FAPI PET Imaging – a multicentric exploratory evaluation

Study Type:	Clinical trial with Investigational Medicinal Product (IMP)
Study Categorisation:	Risk category according to ClinO: C
Study Registration:	HumReS (via BASEC), registration number: 2026-00454 Clinical Trials (https://clinicaltrials.gov/) XXXX
Study Identifier:	FAPIPET
Sponsor, Sponsor-Investigator or Principal Investigator:	Prof. Dr. med. Martin Hüllner Klinik für Nuklearmedizin Universitätsspital Zürich / Universität Zürich Rämistrasse 100 / Wagistrasse 14 CH-8091 Zürich / CH-8952 Schlieren Schweiz Telefon: +41 43 253 8798 Fax: +41 44 255 4428 E-mail: martin.huellner@usz.ch
Investigational Product:	[18F]FAPI-74
Protocol Version and Date:	Version 1.0, 16.Feb.2026

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Signature Page(s)

Note: Add more lines, functions and pages if relevant, e.g. for trial statistician, if relevant or protocol contributors

Study number	intended registry: HumRes, registration number: XXXX
Study Title	FAPI PET Imaging – a multicentric exploratory evaluation

The Sponsor-Investigator and trial statistician have approved the protocol version 1.0, dated 16.02.2026, and confirm hereby to conduct the study according to the protocol, current version of the World Medical Association Declaration of Helsinki, the ICH-GCP guidelines and the local legally applicable requirements.

Sponsor-Investigator:

Prof. Dr. med. Martin Hüllner

Zürich, _____ _____

Place/Date Signature

Local Principal Investigator at study site*:

I have read and understood this trial protocol and agree to conduct the trial as set out in this study protocol, the current version of the World Medical Association Declaration of Helsinki, ICH-GCP guidelines and the local legally applicable requirements.

Site	Universitätsspital Zürich / Universität Zürich Klinik für Nuklearmedizin Rämistrasse 100 / Wagistrasse 14 CH-8091 Zürich / CH-8952 Schlieren Schweiz
Principal investigator	Prof. Dr. med. Martin Hüllner

Zürich, _____ _____

Place/Date Signature

*Note: In multicentre studies, this page must be individually signed by all participating Local Principal Investigators.

Local Principal Investigator at study site*:

I have read and understood this trial protocol and agree to conduct the trial as set out in this study protocol, the current version of the World Medical Association Declaration of Helsinki, ICH-GCP guidelines and the local legally applicable requirements.

Site	Luzerner Kantonsspital Radiologie und Nuklearmedizin Spitalstrasse CH-6000 Luzern Schweiz
Principal investigator	Prof. Dr. med. Klaus Strobel

Luzern, _____ _____

Place/Date Signature

*Note: In multicentre studies, this page must be individually signed by all participating Local Principal Investigators.

Local Principal Investigator at study site*:

I have read and understood this trial protocol and agree to conduct the trial as set out in this study protocol, the current version of the World Medical Association Declaration of Helsinki, ICH-GCP guidelines and the local legally applicable requirements.

Site	Kantonsspital Baden AG Klinik für Nuklearmedizin Im Ergel 1 CH-5404 Baden Schweiz
Principal investigator	Prof. Dr. med. Irene Burger

Baden, _____ _____

Place/Date Signature

*Note: In multicentre studies, this page must be individually signed by all participating Local Principal Investigators.

Local Principal Investigator at study site*:

I have read and understood this trial protocol and agree to conduct the trial as set out in this study protocol, the current version of the World Medical Association Declaration of Helsinki, ICH-GCP guidelines and the local legally applicable requirements.

Site	Clinique de Genolier Centre de Médecine nucléaire Route du Muids 3 CH-1272 Genolier
Principal investigator	Dr. med. Antoine Leimgruber

Genolier, _____ _____

Place/Date Signature

*Note: In multicentre studies, this page must be individually signed by all participating Local Principal Investigators.

Local Principal Investigator at study site*:

I have read and understood this trial protocol and agree to conduct the trial as set out in this study protocol, the current version of the World Medical Association Declaration of Helsinki, ICH-GCP guidelines and the local legally applicable requirements.

Site	Hôpitaux Universitaires Genève Centre de Médecine nucléaire Rue Gabrielle-Perret-Gentil 4 1205 Genève
Principal investigator	Dr. med. Ismini Mainta

Geneve, _____ _____

Place/Date Signature

*Note: In multicentre studies, this page must be individually signed by all participating Local Principal Investigators.

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STUDY SYNOPSIS

Sponsor - Investigator	Prof. Dr. med. Martin Hüllner
Study Title:	FAPI PET Imaging – a multicentric exploratory evaluation
Short Title / Study ID:	FAPIPET
Protocol Version and Date:	Version 1.0 of 16. February.2026
Trial Registration:	HumRes (via BASEC), registration number: XXXX Clinical Trials (https://clinicaltrials.gov/): XXXX
Study category and Rationale	This study is classified as Category C under ClinO, as it involves the administration of a novel, non-authorized radiopharmaceutical in humans. The project is an exploratory, observational diagnostic study aimed at evaluating the biodistribution and uptake pattern of the investigational radiotracer [18F]FAPI-74. No therapeutic or interventional procedures are being tested.
Clinical Phase:	Exploratory diagnostic (non-therapeutic) study
Background and Rationale:	The study investigates the novel fibroblast-activation-protein-targeted PET radiotracer [18F]FAPI-74 across a range of oncologic and non-oncologic diseases, in which either no clinically established radiotracer is available, or currently used tracers provide limited diagnostic accuracy or sensitivity. By characterizing [18F]FAPI-74 uptake patterns in these disease settings, the study aims to expand the clinical understanding of FAP-targeted molecular imaging and to identify indications in which FAPI imaging may offer superior diagnostic value compared with existing imaging modalities.
Objective(s):	Primary Objective To explore and characterize the uptake pattern of [18F]FAPI-74 across a range of oncologic and non-oncologic diseases. Secondary Objectives • To compare [18F]FAPI-74 uptake with standard-of-care imaging modalities, such as other PET tracers or morphological imaging techniques (CT/MRI). • To evaluate the clinical relevance of [18F]FAPI-74 uptake, specifically its impact on diagnostic confidence and patient management.

