radiopharmaceutical, potential hypersensitivity reactions, and insertion of the venous catheter.

Participants will be exposed to ionising radiation from the [^{18}F]AIF-FAPI-74 PET/CT scan, including the low-dose CT component. The total radiation burden is described in Section 5.1. The estimated radiation burden is 7.7 mSv per [^{18}F]AIF-FAPI-74 PET/CT scan, with an additional 0.8 mSv in case an optional NeuroEXPLORER PET/CT scan is performed due to the additional low-dose CT. In participants undergoing a second [^{18}F]AIF-FAPI-74 PET/CT scan after initiation of GnRH agonist or antagonist treatment, the radiation exposure will be cumulative. The radiation exposure is considered justified by the potential diagnostic value of the study and the expected societal benefit of improving non-invasive diagnosis of endometriosis. Pregnant participants are excluded from the study, and pregnancy testing and contraception requirements are described in the protocol.

[^{18}F]AIF-FAPI-74 is administered as a radiopharmaceutical tracer in microdose amounts, below the pharmacological threshold, and no pharmacological effect is expected. Nevertheless, as with any administered medicinal product, hypersensitivity reactions, including rare anaphylactic reactions, cannot be fully excluded. Participants with known hypersensitivity to [^{18}F]AIF-FAPI-74 or its excipients are excluded. Participants will be monitored during and after administration and imaging. Suspected hypersensitivity or anaphylactic reactions will be managed according to local UZ Leuven emergency procedures and the protocol safety reporting procedures.

The insertion of the venous catheter and intravenous administration may cause transient pain, bruising, ecchymosis, haematoma, local inflammation, vasovagal reaction, or paravenous injection/extravasation. These risks will be minimized by having experienced qualified staff place and check the IV line. The IV line will be flushed before tracer administration. If paravenous injection occurs, it will be managed according to the standard operating procedure of the nuclear medicine department. All clinically relevant adverse events will be documented and reported according to the protocol safety reporting procedures.

2 Trial Objectives and Design

2.1 Trial objectives

The aim of this project is to evaluate the diagnostic performance of non-invasive [^{18}F]AIF-FAPI-74 PET/CT compared to laparoscopy, which is the current standard-of-care, invasive examination to diagnose endometriosis, in patients with a suspicion of deep infiltrating endometriosis and/or superficial peritoneal endometriosis.

We hypothesize that [^{18}F]AIF-FAPI-74 PET/CT may detect endometriotic lesions and provide diagnostic information in patients with suspected endometriosis.

Additional objectives related to the clinical investigational NeuroEXPLORER device: See Master Protocol EUDAMED_CIV-25-06-053398.

2.2 Primary Endpoints

Evaluation of the diagnostic performance of [^{18}F]AIF-FAPI-74 PET/CT as a non-invasive tool to diagnose deep infiltrating endometriosis and/or superficial peritoneal endometriosis, in comparison with intra-operative laparoscopic findings (current gold-standard) in women with suspected endometriosis. The diagnostic performance is evaluated by correlating the locations of endometriotic lesions on [^{18}F]AIF-FAPI-74 PET/CT and the locations of endometriotic lesions detected during laparoscopy.

Additional primary endpoints related to the clinical investigational NeuroEXPLORER device: See Master Protocol EUDAMED_CIV-25-06-053398.

2.3 Secondary Endpoints

1. Sensitivity, specificity, positive predictive value, negative predictive value, accuracy of [^{18}F]AIF-FAPI-74 PET/CT in detecting endometriotic lesions.
2. Semi-quantitative uptake measurements (maximal standardized uptake value (SUV_{max}), average SUV (SUV_{mean}), peak SUV (SUV_{peak}) of endometriotic lesions on [^{18}F]AIF-FAPI-74 PET/CT.

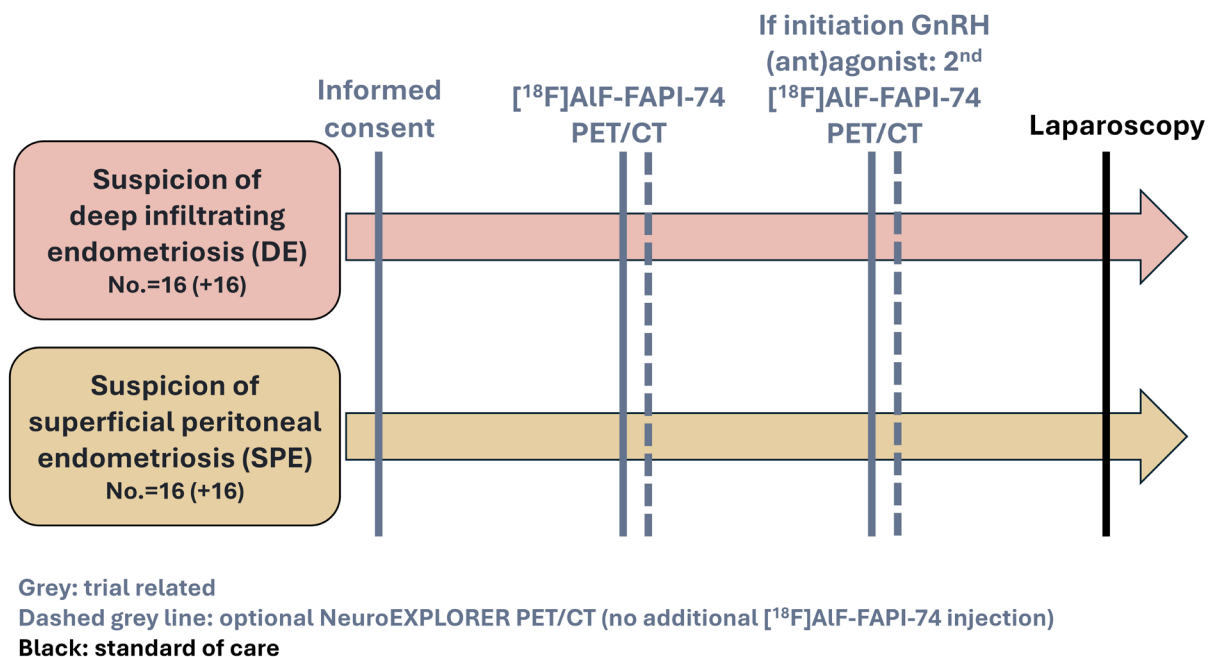
3. Endometriotic lesion-to-background uptake values (SUV lesion divided by SUV background) for [^{18}F]AIF-FAPI-74 PET/CT, using following background organs: liver, lung, gluteus muscle, mediastinal bloodpool, bowel, bone marrow (L4 if no abnormal uptake).
4. Total FAP-positive endometriotic burden, defined as the sum of the volumes of all lesions deemed to be endometriotic in nature.
5. Number of additional endometriotic lesions recorded after unblinding of the surgeon during laparoscopy.
6. Diagnostic performance of MRI in detecting endometriotic lesions, in patients in which MRI is available, and comparison with [^{18}F]AIF-FAPI-74 PET/CT, laparoscopy and if available ultrasound.
7. Diagnostic performance of ultrasound in detecting endometriotic lesions, in patients in which ultrasound is available, and comparison with [^{18}F]AIF-FAPI-74 PET/CT, laparoscopy and if available MRI.
8. Impact on clinical management.
9. Psychological impact on patient of [^{18}F]AIF-FAPI-74 PET/CT procedure.
10. Intra- and interobserver reproducibility of [^{18}F]AIF-FAPI-74 PET/CT.
11. Patient safety: adverse events of [^{18}F]AIF-FAPI-74 PET/CT.
12. Correlation of [^{18}F]AIF-FAPI-74 biodistribution with FAP tissue expression as measured by immunohistochemistry (IHC).
13. Evolution of [^{18}F]AIF-FAPI-74 PET/CT scans in patients initiating GnRH-agonist or GnRH-antagonist medication and receiving 2 [^{18}F]AIF-FAPI-74 PET/CT (prior and post initiation of GnRH-agonist or GnRH-antagonist medication) : (i) number of lesion; (ii) uptake; (iii) endometriotic lesion-to-background value; (iv) correlation with laparoscopy and if available MRI and/or ultrasound.
14. Additional secondary endpoints related to the clinical investigational NeuroEXPLORER device: See Master Protocol EUDAMED_CIV-25-06-053398.

2.4 Exploratory endpoints

- I. Comparison of NeuroEXPLORER PET/CT for detection and characterization of endometriotic lesions, compared with standard [^{18}F]AIF-FAPI-74 PET/CT acquisitions obtained after the same tracer injection.

2.5 Trial Design

The design of the trial is a prospective, non-randomized, single center, multi-cohort, interventional phase II trial.



2.5.1 Use of In-Vitro Diagnostic (IVD) or Medical Device (MD)

This trial is not investigating an IVD. The optional NeuroEXPLORER PET/CT acquisition is performed under the separately approved Master Clinical Investigation Protocol EUDAMED_CIV-25-06-053398.

2.6 Expected Duration of the Trial

Expected trial duration for a single participant: cfr. figure above and trial flowchart. The expected trial duration for participants receiving only 1 [¹⁸F]AIF-FAPI-74 PET/CT is 3 months. The expected trial duration for participants receiving 2 [¹⁸F]AIF-FAPI-74 PET/CT is 6 months.

Expected overall trial duration: see table below.

	Year 1				Year 2				Year 3			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Clinical trial execution												
First patient inclusion												
Last patient inclusion												
Last data collected												
Image analysis												
Statistical analysis and reporting												

The End of Trial is defined as Last Patient Last Visit (LPLV). The CI shall notify the CA/EC of the end of the Trial using the CTIS portal. The CI will submit a final report with the results of the study, including any publications/abstracts, to the CA/EC within 1 year of trial termination. The CTIS portal will be used for communication with the CA/EC of all participating Member States.

The Sponsor, CA/EC can decide to halt or prematurely terminate the Trial when new information becomes available whereby the rights, safety and well-being of Trial participants can no longer be assured, when the integrity of the Trial has been compromised, or when the scientific value of the Trial becomes obsolete and/or unjustifiable.

Circumstances requiring premature treatment interruption or discontinuation of the Trial, include but are not limited to:

- Safety concerns related to IMP or unacceptable intolerability

- Unexpected claustrophobia

Should the Trial be temporarily suspended or, ended prematurely, the CI will notify the CA/EC and include the reasons for suspension/premature termination within 15 days of the decision.

3 Trial Population / Eligibility Criteria

3.1 Inclusion criteria

Participants eligible for inclusion in this Trial must meet **all** of the following criteria:

DE (deep infiltrating endometriosis) cohort:

1. Voluntary written informed consent of the participant has been obtained prior to any screening procedures.
2. At least 18 years of age at the time of signing the Informed Consent Form (ICF).
3. At least one of the following:
 - Clinical suspicion of DE, defined as the presence of deep nodule(s) during vaginal examination determined by a clinician who is an expert in endometriosis.
 - Diagnostic suspicion of DE, defined as an ultrasound and/or MRI that shows lesions suspicious for DE.
4. Planned laparoscopy for suspected endometriosis.

SPE (superficial peritoneal endometriosis) cohort:

1. Voluntary written informed consent of the participant has been obtained prior to any screening procedures.
2. At least 18 years of age at the time of signing the Informed Consent Form (ICF).
3. At least one of the following:
 - Clinical suspicion of SPE, defined as clinical symptoms suspicious of SPE determined by a clinician who is an expert in endometriosis. These clinical symptoms include dysmenorrhea, deep dyspareunia, dysuria, dyschezia, painful rectal bleeding or haematuria, shoulder tip pain, catamenial pneumothorax, cyclical cough/haemoptysis/chest pain, cyclical scar swelling and pain, fatigue, and infertility.
 - Diagnostic suspicion of SPE, defined as an ultrasound and/or MRI that shows lesions suspicious for SPE.
4. Planned laparoscopy for suspected endometriosis.

All participants that are considered for Trial participation, per the above criteria will be documented via applicable log forms in Investigator Site File (including Screen Failures).

3.2 Exclusion criteria

Participants eligible for this Trial must **not** meet any of the following criteria:

DE cohort:

1. Prior abdominal surgery less than one year ago.
2. Female who is pregnant, breast-feeding or is of child-bearing potential and not using an adequate, highly effective contraceptive or no usage of contraception when sexually active are not accepted.
3. Participant is mentally or legally incapacitated, does not understand the study design or is not willing or capable to undergo all study-specific procedures.
4. Any disorder or condition, which in the Investigator's opinion might jeopardise the participant's safety or compliance with the protocol, or may influence the result of the study.

5. Any prior or concomitant treatment(s) that might jeopardise the participant's safety or that would compromise the integrity of the Trial.
6. Participation in an interventional Trial with an investigational medicinal product (IMP) or device when the trial designs are not considered compatible by the study team.
7. Participation in a clinical scientific study in the last 12 months with a radiation exposure caused by the experimental procedures greater than 1 mSv.
8. Participant has a known hypersensitivity to [¹⁸F]AIF-FAPI-74 or the used excipients.

SPE cohort:

1. Ultrasound and/or MRI with lesions suspicious of ovarian endometriosis and/or DE.
2. Clinical symptoms suspicious of ovarian endometriosis and/or DE, determined by a clinician who is an expert in endometriosis.
3. Prior abdominal surgery less than one year ago.
4. Female who is pregnant, breast-feeding or is of child-bearing potential and not using an adequate, highly effective contraceptive or no usage of contraception when sexually active are not accepted.
5. Participant is mentally or legally incapacitated, does not understand the study design or is not willing or capable to undergo all study-specific procedures.
6. Any disorder or condition, which in the Investigator's opinion might jeopardise the participant's safety or compliance with the protocol, or may influence the result of the study.
7. Any prior or concomitant treatment(s) that might jeopardise the participant's safety or that would compromise the integrity of the Trial.
8. Participation in an interventional Trial with an investigational medicinal product (IMP) or device when the trial designs are not considered compatible by the study team.
9. Participation in a clinical scientific study in the last 12 months with a radiation exposure caused by the experimental procedures greater than 1 mSv.
10. Participant has a known hypersensitivity to [¹⁸F]AIF-FAPI-74 or the used excipients.

Participants who meet one or more of the above exclusion criteria **must not proceed** to be enrolled in the Trial and will be identified via applicable log forms in Investigator Site File.

4 Trial Procedures

4.1 Selection of Participants / Recruitment

Potential participants will be identified and recruited during patient consultations in UZ Leuven. No additional recruitment material (such as for example flyers, social media advertising, audio/video recordings) will be used.

For all the included patient cohorts, patients will be identified at outpatient clinic of gynaecology. Participation to the trial will be proposed by the treating physician. He/ she will inform the patient about the aims, risks, study design and implications for the patient. If the patient is interested in participation, a screening visit will take place. The informed consent will be discussed and given to the patient (either by the treating physician or someone from the study team). Between 48 hours and one week after the discussion of the informed consent, the participant will be contacted to ask more questions if needed and to confirm their decision. The ICF will be signed on the day of the [¹⁸F]AIF-FAPI-74 PET/CT (or prior if wanted by the patient). We assume that many patients will seize the opportunity to clarify their situation with this novel and promising scan.

4.2 Trial assessments and procedures

Trial procedures and their timing are summarized in the Trial Flowchart.

4.2.1 Participant consent and withdrawal of consent

The Trial will be conducted only on the basis of prior informed consent by the Trial participants and/or their legally authorized representative(s). As such, no Trial-related procedures will be conducted prior to obtaining written informed consent from potential Trial participants.

The process for obtaining and documenting initial and continued informed consent from potential Trial participants will be conducted in accordance with GCP, applicable regulatory requirements and internal Standard Operating Procedures (SOPs).

All originally signed obtained Informed Consent Forms (ICFs) must be retained/archived in the Investigator Site File (ISF) at the Participating Site and must not be destroyed (even when a scanned copy is available) before expiration of the legal archiving term as defined in the protocol section entitled "Archiving".

Participants may voluntarily withdraw consent to participate in the Trial for any reason at any time. The participant's request to withdraw from the Trial must always be respected without prejudice or consequence to further treatment. Consent withdrawal will be documented in the participant's medical record.

Trial data and samples collected before withdrawal can be used in the trial. No new trial data or samples will be collected after withdrawal of the participant.

4.2.2 Randomization Procedure / Blinding (if applicable)

Randomization: not applicable

Blinding:

To avoid bias, reference readers of the [^{18}F]AIF-FAPI-74 PET/CT will be blinded as follows:

The [^{18}F]AIF-FAPI-74 PET/CT images will be centrally collected in UZ Leuven and pseudo-anonymized. The investigational [^{18}F]AIF-FAPI-74 PET/CT will be collected, assessed for quality and prospectively scored and semi-quantified by two blinded readers, blinded for clinical and/or other imaging information. A third blinded reader will arbitrate in case of discordant findings. The final score will be recorded and locked.