Outcome(s):	Primary Outcome: A qualitative assessment of [18F]FAPI-74 uptake based on predefined reading ratings, classified as either FAPI-positive or FAPI-negative in target lesions or disease-specific regions, including an overall evaluation of diagnostic image quality. Secondary Outcome: • A qualitative and semi-quantitative comparison of [18F]FAPI-74 uptake using lesion-wise uptake ratings, compared to standard-reference imaging (e.g., other PET radiotracer or morphological imaging). • Change in diagnostic confidence and clinical management recommendations before vs. after [18F]FAPI-74 imaging (e.g., % change, number of participants with altered treatment path).
Study Design:	Open label, non-randomized, single-arm exploratory diagnostic study. Each participant will undergo one [18F]FAPI-74 PET examination for qualitative assessment and comparison with available standard-of-care imaging.
Inclusion / Exclusion Criteria:	Inclusion Criteria: - Written informed consent obtained and documented by the participant's signature. - Age ≥18 years at the time of consent. - Clinically established or suspected diagnosis or recurrence of an oncologic or non-oncologic disease as defined in chapter 7.1. - Availability of standard-of-care imaging (e.g., clinically established PET tracer or anatomical imaging such as CT/MRI) to allow comparative evaluation. Key exclusion criteria: - Severe claustrophobia that would preclude PET imaging. - Inability to remain still for the duration of the PET/MR examination. - Current pregnancy or breastfeeding; no pregnancy test is required for women who are postmenopausal for ≥12 months or have undergone surgical sterilization, bilateral oophorectomy, or hysterectomy. -Previous hypersensitivity reactions to radiotracer administration - Inability to understand the study information, for example due to language barriers. - Subjects incapable of judgment (e.g. individuals under legal or medical incapacity).
Measurements and Procedures:	Participants will undergo a single [18F]FAPI-74 PET/CT or PET/MR examination. Following intravenous administration of approximately 250 MBq of [18F]FAPI-74, a resting uptake period of 45-60 minutes will be observed. PET imaging will then be performed on an integrated PET/CT or PET/MR scanner. A low-dose CT scan or an MR sequence will be acquired for attenuation correction and anatomical co-registration. No additional diagnostic or therapeutic interventions are performed as part of this study.

Study Product / Intervention:	The investigational product [18F]FAPI-74 is a quinoline-based PET radiotracer targeting the fibroblast activation protein (FAP), particularly cancer-associated fibroblasts within the tumour microenvironment. Each participant will receive a single intravenous slow-bolus injection (administered over 5-15 seconds) of ~ 250 MBq [18F]FAPI-74. No repeated tracer administrations or therapeutic interventions are planned.
Control Intervention (if applicable):	No active comparator or placebo will be administered. Historical standard-of-care imaging (e.g., PET/CT with established radiotracers or morphological imaging such as CT/MRI) together with clinical assessments, will serve as the reference standard for comparative evaluation of [18F]FAPI-74 uptake.
Number of Participants with Rationa le:	This exploratory multicentre study aims to enrol approximately 770 participants across multiple oncologic and non-oncologic disease groups. Eligible patients will present with conditions in which currently established PET radiotracers have limited specificity, sensitivity, or diagnostic value, or for which no standard PET tracer is currently available. The project sample size is based on: 1. Previous experience with patient numbers in comparable diagnostic imaging studies, 2. Published data reported from relevant literature, 3. Feasibility considerations, including anticipated rates of eligibility and case volumes across the targeted indications. Participants will be enrolled at various stages of their disease, including ID (initial diagnosis), SRP (suspected recurrence/persistence), or other specific indications as applicable. Projected total number of participants: approximately 770; distributed as follows: - Thyroid Pathology: 50 - Head and neck cancer (including cancer of unknown primary): 50 - Neck node metastases from cancer of unknown primary: 30 - Sinonasal tract tumor (SNT): 50 - Sarcoidosis: 50 - Thyroid cancer (SRP): 50 - Breast cancer (ID, SRP): 50 - Hepatocellular carcinoma (ID, SRP): 50 - Gastric cancer (not: esophagogastric junction cancer) (ID, SRP): 50 - Pancreatic cancer (ID, SRP): 50 - Prostate cancer (biochemical recurrence and negative PSMA-PET): 50 - Urothelial carcinoma (ID): 50 - Multiple myeloma / plasmocytoma (ID): 20 - Mesothelioma (ID, SRP): 50 - Hepatic fibrosis (ID, SRP): 20 - Endometriosis (ID, SRP): 50 - Lung fibrosis: 50