4.2.3 Unblinding

Participants, referring physicians and the study team will be aware of the fact that the patient undergoes a [^{18}F]AIF-FAPI-74 PET/CT. The surgeon who performs the laparoscopy for suspected endometriosis will perform the initial laparoscopic assessment blinded to the [^{18}F]AIF-FAPI-74 PET/CT findings. An Investigator or delegated study representative will be present during the laparoscopic procedure to support study-specific documentation and to manage the predefined unblinding process. During the blinded part of the laparoscopy, the surgeon will inspect and document the laparoscopic findings using the predefined laparoscopic documentation template. This blinded laparoscopic assessment must be completed and documented before the [^{18}F]AIF-FAPI-74 PET/CT findings are disclosed to the surgeon. After completion and documentation of the initial blinded laparoscopic assessment, the surgeon will be unblinded by default to the [^{18}F]AIF-FAPI-74 PET/CT findings in the operating room by the Investigator or delegated study representative. The time and date of unblinding will be recorded. After unblinding, a PET-guided second-look will be performed only if the [^{18}F]AIF-FAPI-74 PET/CT shows one or more lesions suspicious for endometriosis that were not identified or documented during the initial blinded laparoscopic assessment. In that case, the surgeon will perform a focused second-look of the corresponding anatomical region(s), provided that this is considered safe and clinically appropriate. If no PET/CT-suspected additional lesions are present, or if all PET/CT-suspected lesions have already been identified during the blinded laparoscopic assessment, no PET-guided second-look is required. If a PET-guided second-look is not performed despite PET/CT-positive, laparoscopy-negative findings, the reason will be documented in the source documents and/or eCRF. Participant safety remains the first priority. The surgeon may decide not to perform or to stop the PET-guided second-look if further inspection is considered unsafe or clinically inappropriate, for example due to anaesthetic or surgical concerns, anatomical inaccessibility, adhesions, technical limitations, or any other participant safety consideration. Detailed description of the lesion matching methodology can be found in Section 7.2.1.

In case of unsuspected non-endometriosis related findings, the PI can communicate these findings to the treating physician if this is deemed necessary from a medical point of view.

4.2.4 Other Trial assessments and procedures

Screening visit

Participation to the trial will be proposed by the treating physician. He/ she will inform the patient about the aims, risks, study design and implications for the patient. If the patient is interested in participation, a screening visit will take place. During the screening visit, performed either by the treating physician or someone from the study team, the informed consent will be discussed and given to the patient. The inclusion and exclusion criteria will be assessed. Upon successful recruitment subjects will get a study number that makes them pseudonymized. Their demographics, relevant medical or surgical history and concomitant medication will be registered. Potential factors that may influence [^{18}F]AIF-FAPI-74 uptake will be documented at screening, where applicable. These include prior abdominal or pelvic surgery, adhesions, known inflammatory bowel disease, pelvic inflammatory disease, recent infection or inflammation, autoimmune or systemic inflammatory disease, known fibrotic disease, malignancy, and relevant concomitant medication, including hormonal, anti-inflammatory or immunomodulatory treatment.

At screening, baseline vital signs (including heart rate, blood pressure and oxygen saturation) and baseline laboratory parameters will be documented to support safety assessment and AE monitoring. Laboratory parameters will include haematology, clinical chemistry and coagulation parameters. Where available, standard-of-care laboratory results obtained during the gynaecology consultation or pre-operative work-up may be used as baseline safety parameters, provided they are available before [^{18}F]AIF-FAPI-74 administration and are considered sufficiently recent and clinically representative by the Investigator. If no suitable standard-of-care laboratory results are available, these assessments will be performed as part of the screening assessment. Clinically relevant abnormalities in vital signs or laboratory parameters will be assessed by the Investigator. If such abnormalities are considered to jeopardise participant safety, protocol compliance, or the integrity or interpretability of the study results, the participant will not proceed to study-related radiopharmaceutical administration or participation may be postponed.

The screening visit will take place maximum two months before the first imaging scan of the diagnostic period. The estimated duration of this screening is one hour. Between 48 hours and one week after the discussion of the informed consent, the participant will be contacted to pose more questions if needed and to confirm their decision on inclusion.

Diagnostic period

Maximum two months after the screening visit, visit 2 will take place, during which a [^{18}F]AIF-FAPI-74 PET/CT will be performed. Standard PET/CT scanners available at UZ Leuven are a Siemens Vision-X (Siemens Healthineers, Forchheim, Germany) or a GE Discovery MI4 (GE Healthcare, Chicago, USA). Subjects are required to be sober four hours before the scan. There are no other dietary restrictions. All concomitant medication is allowed and can be taken (at home) on the day of the scan. Participants will be instructed to maintain adequate hydration before and after each [^{18}F]AIF-FAPI-74 PET/CT scan in order to support urinary elimination of radioactivity. Unless medically contraindicated, participants will be advised to drink one to two litres of additional water during the 24 hours before the examination. After the examination, participants will be advised to drink sufficiently during the first hours and to urinate regularly, as radioactivity is eliminated from the body via the urine. Participants with a medical contraindication to increased fluid intake, should follow the advice of the Investigator or treating physician. Prior to [^{18}F]AIF-FAPI-74 administration, baseline vital signs (including heart rate, blood pressure and oxygen saturation) will be documented to support safety assessment and AE monitoring, and a pregnancy test will be performed in women of childbearing potential. Participants with a positive pregnancy test will not proceed to [^{18}F]AIF-FAPI-74 administration or any further study-specific procedures.

Hereafter, the patient will get an intravenous line, through which the [^{18}F]AIF-FAPI-74 will be injected in one bolus (3.5 MBq/kg). After 60 minutes, the acquisition on the PET/CT scan will take place.

Patients will receive an IV injection of Buscopan (20 mg, unless contra-indicated) before the PET/CT scan, which is used in routine clinical practice to reduce bowel peristalsis in high-resolution imaging. After Buscopan administration, participants will be clinically observed for potential adverse reactions. Participants will be informed that temporary visual disturbances may occur after Buscopan administration and that driving a vehicle is not recommended during the first hours after the examination if such symptoms occur. Any adverse event occurring after Buscopan administration will be documented and reported in accordance with the protocol safety reporting procedures.

After the scan, participants will be asked to stay for at least 30, up to 60 minutes at the department in case of adverse events. The estimated duration of this visit is three hours. If the patient has initiated GnRH (anta)gonist medication after the first [^{18}F]AIF-FAP-74 PET/CT was performed, we will perform a second [^{18}F]AIF-FAP-74 PET/CT maximum one month before laparoscopy.

Participants may additionally undergo imaging on the NeuroEXPLORER PET/CT system on the same day as the corresponding standard [^{18}F]AIF-FAP-74 PET/CT acquisition. This additional NeuroEXPLORER PET/CT acquisition is optional. The NeuroEXPLORER PET/CT acquisition will use the same [^{18}F]AIF-FAP-74 injection administered for the corresponding standard PET/CT acquisition. No additional radiotracer injection is required. The optional NeuroEXPLORER PET/CT acquisition may be performed after the first standard [^{18}F]AIF-FAP-74 PET/CT and, where applicable, after the second standard [^{18}F]AIF-FAP-74 PET/CT performed after initiation of GnRH agonist or antagonist treatment. When performed, the NeuroEXPLORER PET/CT acquisition should start as soon as feasible after the corresponding standard PET/CT acquisition and no later than 220 minutes after the start of the corresponding standard PET/CT acquisition. The timing of tracer injection, standard PET/CT acquisition and NeuroEXPLORER PET/CT acquisition will be documented.

In patients who have undergone tissue removal of endometriotic lesions during their laparoscopy, we will perform additional immunohistochemical staining with a validated FAP antibody (Anti-Fibroblast activation protein, alpha antibody [EPR20021]) on the endometriotic lesion.

4.3 Premature discontinuation of Trial treatment

Participants may voluntarily discontinue from Trial treatment and/or prematurely end their participation in the Trial for any reason at any time. In such case the Investigator must make a reasonable effort to contact the participant (e.g. via telephone, e-mail) in order to document the primary reason for this decision.

The Investigator may also decide at any time during the course of the Trial, to temporarily interrupt or permanently discontinue the Trial treatment if it is deemed that continuation would be detrimental to, or not in the best interest of the participant.

Circumstances requiring premature treatment interruption or discontinuation of the Trial, include but are not limited to:

- Trial participation while in violation of the inclusion and/or exclusion criteria
- Pregnancy
- Intention of becoming pregnant

In any such case of early Trial termination and/or treatment interruption/discontinuation, the Investigator will continue to closely monitor the participant's condition and ensure adequate medical care and follow-up.

For participants whose status is unclear because they fail to appear for Trial visits without stating an intention to discontinue or withdraw, the Investigator must make every effort to demonstrate "due diligence" by documenting in the source documents which steps have been taken to contact the participant to clarify their willingness and ability to continue their participation in the Trial (e.g. dates of telephone calls, , etc.).

A participant should not be considered lost to follow-up until due diligence has been completed.

Subjects who have signed an informed consent form, but are ultimately not enrolled in the trial, will be considered as screen failures. For these subjects, only the selection data and the reason for no inclusion will be noted in the eCRF.

For subjects withdrawn from the trial after the injection of the study drug, all data available at the time of withdrawal will be reported in the eCRF (e.g.: inclusion data, safety data, administration data, imaging data, reason for withdrawal...). The investigator will try to collect and record all follow-up safety information (i.e., adverse experiences, injection-site tolerance, and vital signs, as appropriate), unless the subject withdraws consent for further participation in the study.

5 Trial Medication / Drug

Generic Drug Name (& company brand name)	IMP or non-IMP	Used within Indication? (Y or N)	Route of administration (po,sc,iv,...)	Dose/dosage and units
[¹⁸ F]AIF-FAPI-74	IMP	N	IV	3.5 MBq/kg

5.1 Investigational Medicinal Product and Dosing Regimen

All aspects of this study have been designed to qualify for consideration under the EU regulations for “microdosing”. A detailed description of the radiosynthesis is provided in the Investigational Medicinal Product Dossier (IMPD) and preclinical information together with a summary of human clinical findings if given in the IB.

[¹⁸F]AIF-FAPI-74 will be synthesized under GMP circumstances as described in the IMPD at UZ Leuven. The radiopharmaceutical will be administered by a slow single intravenous injection.

The injected activity is 3.5 MBq/kg (resulting in 3.4 mSv effective dose for a person of 70kg) [12]. If the production yield is insufficient, the injected activity can be lowered to 50% (increasing the scanning time). The minimal injected activity is 100 MBq, the maximal injected activity is 550 MBq. The mass dose range is 0.1 µg - 30 µg.

Patients are required to fast for four hours in advance. Patients will get oral contrast during the one hour waiting time before the scan (three cups of 4ml Telebrix (30g/100ml), dissolved in 300ml water or similar product). The oral contrast will be the same that is used in routine clinical practice for PET/CT scans. The CT will be a low dose CT. Patients will receive an IV injection of Buscopan (20 mg, unless contra-indicated) before the scan, which is used in routine clinical practice to reduce bowel peristalsis in high-resolution imaging. [¹⁸F]AIF-FAPI-74 PET/CT will have a field of view limited to the suspected areas.

The total radiation burden for the participants will be 7.7 mSv per [¹⁸F]AIF-FAPI-74 PET/CT (+ 0.8 mSv in case an additional NeuroEXPLORER scan is performed (low dose CT)), less than the 10 mSv value used for clinical trials in healthy volunteers (category IIb, where the benefit to society from the study should be “moderate”, with a benefit expected to be “aimed directly at the diagnosis, cure or prevention of disease” (in this case, the first applies, “diagnosis”) [13].

5.2 Drug Accountability

Onsite production at UZ Leuven of the tracer [¹⁸F]AIF-FAPI-74.

An appropriate accountability log will be maintained on site in the ISF.

Upon release of the tracer vial, the UZ Leuven Radiopharmacy department provides a “conditional release certificate”, containing all required details. Per study subject, this certificate is then completed with additional information on tracer administration details (radioactivity dosage, time of administration...). Hence, there is no need for a separate Drug Accountability Log, as per study subject detailed documentation of tracer administration is already available on the “conditional release certificate” (filed in ISF/TMF).

5.3 Concomitant / Prohibited Medication / Treatment

All concomitant medication or treatment will be tolerated. In line with the ‘tracer principle’ (tracers are administered in very low mass amounts, below the pharmacological threshold, hence no pharmacological

response will be triggered), no drug interactions are expected and none have been described so far [14]. Concomitant medication use will be documented at the screening visit.

5.4 Rescue Medication

Not applicable as the IMP is a radiopharmaceutical without pharmacological effects.

6 Safety reporting

6.1 Definitions

6.1.1 Adverse Event (AE)

An AE is any untoward medical occurrence in a patient or subject during a trial, and which does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a product, whether or not considered related to the product. Any worsening (i.e., any clinically significant adverse change in the frequency or intensity of a pre-existing condition) should be considered an AE.

6.1.2 Adverse Reaction (AR) or Adverse Drug Reaction (ADR)

An AR is all untoward and unintended responses to an investigational medicinal product related to any dose administered.

6.1.3 Serious Adverse Event (SAE)

An SAE is any untoward medical occurrence that results in any of the following:

- Inpatient hospitalisation or prolongation of existing hospitalization
- A persistent or significant disability or incapacity
- A congenital anomaly or birth defect
- A life-threatening^a experience
- Death
- Important medical events that may be considered an SAE when - based on appropriate medical judgement - they may jeopardise the subject and may require medical or surgical intervention to prevent one of the above outcomes

^a The term "life threatening" in the definition of SAE refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it was more severe.

6.1.4 Serious Adverse Reaction (SAR)

A SAR is an Adverse Reaction that meets the criteria for a Serious Adverse Event (as defined under SAE).

6.1.5 Suspected Unexpected Serious Adverse Reaction (SUSAR)

A SUSAR is a serious adverse reaction, the nature, severity or outcome of which is not consistent with the applicable product reference safety information (e.g. investigator's brochure (IB) for an unauthorised investigational product or the patient leaflet joined to the summary of product characteristics (SmPC) for an authorised product).

Therefore, a SUSAR is assessed by the sponsor and/or investigator as:

- **Serious:** The event is classified as an SAE.
- **Unexpected:** The nature, severity or outcome of the adverse event is not consistent with the information provided in the IB or SmPC.
- **Suspected (causality):** There is a reasonable possibility that the adverse event may be related to the IMP.

6.1.6 Adverse Events of Special Interest (AESI)

The following events should be reported within the same timelines as SAEs:

- Overdose
- Misuse/abuse
- Medication error
- Pregnancy

6.1.7 Unexpected events that might influence the benefit-risk balance

The following unexpected events that might materially influence the benefit-risk balance, and which are not considered SUSARs, should be reported to the Member States:

- Increase in rate of occurrence of expected serious adverse events which may be clinically important
- Significant hazard to patient population

Unexpected events that are likely to seriously affect the benefit-risk balance and emergency safety measures which have been taken to protect the subjects are considered urgent safety measures.

6.2 Adverse Events that do not require reporting

In general, the following should not be reported as AEs:

- Pre-existing conditions, including those found as a result of screening (these should be reported as medical history or concomitant illness). However, in case the pre-existing condition appears to be enhanced by the IMP, this should be reported as an AE.
- Pre-planned procedures, unless the condition for which the procedure was planned has worsened from the first trial-related activity after the subject has signed the informed consent.

The following events are commonly observed and are therefore not considered as adverse events for the purpose of the trial:

- Ecchymosis or hematoma at the injection site (related to the insertion of the venous catheter). We will try to avoid this by having experienced technologists/nurses place the IV line.
- Pain due to insertion of the venous catheter. We will try to avoid this by having experienced technologists/nurses place the IV line.
- Dorsolumbal pain immediately or the day after the scan.
- Paravenous injection of the tracer: this will be avoided by flushing the IV line before injection of the tracer. If it does occur, it will be handled according to the standard operating procedure of our nuclear medicine unit.

Although these events should not be reported to the Sponsor, these should be recorded in the patient's medical notes according to routine practice.

The following events not to be considered as SAEs are:

- Pre-planned hospitalisations unless the condition for which the hospitalisation was planned has worsened from the first trial-related activity after the subject has signed the informed consent.
- Hospitalisation as part of a standard procedure for protocol therapy administration. However, hospitalisation or prolonged hospitalisation for a complication of therapy administration will be reported as an SAE.
- Hospitalisation or prolongation of hospitalisation for technical, practical, or social reasons, in absence of an AE.

6.3 Recording and reporting of Adverse Events

Investigators will seek information on AEs during each patient contact. All events, whether reported by the patient or noted by trial staff, will be recorded in the patient's medical record and in the (e)CRF within a

reasonable time after becoming aware. The diagnosis rather than the individual signs or symptoms should be reported, if available. If no diagnosis is available, the Investigator should record each sign and symptom as individual AEs.

The following minimum information should be recorded for each AE:

- AE description
- start and stop date of the AE
- severity
- seriousness
- causality assessment to the Investigational Medicinal Product (IMP)
- outcome

6.3.1 Assessment

All AEs must be evaluated by an Investigator as to:

- **Seriousness:** whether the AE is an SAE. See above for the seriousness criteria.
- **Severity:** Severity must be evaluated by an Investigator according to the following definitions:
 - *Mild* – no or transient symptoms, no interference with the subject's daily activities
 - *Moderate* – marked symptoms, moderate interference with the subject's daily activities
 - *Severe* – considerable interference with the subject's daily activities, unacceptable
- **Causality:**
 - *None* – An AE which is not related to the IMP
 - *Unlikely* – An AE for which an alternative explanation is more likely (e.g. concomitant medication(s), concomitant disease(s)), and/or the relationship in time suggests that a causal relationship is unlikely
 - *Possible* – An AE which might be due to the use of the IMP. An alternative explanation is inconclusive. The relationship in time is reasonable; therefore the causal relationship cannot be ruled out.
 - *Probable* - An AE which might be due to the use of the IMP. The relationship in time is suggestive (e.g. confirmed by dechallenge). An alternative explanation is less likely.
 - *Definitely* – An AE which is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation. The relationship in time is very suggestive (e.g. it is confirmed by dechallenge and rechallenge).

Management of hypersensitivity and anaphylactic reactions:

In case of suspected hypersensitivity, the participant will be assessed immediately. Mild reactions, such as limited rash, pruritus or urticaria without respiratory, cardiovascular or systemic symptoms, will be managed according to local institutional procedures and clinical judgement, with continued observation until symptoms resolve.