Study Duration:	The total duration of the clinical investigation - from enrolment of the first participant to completion of the last participant's study visit - is estimated to be approximately 3 years.
Study Schedule:	First-Participant-In (planned): Apr 04/2026 Last-Participant-Out (planned): May 05/2029
Investigator(s):	Prof. Dr. med. Martin Hüllner Klinik für Nuklearmedizin Universitätsspital Zürich / Universität Zürich Rämistrasse 100 CH-8091 Zürich Schweiz Telefon: +41 43 253 8798 E-mail: Martin.huellner@usz.ch Prof. Dr. med. Klaus Strobel Radiologie und Nuklearmedizin Luzerner Kantonsspital Spitalstrasse CH-6000 Luzern Schweiz E-mail: Klaus.strobel@luks.ch Dr. med. Ismini Mainta Centre de Médecine nucléaire Hôpitaux Universitaires Genève Rue Gabrielle-Perret-Gentil 4 1205 Genève E-mail: isminicharis.mainta@hug.ch Prof. Dr. med. Irene Burger Klinik für Nuklearmedizin Kantonsspital Baden AG Im Ergel 1 CH-5404 Baden E-mail: irene.burger@ksb.ch Dr. med. Antoine Leimgruber Clinique de Genolier Centre de Médecine nucléaire Route du Muids 3 CH-1272 Genolier E-mail : Aleimburger@swissmedical.net

Study Centre(s):	This is a multi-centre study conducted at several sites in Switzerland. Projected number of participating centres: 5 Coordinating Center : Universitätsspital Zürich / Universität Zürich Klinik für Nuklearmedizin Rämistrasse 100 / Wagistrasse 14 CH-8091 Zürich / 8952 Schlieren Schweiz Participating centers: - Luzerner Kantonsspital (LUKS), Luzern - Kantonsspital Baden (KSB), Baden - Clinique de Genolier, Genolier - Hôpitaux Universitaires de Genève (HUG), Genève
Statistical Considerations:	The study will employ descriptive statistical methods, including qualitative and semi-quantitative assessments of [18F]FAPI-74 uptake patterns. The primary analysis will focus on visual classification of tracer uptake (e.g., positive vs. negative, diagnostically interpretable vs. non-interpretable) and on the comparison of these findings with standard-of-care imaging obtained as part of routine clinical practice. The sample size (see Section Number of Participants with Rationale) is based on: 1. prior experience with patient numbers from comparable diagnostic imaging studies; 2. published data in the relevant literature, and 3. feasibility considerations, including anticipated rates of eligibility and case volumes across the targeted indications. As this is an exploratory, non-comparative diagnostic study, no formal power calculation or confirmatory hypothesis testing is planned. Instead, the analyses will aim to describe uptake patterns, assess diagnostic feasibility, and identify potential trends warranting future confirmatory studies.
GCP Statement:	This clinical study will be conducted in compliance with the study protocol, the current version of the Declaration of Helsinki, the International Council for Harmonisation (ICH) Guidelines on Good Clinical Practice (GCP), and all national, legal and regulatory requirements.

ABBREVIATIONS

[18F]FAPI-74	18F-labelled fibroblast activation protein inhibitor 74
[18F]FDG	18F-labelled fluorodeoxyglucose
AE	Adverse Event
ASR	Annual Safety Report
BASEC	Business Administration System for Ethical Committees, (https://submissions.swissethics.ch/en/)
CA	Competent Authority (e.g. Swissmedic)
CAF	Cancer-associated fibroblast
CCC	Cholangiocellular carcinoma
CEC	Competent Ethics Committee
CRF	Case Report Form
CRC	Colorectal Cancer
ClinO	Ordinance on Clinical Trials in Human Research (in German: KlinV, in French: OClin, in Italian: OSRUm)
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
DSUR	Development safety update report
eCRF	Electronic Case Report Form
GCP	Good Clinical Practice
GMP	Good Manufacturing Process
HCC	Hepatocellular carcinoma
Ho	Null hypothesis
HPLC	High pressure liquid chromatography
HRA	Federal Act on Research involving Human Beings (in German: HFG, in French: LRH, in Italian: LRUm)
IB	Investigator's Brochure
ID	Initial diagnosis
IgG4	Immunglobuline G4
IIT	Investigator-initiated Trial
IMP	Investigational medicinal product
IMPD	Investigational medicinal product dossier
ITT	Intention to treat
MR	Magnetic resonance
PET	Positron emission tomography
PI	Principal Investigator
SDV	Source Data Verification
SOP	Standard Operating Procedure
SPC	Summary of product characteristics
SRP	Suspected recurrence / persistence

SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File

SUMMARY OF THE REVISION HISTORY IN CASE OF AMENDMENTS

Version Nr,	Version Date	Description of change	Reason for the change
1.0	16.Feb.2026	Initial Version	n/a

STUDY SCHEDULE

PROCEDURE	PRE-SCREENING	PATIENT INFORMATION	DAY 0 (PET SCAN)
Patient Information and Informed Consent		√ Remote information & scheduling of PET/CT or PET/MR	√
Inclusion / Exclusion Criteria Check	√ eligible patients pre-identified via clinical systems		√ (after informed consent)
Demographic Data			√
Medical History including Historical Imaging			√
[18F]FAPI-74 PET/CT or PET/MR Scan			√
Adverse Events Recording			√

1. STUDY ADMINISTRATIVE STRUCTURE

1.1 Sponsor, Sponsor -Investigator

Prof. Dr. med. Martin Hüllner
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CH-8091 Zürich
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Telefon: +41 43 253 8798
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The Sponsor-Investigator is responsible for the overall conduct of the study, including its design, execution, data integrity, analysis, and reporting. All essential trial activities (data management, monitoring, safety oversight, and archiving) are delegated only to qualified institutions as outlined below.

1.2 Principal Investigator(s)

Prof. Dr. med. Martin Hüllner
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The Principal Investigator at each participating site is a qualified physician responsible for all site-specific medical decisions and clinical oversight. A full list of investigators and study sites may also be included in the contractual documentation.

1.3 Statistician ("Biostatistician")

Data analysis will be primarily descriptive and will be performed by the Sponsor-Investigator or a delegated qualified researcher with expertise in medical imaging data evaluation.

1.4 Laboratory

Not applicable.

No central or clinical laboratory services are involved. All procedures are limited to diagnostic imaging.

1.5 Monitorin g institution

Clinical Trials Center (CTC)
Universitätsspital Zürich
Moussonstrasse 2
8044 Zürich

Monitoring will be conducted in accordance with the study-specific monitoring plan, relevant CTC SOPs and applicable ICH-GCP requirements. The CTC operates independently of the Department of Nuclear Medicine and from the Sponsor-Investigator's clinical team, ensuring an unbiased review of study conduct and data integrity.

1.6 Data Safety Monitoring Committee

Not applicable.

This is a non-interventional, exploratory diagnostic imaging study without therapeutic intervention. Study endpoints are descriptive and qualitative and do not involve efficacy or safety comparisons requiring formal interim review. Accordingly, the establishment of a Data Safety Monitoring Committee is not required.

1.7 Any other relevant Committee, Person, Organisation, Institution

Not applicable.

2. ETHICAL AND REGULATO RY ASPECTS

The decision of the CEC and Swissmedic concerning the conduct of the study will be made in writing to the Sponsor-Investigator before commencement of this study. The clinical study can only begin once approval from all required authorities has been received. Any additional requirements imposed by the authorities shall be implemented.

FAPI radiotracers have demonstrated encouraging clinical potential in both oncologic and non-oncologic imaging, as FAP is overexpressed in various malignant and fibrotic diseases (10, 11). Prior clinical studies indicate that FAPI PET may provide additional and clinically relevant information, in some cases superior to existing tracers such as fluorodeoxyglucose (FDG) and may offer imaging options in indications lacking an established radiotracer. This study aims to expand scientific and clinical knowledge on [18F]FAPI-74 uptake patterns across multiple disease settings and to evaluate whether FAPI-PET may contribute incremental diagnostic value.

Data will be acquired through standardized [18F]FAPI-74 PET/CT or PET/MR procedures, and interpreted using qualitative and semi-quantitative methods to ensure objective and reproducible results.

Participants will be included based on pre-defined inclusion and exclusion criteria, and enrolled consecutively on a first-come, first-served basis. Screening will be performed primarily via radiological or clinical information systems, used for routine patient evaluations.

The study population consists of patients with malignant and fibrotic diseases, conditions often associated with chronic morbidity or reduced life expectancy. Each participant will undergo a single PET/CT or PET/MR scan comprising a low-dose CT (~3.5 mSv) for attenuation correction and anatomical localization, and a PET scan following an injection of approximately 250 MBq [18F]FAPI-74 (effective dose: 0.014 +/- 0.002 mSv / MBq, i.e. ~3.5 +/- 0.5 mSv) (12). The combined effective radiation dose (~7 mSv) is comparable to standard PET/CT examinations and within range of the average annual background radiation exposure in Switzerland (~6 mSv) (13). Given the low- risk imaging procedures and the potential to generate clinically relevant insights for future diagnostic advances, the overall risk–benefit ratio is considered highly favourable.

The study will undergo independent review and approval by the CEC and Swissmedic and, where applicable, local institutional review boards at participating centres.

Written informed consent will be obtained from each participant prior to conducting any study-related procedures. The patient information and consent form will clearly explain the study's purpose, procedures, potential risks, expected benefits, and measures taken to ensure data confidentiality. Consent will be obtained exclusively by qualified medical investigators.

All study procedures will be performed by authorized and appropriately trained and licenced personnel. Data confidentiality will be ensured according to institutional policies and applicable data protection laws. Participants may withdraw consent at any time without prejudice to their ongoing medical care.

2.1 Study Registration

In accordance with ClinO Art. 64, the study will be prospectively registered in a publicly accessible trial registry listed in the WHO International Clinical Trials Registry Platform (ICTRP).

Registration in HumRes (Swiss Clinical Trial Portal: Human Research Switzerland) via BASEC is mandatory and will be completed prior to inclusion of the first participant.

- HumRes (via BASEC), registration number: XXXXXX
- Clinical Trials (https://clinicaltrials.gov/): XXXXXX

2.2 Categorisation of study

This study is categorised as Category C according to ClinO Art. 19, paragraph 3.

The investigational product, FAPI-74, is a radiopharmaceutical that has not yet been authorized in Switzerland and therefore qualifies as a medicinal product under investigation without existing Swiss marketing authorisation.

The study is exploratory and diagnostic in nature. Participants will receive a single intravenous injection of [18F]FAPI-74 followed by a PET/CT or PET/MR acquisition. The expected risk is

comparable to that of other PET radiotracers used routinely in clinical practice. Potential risks are limited to the low-dose radiation exposure and to the injection procedure (e.g., mild discomfort, paravenous injection). No therapeutic intervention is involved.

2.3 Competent Ethics Committee (CEC)

The responsible investigator at each site shall ensure that approval from an appropriately constituted CEC is obtained prior to the initiation of the clinical study at their site. No site may begin recruitment before written approval has been received.