In case of suspected anaphylaxis, the injection or procedure will be stopped immediately if still ongoing, urgent medical assistance will be called, and the participant will be managed according to the local UZ Leuven emergency procedures for anaphylaxis. Management will include assessment according to the ABCDE approach, appropriate positioning, monitoring of vital signs, oxygen administration and intravenous fluids when clinically indicated, and administration of intramuscular adrenaline/epinephrine as first-line treatment according to local procedures.

Participants experiencing anaphylaxis or a clinically significant hypersensitivity reaction will not receive further [¹⁸F]AIF-FAPI-74 administration within the study. The event will be documented and reported according to the protocol safety reporting procedures and followed until resolution or stabilization.

6.3.2 Timelines for reporting

- After informed consent has been obtained but prior to initiation of Trial treatment, only adverse events caused by a Trial specific procedure should be reported.
- After initiation of trial treatment, adverse events will be reported as follows:
 - o All AEs, SAEs and AESIs will be reported until 30 days after last trial treatment administration.

All SAEs and AESI as defined in the protocol must be reported to the Sponsor within 24 hours of the trial staff becoming aware of the event. The immediate report shall be followed by detailed, written reports. The immediate and follow-up reports shall identify subjects by Trial identification.

SAE details will be reported by the Investigator to the Sponsor by completing the SAE form in the (e)CRF.

Unexpected events affecting the benefit-risk balance must be reported ad hoc to the sponsor as soon as possible after becoming aware of the event.

6.3.3 Follow-up

The Investigator must record follow-up information by updating the patient's medical records and the appropriate forms in the (e)CRF. The worst case severity and seriousness of an event must be kept throughout the trial.

SAE follow-up information should only include new (e.g. corrections or additional) information and must be reported within 24 hours of the Investigator's first knowledge of the information. This is also the case for previously non-serious AEs which subsequently become SAEs.

- All SAEs must be followed up until the outcome of the event is 'recovered', 'recovered with sequelae', 'not recovered' (in case of death due to another cause) or 'death' (due to the SAE) and until all related queries have been resolved, or until end of trial (whichever occurs first).
- *Non-serious AEs* must be followed up until the patient's last Trial visit, and until all related queries have been resolved.

SAEs after the end of the Trial: If the Investigator becomes aware of an SAE with suspected causal relationship to the IMP or the Trial after the subject has ended the Trial, the Investigator should report this SAE within the same timelines as for SAEs during the Trial.

6.3.4 Pregnancy

Because the effects of [¹⁸F]AIF-FAPI on an unborn child or baby are unknown, you may not participate in this study if you are pregnant, wish to become pregnant in the near future or are breastfeeding. When participating in the study, you must be using one of the approved contraceptive methods, during the study and up to seven days after the last administration in the study.

All highly effective contraceptive measures are allowed (with a relatively low Pearl Index).

Such methods include (Reference: CTFG Contraception Guidance, Version 1.2, March 2024):

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
 - o oral
 - o intravaginal
 - o transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation:
 - o oral
 - o injectable
 - o implantable
- intrauterine device (IUD)
- intrauterine hormone-releasing system (IUS)
- bilateral tubal occlusion

- vasectomised partner (provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success.)
- sexual abstinence (only if defined as refraining from heterosexual intercourse from the start of the trial up to seven days after the last administration in the study)

Natural methods, minipill outside postpartum period, spermicides or condoms in monotherapy or no usage of contraception when sexually active are not accepted.

A urinary hCG pregnancy test will be conducted in all WOCBP before each administration of [¹⁸F]AIF-FAPI. A woman of childbearing potential is defined as a female participant who is fertile, from menarche until becoming post-menopausal, unless permanently sterile. Permanent sterilisation includes hysterectomy, bilateral salpingectomy or bilateral oophorectomy. A post-menopausal state is defined as absence of menses for at least 12 months without an alternative medical cause.

Female subjects must be instructed to notify the Investigator immediately if they become pregnant during the trial. The Investigator must report any pregnancy in subjects who have received Trial product(s) to the Sponsor within 24 hours of becoming aware of the event.

Pregnancies occurring during the trial or within 90 days after the last administration of the IMP must be reported by the investigator to the Sponsor as soon as possible.

Any pregnancy complication or adverse outcome, such as congenital anomaly, spontaneous abortion, fetal death, etc, must be reported and documented as an SAE in accordance with standard safety reporting procedures.

Oocyte donation, oocyte retrieval, or fertility preservation procedures involving oocyte collection are not permitted from the time of [¹⁸F]AIF-FAPI-74 administration until at least 1 month after each [¹⁸F]AIF-FAPI-74 PET/CT scan.

6.3.5 Technical Complaints

Technical complaints can be reported to the Sponsor (eg. change in color, unequal sizes, broken vials/pills, sedimentation, ...).

6.3.6 Death

All deaths will be reported without delay to the sponsor (irrespective of whether the death is related to disease progression, the IMP, Trial procedure or is an unrelated event).

6.4 Reporting requirements to the Member states

The Investigator is responsible for ensuring that all safety events are recorded in the (e)CRF and reported to the Sponsor in accordance with instructions provided below.

The Sponsor will promptly evaluate all SAEs and AESIs against medical experience to identify and expeditiously communicate possible new safety findings to the Investigators.

6.4.1 Sponsor's reporting of Suspected Unexpected Serious Adverse Reactions (=SUSARs)

After receiving the SAE report form with causality (relationship) assessment from the Investigator, the sponsor can also make a causality assessment. The term SADR (Serious Adverse Drug Reaction) is to be used whenever either the Investigator or the Sponsor deems the SAE as possibly or probably related to the IMP.

The Sponsor must evaluate (and document the evaluation of) the expectedness for each SADR against the Reference Safety Information, e.g. in the Investigator's Brochure or applicable product information. In case the event is Unexpected (= a SUSAR) it must be reported by the Sponsor to Member states (through the EudraVigilance database) and other participating Investigators within the following timelines:

- 7 calendar days if fatal or life-threatening event (follow-up information within an additional 8 days)

- **15** calendar days if non-fatal or non-life-threatening event (follow-up information as soon as possible)

For reporting to the EudraVigilance database, all information related to the SUSAR should be provided by the Sponsor to the CTC of UZ Leuven as soon as possible. Contact details: CTC.safety@uzleuven.be and tel. 016 34 19 98.

6.4.2 Sponsor's reporting of unexpected events that might influence the benefit-risk balance

The sponsor has the obligation to notify the Member states through the EU portal (CTIS) for all unexpected events, that are not SUSARs, and which affect the benefit-risk balance within the following timelines:

- **7** calendar days for serious urgent safety measures
- **15** calendar days for other events

6.4.3 Temporary halt or early termination of the clinical Trial for reasons of subject safety

The sponsor has the obligation to notify the concerned Member States through the EU portal (CTIS) in case of early termination of the clinical Trial for safety reasons. The notification (containing information on the reasons for such action and follow-up measures) should be made immediately, but not later than 15 calendar days after the temporary halt or termination.

6.4.4 Annual reporting

The Sponsor has the obligation to, once a year throughout the clinical trial (or on request), submit a Development Safety Update Report (DSUR) through the EU portal (CTIS), taking into account all new available safety information received during the reporting period.

6.4.5 Overview reporting requirements

	WHAT	HOW	TO	TIMELINES
Investigator	AE	AE form	sponsor	Within 10 calendar days
	SAE	SAE form	sponsor	Immediately (within 24 hours of becoming aware of the event) <u>Exceptions:</u> as defined in protocol
	death	SAE form	sponsor	asap
	Unexpected events affecting the benefit-risk balance	ad hoc	sponsor	asap
Sponsor	SUSAR	EudraVigilance	unblinded: - Member states (via EudraVigilance) - MAH (SOFIE/GE HealthCare)	asap, but no later than - 7 calendar days (in case of fatal or life-threatening SUSAR) - 15 calendar days (other SUSAR)

	Unexpected events affecting the benefit-risk balance	EU portal (CTIS)	EU portal (CTIS)	asap, but not later than - 7 calendar days (serious urgent safety measures) - 15 calendar days (other unexpected events)
	Annual Safety/ Development Safety Update Report	DSUR template	EU portal (CTIS)	annually

6.5 Data Safety Monitoring Board (DSMB)

After a thorough evaluation of the potential risks to Trial participants and considering the nature and design of this clinical Trial, the Sponsor has determined not to establish a DSMB. This decision is grounded in our conclusion due to the following reasons:

- The goal of the IMP is for diagnostic use, not for therapeutic.
- The IMP has already been tested in-human.
- The IMP is a radiopharmaceutical. In line with the 'tracer principle' (tracers are administered in very low mass amounts, below the pharmacological threshold, hence no pharmacological response will be triggered), no drug interactions are expected and none have been described so far.
- The total radiation dose exposure for the subject is low in this trial and under general accepted exposure ranges.
- The study will be of short duration, including only one or two visits for nuclear imaging with close monitoring by the research team.

The Trial is committed to ensuring the safety and well-being of all participants at all times by adhering to the latest version of GCP and other relevant and applicable standards and legislations.