No changes may be made to the protocol without prior approval from the Sponsor-Investigator and the CEC, except when necessary to eliminate immediate hazards to study participants. In such urgent cases, the CEC shall be informed immediately after implementation of the change.

The CEC will be informed within 30 days of the first visit of the first participant and 30 days after completion of the study of according to ClinO Art. 38.

All changes in the research activity or unanticipated problems involving risks to humans must be reported to the CEC within 15 days.

Premature study termination or interruption is to be reported within 15 days, the regular end of the study within 90 days, and the final study report within one year after completion.

Amendments are reported and handled according to Chapter 2.10 of this protocol.

2.4 Competent Authorities (CA)

The Sponsor-Investigator will obtain approval from Swissmedic before study initiation, as required for all Category B and C trials under ClinO Art. 23.

No changes will be made to the protocol without prior Swissmedic approval, except where necessary to eliminate immediate hazards to study participants. In such cases, Swissmedic will be informed immediately after implementation.

Swissmedic will be informed within 30 days of the first visit of the first participant and 30 days after completion of the study according to ClinO Art. 38.

All changes in the research activity or unanticipated problems involving risks to humans must be reported to Swissmedic within 15 days.

Premature study end or interruption of the study is to be reported to Swissmedic within 15 days, the regular end of the study within 30 days, and the final study report within one year after completion.

Amendments are reported according to Chapter 2.10.

2.5 Ethical Conduct of the Study

The study will be carried out in accordance to the protocol and with the principles enunciated in the current version of the Declaration of Helsinki, the guidelines of Good Clinical Practice (GCP) issued by ICH, and Swiss Law and Swiss regulatory authority's requirements. The CEC and regulatory authorities will receive annually a safety report and interim reports and be informed about study stop/end in agreement with local requirements. The CEC will also be informed annually about the general progress of the clinical trial. The ASR may be submitted in the format of the Development Safety Update Report (DSUR).

2.6 Declaration of interest

The Sponsor-Investigator has received research grants and speaker honoraria from GE HealthCare. In addition, the Sponsor-Investigator has received funding for completed studies from the Alfred and Annemarie von Sick legacy, and from the Clinical Research Priority Program (CRPP) "Artificial Intelligence in Oncological Imaging Network" of the University of Zurich.

All other investigators involved in the study declare no conflict of interest.

2.7 Patient Information and Informed Consent

Potential Participants will be identified during pre-screening by site investigators through clinical conferences, review of clinical, laboratory and radiological information available within the institutional clinical information systems. This includes review of clinical notes, radiological information systems, and imaging records that are already available as part of the patient's standard care. Pre-screening is performed solely to determine whether a patient potentially meets the study's inclusion and exclusion criteria. At this stage, no study-specific procedures or interventions are performed.

Following pre-screening, eligible patients with an existing case within the Department of Nuclear Medicine (NUK) may be contacted directly by the site investigator by telephone or e-mail. The investigator or qualified delegate will inform each potential participant about the study's nature, purpose, procedures, expected duration, potential risks, anticipated benefits and possible inconveniences. Patients will also be informed that participation is voluntary and that they may withdraw consent at any time, without providing reasons and without consequences for their further medical treatment. Participants are encouraged to ask questions and consult family members, treating physicians or other advisors before deciding.

If a potentially eligible participant does not have an active case within the Department of Nuclear Medicine and thus has not yet been under the clinical responsibility of the NUK team, initial contact will not be made directly by NUK investigators. Instead, contact will be performed either by the patient's treating physician in the relevant specialty (e.g., oncology, immunology, cardiology) or jointly, with the treating physician acting as co-sender or co-caller. The study coordinator may perform the call or send the written communication on behalf of both the treating physician and the NUK investigator. This procedure ensures that initial outreach always originates from clinicians who are already involved in the patient's care.

Due to the nature of radiopharmaceuticals and their physical half-life, [18F]-FAPI-47 must be pre-ordered to ensure the production of an adequate supply of investigational medicinal product for distribution to the study sites. This process allows participants more than 24 hours to consider their participation, in contrast to conventional IMPs, where such preparation time is typically not required.

Participants are informed that authorised individuals other than their treating physician (e.g. monitors, auditors, regulatory authorities, ethics committees) may review relevant sections of their medical records.

All participants will receive a subject information sheet and informed consent form (ICF). Formal consent will be obtained prior to any study-related procedure. The ICF will be signed and dated both by the participant and by the investigator (or delegate), retained in the study records, and a copy provided to the participant.

No vulnerable population (e.g., children, pregnant or breastfeeding women, prisoners, debilitated persons, subjects lacking capacity of judgment or those under tutelage) will be included.

No financial compensation will be provided for participation.

2.8 Participant Privacy and Confidentiality

The investigator affirms and upholds each participant's right to privacy and will comply with applicable privacy and data protection laws.

Anonymity will be preserved in all data analysis, presentations or publications. Participants will be identified only by a unique subject identification number (e.g., USZ-001, LUKS-002). Identifiable personal information will not appear in the study database.

For data verification purposes, authorised representatives of the Sponsor-Investigator, Swissmedic, the CEC, or other regulatory authorities may be granted direct access to relevant parts of medical records in compliance with confidentiality requirements.

2.9 Premature Termination of the Study

The Sponsor-Investigator reserves the right to terminate the study prematurely at any time for reasons including, but not limited to:

- Ethical or safety concerns,
- Insufficient participant recruitment,
- Emerging safety issues or unacceptable risks to participants,

- Changes in accepted clinical practice that render continuation inappropriate,
- Early evidence of clear benefit or harm of the investigational product

Any premature study termination will be reported directly to both the CEC and Swissmedic.

2.10 Protocol Amendments

Only the Sponsor-Investigator is authorised to amend the study protocol. Suggestions for amendments from investigators, monitors, or other collaborators will be reviewed and may be incorporated at the Sponsor-Investigators direction.

Substantial amendments (e.g., changes in eligibility criteria, outcomes, study design, or analyses) will only be implemented after approval by the CEC and Swissmedic.

In emergency situations, deviations from the protocol to protect the rights, safety and well-being of participants may be implemented immediately without approval; such deviations will be documented and reported to both authorities as soon as possible.

Non-substantial amendments will be communicated to the competent authorities as soon as possible, as well as to the CEC within the context of the ASR.

3. BACKGROUND AND RATIO NALE

3.1 Background and Rationale

Most clinically established oncologic PET radiotracers visualize tumour cell metabolism, typically through glucose or amino acid intake, as exemplified by [^{18}F]fluorodeoxyglucose (FDG). While FDG-PET has transformed cancer diagnostics, it has well-recognized limitations in several tumour types, anatomical lesions and clinical scenarios.

In recent years, increased attention has shifted towards the tumour microenvironment as both a diagnostic and therapeutic target. One promising target is the fibroblast activation protein (FAP), a transmembrane glycoprotein selectively expressed on activated fibroblasts, particularly cancer-associated fibroblasts (CAF), which are abundant within the stroma of many tumours. FAP expression in normal adult tissue is minimal, making it an attractive target for molecular imaging.

Quinoline-based FAP inhibitors (FAPI) labelled with positron emitters such as [18F]FAPI-74 have recently emerged as promising radiotracers for in vivo visualization of FAP expression. Several studies have provided clinically relevant information across a wide spectrum of malignant and selected benign diseases (10, 11). These studies have shown that FAPI imaging can provide information that is in part superior to clinically established radiotracers, such as FDG PET/CT, or novel in diseases where no suitable radiotracer currently exists (10, 11).

Compared with FDG and other standard radiotracers, FAPI imaging has demonstrated added diagnostic value in various scenarios, for example:

- tumors with intrinsically low glucose or amino acid metabolism, such as salivary gland carcinomas or hepatocellular carcinomas, which may appear inconspicuous on FDG PET but show pronounced uptake of [18F]FAPI-74.
- lesions adjacent to tissues with high physiological FDG uptake, such as sinonasal and nasopharyngeal carcinomas, or brain metastases, where [18F]FAPI-74 provides improved lesion-to-background contrast due to negligible uptake in normal brain tissue.

These observations suggest that [18F]FAPI-74 may enhance diagnostic accuracy, staging and treatment planning in several tumor types, including gastric and hepatopancreatobiliary neoplasms. However, while international pilot studies have produced encouraging results, there remains a lack of systematic evaluation in a Swiss multicentre clinical setting and across diverse tumour types in clinical practice.

This exploratory, open-label diagnostic study therefore aims to evaluate the diagnostic performance and clinical relevance of [18F]FAPI-74 PET/CT or PET/MR, using current standard-of-care imaging modalities as comparators. Specifically, the study will:

- assess overall diagnostic image quality and uptake pattern of [18F]FAPI-74,
- compare [18F]FAPI-74 uptake qualitatively and semi-quantitatively with clinically established tracers (e.g., FDG), and
- evaluate the potential clinical impact of [18F]FAPI-47 uptake on diagnostic interpretation and patient management in selected tumour types.

By addressing these objectives, the study will help define the potential role of FAPI PET imaging within the Swiss diagnostic landscape and contribute valuable evidence to the growing international clincal experience with FAP-targeted molecular imaging.

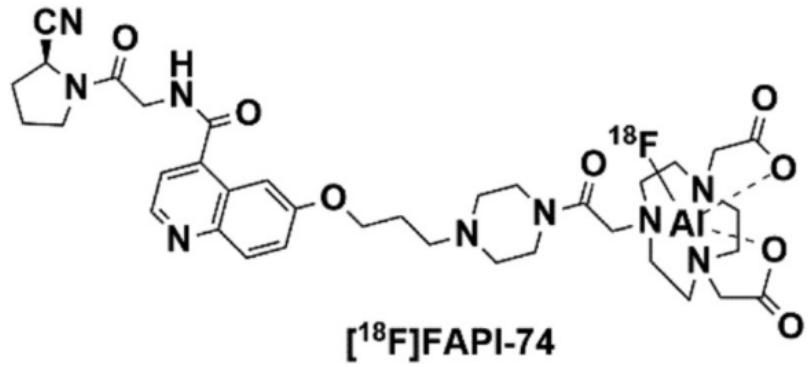
3.2 Investigational Medicinal Product (Treatment) and Indication

Comprehensive information regarding the investigational radiotracer [18F]FAPI-74 is provided in the Investigator's Brochure.

The investigational product is manufactured at the Radiopharmacy of the University Hospital Zurich according to the specifications outlined in the Investigational medicinal product dossier (IMPD). The product is supplied as sterile, ready-to-use clear colourless solution for intravenous injection, contained in a Type I glass vial with a nominal capacity of 10mL.

The final injected activity per patient is 250MBq.

Description and physical properties of the product
[18F]FAPI-74 injection contains the active substance: [18F] aluminium fluorine ((S)-2,2`(7-(2-(4- (3-(4-(2-(2-cyanopyrrolidin 1-yl)-2-oxoethylcarbamoyl)quinolin-6-yloxy) propyl)piperazin-1-yl)-2-oxoethyl)-1,4,7-triazonane-1,4-diyl)diacetic acid (Abbreviated as [18F]FAPI-74 , chemical structure shown below). The active substance is formulated as an injectable solution, which contains buffering excipients (ascorbate) that maintain the stability over the injection shelf-life.