6.6 Safety parameters for the investigational NeuroEXPLORER device

See section "Safety Assessment" in Master Protocol EUDAMED_CIV-25-06-053398 for the additional investigational device-related safety assessment of (serious) adverse device effects ((S)ADE) and device deficiencies (DD).

7 Statistics and Data Analysis

Statistical analysis will be performed in accordance with ICH E9; a detailed description of the analysis is provided in the Trial-specific Statistical Analysis Plan (SAP). ICH E3 and E8 will guide the structure and content of the clinical trial report.

7.1 Sample Size Determination

No sample size calculation was performed for the DE and SPE cohorts given that this is a proof-of-concept, pilot study. Our trial will be the first to investigate the diagnostic performance of [¹⁸F]AIF-FAPI-74 PET/CT in patients with endometriosis, therefore a correct assumption about the diagnostic performance (i.e. sensitivity/specificity) of [¹⁸F]AIF-FAPI-74 PET/CT cannot be made to perform a power calculation.

For DE cohort, an interim analysis will be performed after inclusion of 16 patients. The interim analysis will be a futility analysis. The recruitment of participants will not be put on hold for interim analysis. Only if the recruitment surpasses 5% of the total numbers needed, the recruitment will temporarily be put on hold until the interim analysis is finished. If the scan was deemed contributory in at least 20% of patients, an

additional 16 participants on top of the 16 patients in the interim analysis can be recruited, up to a total of 32.

For SPE cohort, an interim analysis will be performed after inclusion of 16 patients. The interim analysis will be a futility analysis. The recruitment of participants will not be put on hold for interim analysis. Only if the recruitment surpasses 5% of the total numbers needed, the recruitment will temporarily be put on hold until the interim analysis is finished. If the scan was deemed contributory in at least 20% of patients, an additional 16 participants on top of the 16 patients in the interim analysis can be recruited, up to a total of 32.

7.2 Statistical Analysis

7.2.1 Efficacy Analysis

Endpoint	Statistical Analysis Methods
Primary	Detection rate of [¹⁸F]AIF-FAPI-74 PET/CT for endometriotic lesions will be determined. The reference standard is defined as finding of an endometriotic lesion during laparoscopy, based on histopathology and/or visual assessment by an endometriosis expert. Descriptive statistics of the correlation between endometriotic lesions on [¹⁸F]AIF-FAPI-74 PET/CT and during laparoscopy will be calculated, both patient-based and lesion-based. Potential confounding factors for [¹⁸F]AIF-FAPI-74 uptake, including prior surgery, adhesions, fibrosis, inflammatory conditions, infection, autoimmune or systemic inflammatory disease, malignancy and relevant concomitant medication, will be summarised descriptively. Discordant PET/CT and laparoscopic findings, including PET-positive/laparoscopy-negative and PET-negative/laparoscopy-positive findings, will be reviewed in relation to these factors. Complete cases analyses will be performed. Patients will be excluded if there is withdrawal of consent between both assessments or if the acquisition of the scan failed (e.g. technical failure). Primary endpoints UHR NeuroEXPLORER PET MDR part: see Master Protocol EUDAMED_CIV-25-06-053398 <u>Lesion matching methodology:</u> Lesion-level concordance between [¹⁸F]AIF-FAPI-74 PET/CT and laparoscopy will be assessed using standardized PET/CT and laparoscopy scoring templates based on predefined anatomical regions. For each PET-positive finding, at least the location, number of lesions and transverse plane will be recorded. During laparoscopy, the surgeon will at least document the location, number of lesions, macroscopic appearance and classification as deep or superficial endometriosis using the corresponding surgical template. The surgeon will first complete the laparoscopic assessment while blinded to the [¹⁸F]AIF-FAPI-74 PET/CT findings. After the blinded assessment is completed, the surgeon will be unblinded according to the protocol, and any additional lesions identified after [¹⁸F]AIF-FAPI-74 PET/CT-guided second-look will be recorded separately. A PET-positive lesion will be considered concordant with laparoscopy if a corresponding laparoscopic lesion is identified in the same predefined anatomical region. When multiple lesions are present within the same region, matching will be supported by PET/CT localisation, if available intra-operative photo number, surgical comments and biopsy specimen identification. If adjacent lesions cannot be reliably separated, they will be analysed as a lesion cluster or anatomical-region-level finding to avoid artificial inflation of lesion counts. PET-positive findings without corresponding laparoscopic confirmation will be classified as PET-positive/laparoscopy-negative findings. Laparoscopic lesions without corresponding PET/CT uptake will be classified as PET-negative/laparoscopy-positive findings. PET-positive lesions identified only after unblinding and second-look laparoscopy will be documented separately as incremental PET-detected lesions.

	Multiple lesions within the same participant will not be treated as statistically independent observations. Lesion-level diagnostic performance will be reported with 95% confidence intervals using generalized linear mixed models for binary responses, including random effects for patient to account for clustering of lesions within participants.
Secondary	• Sensitivity, specificity, positive predictive value, negative predictive value and accuracy of [¹⁸F]AIF-FAPI-74 PET/CT, will be computed at the lesion level (pooling all lesions of all patients) and at the patient level. Calculations done at the lesion level, will be estimated with 95% confidence intervals using generalized linear mixed models for binary responses including random effects for patient to account for clustering of lesions within patients. • Number of additional true positive lesions detected on [¹⁸F]AIF-FAPI-74 PET/CT after unblinding of the surgeon for the [¹⁸F]AIF-FAPI-74 PET/CT during the laparoscopy. • In patients receiving two [¹⁸F]AIF-FAPI-74 PET/CT scans, descriptive statistics and inferential testing (using linear mixed models to account for data clustering) will be performed to estimate the mean difference in SUV values between both PET scans, both on absolute values and values normalized to background organs (TBR). • Detection rate of MRI for endometriotic lesions will be determined. The reference standard is defined as finding of an endometriotic lesion during laparoscopy, based on histopathology and/or visual assessment by an endometriosis expert. Descriptive statistics of the correlation between endometriotic lesions on MRI and during laparoscopy will be calculated, both patient-based and lesion-based. • Detection rate of ultrasound for endometriotic lesions will be determined. The reference standard is defined as finding of an endometriotic lesion during laparoscopy, based on histopathology and/or visual assessment by an endometriosis expert. Descriptive statistics of the correlation between endometriotic lesions on ultrasound and during laparoscopy will be calculated, both patient-based and lesion-based. • Intra- and interobserver agreement will be determined using the GWET agreement coefficient (AC) or intraclass correlation coefficients (ICC). • Spearman or Pearson correlation coefficient will be used to quantify associations among quantification between uptake on [¹⁸F]AIF-FAPI-74 PET and FAP expression measured by IHC. • Descriptive statistics will be performed for all other parameters. • Secondary endpoints UHR NeuroEXPLORER PET MDR part: see Master Protocol EUDAMED_CIV-25-06-053398
Exploratory	• For each evaluable acquisition, lesion detection and characterization on NeuroEXPLORER PET/CT will be compared with the corresponding standard [¹⁸F]AIF-FAPI-74 PET/CT. Where applicable, lesion conspicuity, anatomical localization and uptake parameters, including SUV and/or lesion-to-background ratios, will be summarized descriptively.

7.2.2 Other Analysis

Pharmacokinetic, pharmacodynamic, and biomarker exploratory analysis/analyses will be described in the statistical analysis plan and finalized before database lock. The population for pharmacokinetic analysis and pharmacodynamic analysis will be presented separately from the main clinical Trial report.

7.3 Interim Analysis and Final Database Lock (if applicable)

Cfr. subtitle “7.1 Sample size determination”. The Statistical Analysis Plan will describe the planned interim analysis/analyses in greater detail.

7.4 Statistical analysis for the investigational device NeuroEXPLORER endpoints

See Statistical Analysis paragraph in the Master Protocol EUDAMED_ CIV-25-06-053398.

8 Data handling

Data handling and data flows for the Trial are summarized below and will be described in more detail in the Trial-specific Data Management Plan (DMP).

Study documentation includes all case report forms/signature pages, data correction forms, data handling and entry guidelines, source documents, monitoring logs and appointments schedules, investigator correspondence and regulatory documents (e.g., signed protocol and amendments, Independent Ethics or Institutional Review Committee correspondence and approval, approved and signed subject consent forms, Statement of Investigator form, clinical receipts and distribution records...).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study. Accordingly, source documents include, but are not limited to, laboratory reports, radiologists' reports, radiopharmacy records and any other similar reports or records of any procedure performed in accordance with the protocol.

Data will be entered into the (e)CRF by the study team.

Whenever possible, the original recording of an observation should be retained as the source document; however, a photocopy or electronic copy, scanned and added to the electronic medical file of the participant, is acceptable provided that it is a clear, legible and exact duplicate of the original document.