[18F]FAPI-74

As with other Fluorine(F)-[18] labelled tracers, radioactive decay of [18F]FAPI-74 occurs predominantly by positron emission (β^+ decay, 97%) with a mean positron energy of 0.635 meV and a half-life of 109.7 minutes.

Manufacturing
[18F]FAPI-74 is produced by a fully automatic synthesis procedure using the Trasis Software Suite (version 2.34.0.0, Trasis, Liège, Belgium). Each production run employs a single-use, disposable cassette, which forms the entire fluidic path, and contains the integrated reaction vessel. The cassette is fitted to the synthesizer for each synthesis cycle.

All reagents and auxiliary materials used in the process are commercially available, GMP-grade, single-use kits. The GMP-certified precursor is supplied by SOFIE Biosciences. No synthesis components or materials are re-used.

After synthesis, the mother solution is automatically transferred form the synthesizer to a computer-controlled dispensing system located in a class A clean area. The solution is subsequently diluted with 0.9% NaCl, sterilized by filtration and dispensed into sterile primary glass vials.

Quality control
Before release for clinical use, each batch undergoes a complete quality control procedure in accordance with GMP and internal release specifications. The following analytical tests are performed:

- Identification of the active substance: High-Performance Liquid Chromatography (HPLC) for [18F]FAPI-74 chemical identity
- Identification of radionuclide: measurement of 18-Fluorine half-life

- Chemical and radiochemical purity: HPLC quantification of [18F]FAPI-74 and related compounds.
- Determination of organic solvents: Gas Chromatography-Flame Ionization Detector (GC-FID) for ethanol and acetonitrile content
- pH value: verification of physiological pH range with validated indicator stripes
- Endotoxin content: determination by fast kinetic chromogenic assay

Following release, retained samples from each batch are subjected to sterility testing, performed under validated aseptic conditions.

Specifications

Parameter	Specification
Identity [18F]FAPI-74	HPLC retention time of [18F]FAPI-74 in product radiochromatogram similar to retention time of reference substance [18F]FAPI-74 in UV-chromatogram of reference solution
Identity [18F]-fluorine	Half-life: 105 – 115 minutes
Maximal content long-lived radionuclides	≤ 0.1% at end of shelf-life
Chemical purity: • Maximal content [18F]FAPI-74 • Maximal content of related impurities (total) • Maximal content Acetonitrile	 ≤ 2 μg/ml (or 20 μg/dose) ≤ 3 μg/ml (or 30 μg/dose) ≤ 526 ppm (V/V) (or 4.1 mg/dose)
Ethanol content	≤ 10.0% (V/V)
pH value	5-7
Radiochemical purity	≥ 93% [18F]FAPI-74 of total [18F] activity
Maximal content of [18F]fluoride (non-bounded [18F]fluoride)	≤ 5% of total [18F] activity
Endotoxin limit	≤ 17.5 EU/ml
Sterility	Sterile
Radioactivity concentration	0.05 – 2.5 GBq / ml
Shelf-life	10 hours after manufacturing

3.3 Preclinical Evidence

Preclinical investigations have demonstrated that [18F]FAPI-74 is a promising PET tracer with high binding affinity and selectivity for FAP-expressing cells, resulting in excellent tumour-to-background contrast in vivo. Its physicochemical properties are comparable to earlier members of the FAPI compound family, such as FAPI-46, and FAPI-04 (40).

Multiple in vitro and in vivo studies, including experiments in mouse models bearing FAP-expressing HT-1080 and PANC-1 xenografts (Lindner et al., 2021; Liu et al., 2022) have consistently shown high-affinity FAPI binding ow nonspecific uptake in normal tissues, and reproducible biodistribution across both endogenous and engineered FAP-expression systems.

The biodistribution and pharmacodynamic characteristics of fluorine-18-labelled and gallium-68-labelled FAPI analogues are broadly comparable. However, [18F]FAPI-74 offers practical advantages due to the longer half-life of fluorine-18, enabling large-scale, centralized production at the USZ cyclotron facility and reliable distribution to participating sites.

Taken together, these findings provide a strong scientific and safety rationale for clinical evaluation of [18F]FAPI-74 as a novel PET radiotracer for imaging FAP expression in various oncologic and non-oncologic conditions. Comprehensive preclinical data are provided in the Investigator's Brochure.

3.4 Clinical Evidence to Date

Details on all published and ongoing clinical studies with [18F]FAPI-74 are provided in the Investigators Brochure.

Clinical PET/CT studies with both [18F]FAPI-74 and [68Ga]FAPI-74 have shown favourable tumour-to-background ratios, high SUVmax values, and excellent lesion detectability for both primary and metastatic disease across a variety of cancer types (10, 12, 40, 41, 42, 43). Importantly, no adverse events related to FAPI-47 administration have been reported.

Under the SOFIE Global Distribution Program, which provides FAPI-74 precursor material for investigator-initiated trials worldwide, 17 clinical studies involving approximately 470 patients are currently ongoing. To date, no safety concerns or adverse events have emerged from these investigations.