Government agency regulations and directives require that all study documentation pertaining to the conduct of a clinical trial must be retained by the investigator. Pseudonymized data shall be stored in a secured location for up to 25 years after the end of the study (data on paper at KU/UZ Leuven, digital data in a secure and encrypted digital storage location at UZ Leuven) except for external HD data and reconstructed data in the hospital's drive (for up to 10 years).

The collection, processing, and disclosure of personal data, such as patient health and medical information is subject to compliance with applicable personal data protection and the processing of personal data (REGULATION (EU) 2016/679 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation).

The CRF will be done in RedCap (www.project-redcap.org), as per UZ/KU Leuven guidelines.

8.1 Data Collection Tools and Source Document Identification

8.1.1 Operational aspects

Data collection, handling, processing and transfer for the purpose of this Trial will be performed in compliance with applicable regulations, guidelines for clinical trials and internal procedures, as follows:

8.1.1.1 Data collection

Source Data will be collected and recorded in the Trial participant's files/medical records.

If applicable, worksheets may be used for capturing some specific data in order to facilitate completion of the (e)CRF. Any such worksheets will become part of the Trial participant's source documentation and will be filed together with or as part of the medical records (during but also following completion of the Trial).

It remains the responsibility of the Investigator to check that all data relating to the Trial, as specified in the Trial protocol, are entered into the (e)CRF in accordance with the instructions provided and that the forms are filled out accurately, completely and in a timely manner.

(e)CRFs are provided by the Sponsor for each participant. The Trial data will be transcribed from the source records (i.e. participant's medical file or Trial-specific source data worksheets) into an (e)CRF by Site Trial Staff. Transcription to the (e)CRF will be done as soon as possible after a participant visit and in a pseudonymized manner using a unique identifier assigned by the Sponsor.

8.1.1.2 Data Validation

All data relating to the Trial must be prepared and validated by the Investigator. Any (e)CRF entries, corrections and alterations must be made by the Investigator or other authorized Trial staff.

Proper audit trails must be available to demonstrate the validity of the Trial data collected. This includes historical records of original data entries, by whom and when the data was entered, as well as detailed records of any corrections or additions made to the original data entry (i.e. who made the correction/addition, when and why), without obliterating the original data entry information.

8.1.1.3 Data Management

The Trial Data Manager will perform extensive consistency checks on the received data. Queries will be issued in case of inconsistencies in accordance with internal procedures. A Data Management Plan (DMP) will be developed to map data flows, data validation measures that will be taken, how (interim) database lock(s) will be managed and, as applicable, the role and responsibilities of the Data Safety Monitoring Committee (DSMB).

8.1.1.4 Data Transfer

Any participant records or datasets that are transferred to the Sponsor or any partners of the Sponsor will contain the Trial-specific participant identifier only; participant names or any information which would make the participant identifiable will not be transferred. All pseudonymized data relating to the Trial must be transmitted in a secure manner to the Sponsor or any partners of the Sponsor (see 8.1.2. legal requirements).

8.1.2 Legal requirements

All source data will be kept at a secured location with restricted access at all times. These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data protection laws and regulations and more in particular the GDPR and relevant national laws implementing the GDPR. Appropriate technical and organizational measures to protect the data against unauthorized disclosure or access, accidental or unlawful destruction, or accidental loss or alteration must be established. Trial staff whose responsibilities require access to personal data agree to keep the data confidential.

The Investigator and the Participating Site(s) (as applicable) shall treat all information and data relating to the Trial disclosed to them as confidential and shall not disclose such information to any third parties or use such information for any purpose other than the objectives of the Trial as described in this protocol. The collection, processing and disclosure of personal data, such as participant health and medical information is subject to compliance with applicable laws and regulations regarding personal data protection and the processing of personal data.

The Investigator will maintain all source documents and completed (e)CRFs that support the data collected from each Trial participant, and will maintain a Trial Master File (TMF)/Investigator Site File (ISF) containing all Trial documents as specified in GCP Chapter 8 entitled "Essential Documents for the Conduct of a Clinical Trial", and as specified by applicable regulatory requirement(s). The Investigator will take appropriate measures to prevent accidental or premature destruction of these documents.

Transfer of the pseudonymized data will be performed via a secured method of transfer taking into account all applicable security arrangements and regulations (such as the GDPR).

8.2 Audits and Inspections

The Investigator will permit direct access to Trial data and documents for the purpose of monitoring, audits and/or inspections by authorized entities such as but not limited to: the Sponsor or its designees and competent regulatory or health authorities. As such (e)CRFs, source records and other Trial related documentation (e.g. Investigator Site File, the Trial Master File, pharmacy records, etc.) must be kept current, complete and accurate at all times.

8.3 Monitoring

In accordance with GCP the Sponsor is responsible for monitoring the Trial to ensure compliance with GCP and current legislation, and to verify, among other requirements, that proper written informed consent has been obtained and documented, that the Trial procedures have been followed as shown in the approved protocol, and that relevant Trial data have been collected and reported in a manner that assures data integrity.

UZ Leuven Clinical Trial Center (CTC) performed a risk analysis to determine the monitoring strategy. Based on this risk assessment, the clinical trial was classified as 'intermediate risk' as the potential risks associated to study procedures and protocol design are markedly higher to that of standard medical care since the IMP in this trial is experimental and not yet market approved.

However:

- the goal of the IMP in this trial is for diagnostic use, not for therapeutic use
- the total radiation dose exposure for the subject is low in this trial and under general accepted exposure ranges
- Another intermediate-risk IMP (tracer) study was recently monitored by the CTC in the same department and no major (safety) findings were observed

Based on the above risk assessment and as permitted by GCP, the Sponsor of the study accepts the minimal risks associated with this study and determines that monitoring activities (as defined by GCP) by a qualified individual, independent of the study team, is not necessary as it will provide little or no added value in protecting the safety of study participants and assuring the integrity of collected study data.

Nonetheless, the KU Leuven study team will take all possible measures to assure the quality and integrity of study data and to safeguard the safety and wellbeing of study participants, in accordance with the requirements set out in GCP and ISO:14155.

8.4 Archiving

As specified in GCP, the Sponsor and Investigator/Participating Site will maintain a record of the location(s) of all respective Essential Trial Documents (including but not limited to Source Documents, completed and final (e)CRF and ISF/TMF). The Sponsor should ensure that the Investigator has control of and continuous access to the (e)CRF data reported to the Sponsor during the Trial.

The Investigator/Participating Site should have control of all Essential Documents and records generated by the Investigator/Participating Site before, during and following termination of the Trial.

Trial specific documentation (such as but not limited to the Trial protocol, any modifications thereto, the final Clinical Study Report (CSR) and the Trial database) shall be archived. Source data and site-specific Trial documents (such as but not limited to the original signed ICFs) will be archived by the participating site(s) according to local practice, and for at least 25 years following termination of the Trial. Archived data may be held on electronic record, provided that media back-up exists, hard copies can be obtained, if required and measures are taken to prevent accidental or premature loss or destruction of data. Destruction of Essential Documents prior to, during or upon completion of the required archival period, will require written authorisation from the Sponsor.

8.5 Data handling for the investigational device NeuroEXPLORER

See Data Handling Paragraph in the Master Protocol EUDAMED_ CIV-25-06-053398.

9 Ethical and Regulatory Considerations

9.1 CA/EC review & reports

Before the start of the Trial, this protocol and other related documents (e.g. ICF, advertisements, IB, etc.) will be submitted through the CTIS portal for review to the CA/EC for Trial authorization. The Trial shall not commence until such approvals have been obtained and until other relevant essential Trial documents, such as duly signed contract agreements, evidence of adequate Trial financing etc. are in place.

It is the responsibility of the CI to produce the Development Safety Update Report (DSUR) and submit to the EC/CA through CTIS within 60 days of the anniversary date on which favourable opinion to start the Trial was given, and annually until the Trial is declared ended.

9.2 Peer review (if applicable)

Not applicable.

9.3 Regulatory Compliance

The Trial will be conducted in compliance with the principles outlined in the requirements for the conduct of clinical Trials in the EU as provided for the CTR and any subsequent amendments, as well as in compliance with GCP guidelines, other GxP guidelines, the most recent version of the Declaration of Helsinki, the Belgian law of May 7th 2017 on clinical Trials with medicinal products for human use and with the GDPR, the relevant Belgian laws implementing the GDPR, including the Belgian Law of July 30th 2018 on the protection of natural persons with regard to the processing of personal data and the Belgian Law of August 22nd 2002 on patient rights and all other applicable legal and regulatory requirements.

9.4 Protocol / GCP compliance

The Trial must be performed in accordance with the protocol, current ICH and GCP guidelines, and applicable regulatory and country-specific requirements. ICH guidelines are an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human participants. Compliance with this standard provides public assurance that the rights, safety, and well-being of Trial participants are protected, consistent with the principles that originated in the most recent version of the Declaration of Helsinki, and that the Trial data are credible, reliable and reproducible.

The Investigator and Trial team acknowledge and agree that prospective, planned deviations or waivers to the protocol are not permitted under applicable regulations on clinical studies. However, should there be an unforeseen protocol deviation, such deviation shall be adequately documented in the source documents and on the relevant forms and reported to the CI and Sponsor during the trial. Deviations should also be reported to the EC as part of the EC's continued review of the Trial (e.g. through the DSUR). Protocol deviations which are found to frequently recur, will require (immediate) action. The Investigator acknowledges that such recurring protocol deviations could potentially be classified as a major protocol deviation or serious breach. The Investigator and Trial team understand that in case of a serious breach (as defined in the CTR, an event that is likely to affect to a significant degree the safety or rights of trial participant(s), or the reliability and robustness of the data generated in the clinical trial), immediate action is required. If serious breaches should occur, this shall be appropriately documented and escalated to the Sponsor as soon as possible. In accordance with Art 52 of the CTR, the sponsor shall notify the participating Member States using CTIS without undue delay and not later than 7 days after becoming aware of the breach.

The Investigator is expected to take any immediate action required to protect the safety of any participant included in the Trial, even if this action represents a deviation from the protocol. In such cases, the Sponsor should be notified of this action.

The Sponsor has performed a risk assessment to reduce anticipated risks with regards to the safety, wellbeing and rights of the participants as well as with regards to the reliability and robustness of the clinical Trial data.

9.5 Data protection and participant confidentiality

The Trial will be conducted in compliance with the requirements of the GDPR, the relevant Belgian laws implementing the GDPR including the Belgian Law of July 30th 2018 on the protection of natural persons with regard to the processing of personal data. Any collection, processing and disclosure of personal data, such as participant health and medical information is subject to compliance with the aforementioned personal data protection laws (cfr. Data Processing Annex (DPA) in Appendix). In case personal data is transferred outside the European Economic Area, safeguards will be taken to ensure that appropriate protection travels with the data in accordance with the GDPR. (https://ec.europa.eu/info/law/law-topic/data-protection/international-dimension-data-protection/rules-international-data-transfers_en#documents)

Any personal data shall be treated as confidential at all times including during collection, handling and use or processing, and the personal data (including in any electronic format) shall be stored securely at all times and with all technical and organizational security measures that would be necessary for compliance with EU and national data protection legislation (whichever is more stringent). The Sponsor shall take appropriate measures to ensure the security of all personal data and guard against unauthorized access thereto or disclosure thereof or loss or destruction while in its custody.

9.6 Insurance

The Participating Site, the Investigator and Sponsor shall have and maintain in full force and effect during the term of this Trial, and for a reasonable period following termination of the Trial, adequate insurance coverage for: (i) medical professional and/or medical malpractice liability, and (ii) general liability.

For Belgian Participating Sites

Art 12 of the Belgian Law of May 7th 2017 on clinical Trials with medicinal products for human use applies. Prior to the start of the Trial, the Sponsor shall enter into an insurance contract in order to adequately cover Trial participants from Belgian sites in accordance with art. 12 of the said law.

For non-Belgian Participating Sites

The Participating Site shall have and maintain in full force and effect during the term of this Trial (and for a reasonable period following termination of the Trial, adequate insurance coverage for other possible damages resulting from the Trial at the Participating Site, as required by local law. Each such insurance coverage shall be in amounts appropriate to the conduct of the services of the Participating Site under this Trial. The Participating Site and Sponsor shall be solely responsible for any deductible or self-insured retention under any such policies.

9.7 Modifications

During the Trial the Sponsor may modify the Trial. It is the Sponsor's responsibility to assess whether a modification is substantial or non-substantial, a change relevant to the the supervision of the Trial, or whether a substantial modification leads to changes in the Trial to an extent that it has to be considered as a completely new clinical trial.

A "substantial modification" is defined as any change of the Trial which is made after a decision is issued on a previously submitted application and that is likely to 'substantially impact the subjects' safety or rights or the reliability and robustness of the data generated in the Trial. A non exhaustive list of examples of substantial and non-substantial modifications is available in [Annex III of the CTR Q&A document in Eudralex volume 10](#). Sponsor shall submit the substantial modifications in CTIS which will be evaluated by the CA/EC. A substantial modification may only be implemented if it has been approved by the CA/EC with no prejudice to the right of Sponsor and the Principal Investigator to take urgent safety measures without awaiting prior authorisation. In that case, the event and the measures taken should be reported in CTIS without undue delay but no later than 7 days from the date the measures have been taken.

A "change which is not a substantial modification but relevant to the supervision of the Trial by the CA/EC" shall be permanently updated in CTIS by the Sponsor, in line with article 81(9) of the CTR. An example of such change is an update of sponsor or CRO contact details.

A “non-substantial modification” is any change outside the scope of a substantial modification and irrelevant to the supervision of the Trial. A non-substantial modification should not be notified as such. These changes should be implemented during the next substantial modification. Non-substantial modifications need to be listed and identified as such in the cover letter of the substantial modification application.

9.8 Post-Trial activities (if applicable)

Not applicable.

9.9 Ethical and Regulatory Considerations for the investigational NeuroEXPLORER device

See “Ethical and Regulatory considerations” in the Master Protocol EUDAMED_ CIV-25-06-053398.

10 Research Registration, Dissemination of Results and Publication Policy

The Declaration of Helsinki (latest version) and European and Belgian regulations require that every research Trial involving human participants be registered in a publicly accessible database before recruitment of the first participant. The CI is responsible for registering the Trial.

In addition, the CI will fulfil their ethical obligation to disseminate and make the research results publicly available. As such the CI is accountable for the timeliness, completeness and accuracy of the reports. Researchers, authors, Sponsors, editors and publishers must adhere to accepted guidelines for ethical reporting. Negative and inconclusive, as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in publication.

Publications will be coordinated by the CI. Authorship to publications will be determined in accordance with the requirements published by the International Committee of Medical Journal Editors and in accordance with the requirements of the respective medical journal.

For multicentre Trials, it is anticipated that the primary results of the overall Trial shall be published in a multicentre publication.

Participating Sites are not allowed to publish any subset data or results from the Trial prior to such multicentre publication.

Any publication by a Participating Site must be submitted to the Sponsor for review at least thirty (30) calendar days prior to submission or disclosure. Sponsor shall have the right to delay the projected publication for a period of up to three (3) months from the date of first submission to the Sponsor in order to enable the Sponsor to take steps to protect its intellectual property rights and know-how.

11 Intellectual Property

Any know how, inventions, methods, developments, innovations, discoveries and therapies, whether patentable or not, arising from the Trial or made in the performance of the Trial protocol (“Inventions”) shall vest in the Sponsor. The Participating Site, its employees and Investigator(s) shall promptly disclose to the Sponsor any such Inventions. Parties have expressly agreed that any and all Trial data as collected and prepared in the performance of the Trial protocol shall be the sole property of Sponsor unless otherwise agreed in the clinical trial agreement.

12 References

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APPENDICES

13 Appendix I: Clinical trial protocol history

Original CTP version:	2.1 dated <09072026>
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Amendment #1: <CTP version nbr> dated <09072026>	
Modifications made / Reason for amendment:	
<protocol section reference>	<describe modifications made>
<protocol section reference>	<describe modifications made>
<protocol section reference>	<describe modifications made>
<protocol section reference>	<describe modifications made>

Amendment #2: <CTP version nbr> dated <09072026>	
Modifications made / Reason for amendment:	
<protocol section reference>	<describe modifications made>
<protocol section reference>	<describe modifications made>
<protocol section reference>	<describe modifications made>
<protocol section reference>	<describe modifications made>

14 Appendix 2: Reference to the master clinical investigation protocol (CIP) for the NEUROEXPLORER PET/CT_CIV 25-06-053398

Title: **Ultra-high resolution Positron Emission Tomography studies using the NeuroEXPLORER PET/CT – Master Protocol**

Internal Investigation number: S70841

CIV-ID: CIV-25-06-053398

Sponsor: University Hospitals Leuven (UZ Leuven)
Herestraat 49, B-3000 Leuven

Coordinating Investigator: Prof. Dr. Koen Van Laere

The present study entitled “Prospective trial of [¹⁸F]AIF-FAPI-74 for PET imaging of fibroblast activation protein in patients with endometriosis”, EU CT# 2026-525272-25 will (also) be performed using the NeuroEXPLORER PET/CT to collect Imaging data.

As a new scanner device FAMHP has requested that all studies from September 2025 to September 2032, that will utilize the new scanner device, reference and act as subprotocols under the Master Clinical Investigation Protocol (CIV-25-06-053398) as portrayed in Figure below.

The Master protocol will be performed as an adjunct, device-oriented study and has a separately approved protocol and ICF with separate objectives that only pertain to the operation of the medical device.

No subject or other specific data from this EU CT# 2026-525272-25 study is needed, only the registration according to the endpoints of the CIV-25-06-053398 protocol. The latest version of this CIV-25-06-053398 protocol and PROM questionnaire will be followed at all times during the execution of this study.

Design of the global NeuroEXPLORER protocols/ICF/approvals v1 21/06/2025