Oncolog ic Applications

FAP expression has been observed in more than 90% of epithelial neoplasms (15,16) supporting broad applicability of FAPI imaging. A proof-of-concept study in 2018 first demonstrated high [68Ga]-FAPI uptake in three patients with breast, lung, and pancreatic cancers (17). Subsequent studies across 80 patients and 28 tumour types revealed the highest tracer uptake in sarcomas, cholangiocarcinoma, esophageal, breast, and lung cancers (11). Across these cohorts, FAPI PET/CT consistently outperformed FDG PET/CT in lesion detection, largely due to lower physiological background activity and thus improved lesion contrast (18).

A recent single-centre phase 2 trial (158 patients) demonstrated that [68Ga]FAPI-46 PET/CT reliably detected FAP-expressing tumours with high positive predictive value, confirmed through histopathology, and showed a strong association between tracer uptake and FAP expression (46). These results provide high-quality clinical evidence supporting the diagnostic value of FAPI imaging across multiple cancer types.

Hepatic and Pancreatic Malignancies:

Studies in hepatocellular carcinoma (HCC) and cholangiocarcinoma (CCC) report higher sensitivity for FAPI imaging compared with FDG, including superior detection of poorly differentiated tumours. Shi et al. performed FAPI-04 PET/CT in 25 patients with hepatic nodules suspicious of malignancy (19). Intra-hepatic malignant lesions showed higher tracer uptake, particularly in poorly differentiated tumours. Other prospective studies found FAPI4 PET/CT to have comparable specificity but markedly higher sensitivity than FDG PET/CT (100% vs. 58.8%) for detecting hepatic malignancies (20, 21).

Further reports have demonstrated diagnostic advantages of FAPI PET in pancreatic carcinoma, including improved detection of liver and bone metastases (22), differentiation of autoimmune pancreatitis from pancreatic cancer, which was not sufficiently possible with FDG (23), and identification of TNM stage changes in up to 52 % of patients in some cohorts (24).

Gastrointestinal and Colorectal Malignancies:

FAP overexpression is common in gastrointestinal malignancies, including colorectal cancer (CRC) (25). Pang et al. found FAPI PET/CT superior to FDG PET/CT for detecting primary lesions, nodal-, and distant metastases (sensitivity 100 % vs 53 %, 79 % vs 54 %, and 89 % vs 57 %, respectively) in 35 patients with CRC, gastric and duodenal cancers (26). FAPI use led to upstaging in 21% of the treatment-naïve patients (26), and additional studies confirmed its usefulness in treatment-response monitoring (27).

A meta-analysis of 11 studies including 340 patients reported significantly higher pooled sensitivity for peritoneal metastases detection with FAPI PET/CT (patient-based 98.2% vs. 55.9%; lesion-based 99.9% vs. 27.3%) (28).

Head & Neck and Brain Tumours:

FAPI PET/MR improved assessment of skull base and intracranial invasion in nasopharyngeal carcinoma, altering overall staging in 40% of cases (29). In adenoid cystic carcinoma, FAPI enhanced tumour-volume delineation and upstaged disease in 41.7 % of patients (30).

Breast Cancer:

Given the CAF-rich tumor microenvironment in breast cancer, FAPI PET has shown high uptake in primary lesions and metastatic sites, with higher sensitivity than FDG in several prospective cohorts. A prospective study of 20 women showed that FAPI PET had higher sensitivity than FDG PET (100%

vs. 78.2%), with comparable specificity for detecting primary breast lesions, and demonstrated higher uptake in primary breast lesions, lymph nodal, lung, and bone metastases (31). A retrospective study of 48 patients confirmed higher lesion detectability and tracer uptake, while a small prospective pilot study in non-FDG-avid metastatic invasive lobular breast cancer patients revealed significantly higher lesion detection with FAPI PET/CT compared with CT alone (p = 0.022) (34). FAPI also identified infiltrative soft tissue and serosal involvement that FDG often missed. In contrast, no significant difference in tracer uptake of primary tumours was noted across different grades, receptor statuses, or histologic types (33).

Non-Oncologic Indications

Beyond oncology, FAPI has shown diagnostic potential in IgG4-related disease, providing improved lesion detection of pancreatic, lacrimal gland, and hepatobiliary involvement, compared with FDG (35 - 37). Exploratory studies also suggest potential applications in monitoring diseases characterized by inflammation and fibrotic remodelling, such as systemic sclerosis, sarcoidosis vasculitis, and orthopaedic implant loosening (38, 39).

A published case report in cardiac sarcoidosis demonstrated pronounced 68Ga-FAPI uptake in areas of persistent myocardial remodelling despite complete metabolic remission on FDG-PET, suggesting that FAPI may offer complementary information beyond traditional inflammatory imaging (45).

In summary, published evidence indicates that FAPI-based PET imaging offers superior diagnostic contrast and improved lesion detection compared with FDG PET in numerous clinical settings, while demonstrating an excellent safety profile.

3.5 Rationale for the Dosage, Route, Regimen

The selected administered activity is based on several previous publications with [18F]FAPI-74 and comparable 18F-labelled radiotracers, e.g., Mori et al., 2021 (14). Multiple studies have demonstrated that diagnostic activities in the range of 200–400 MBq provide robust image quality while maintaining radiation exposure within the limits of standard PET imaging practice. This is consistent with current recommendations of the European Association of Nuclear Medicine (EANM) and the International Atomic Energy Agency (IAEA).

Based on these data, this study applies a preferred administered activity of 250 MBq (+/- 20%) per participant. This dosage provides an optimal balance between image quality and radiation exposure. To accommodate differences in scanner sensitivity and reconstruction performance across participating sites, each site may apply its own predefined activity range within 200–300 MBq, defined prospectively before enrolment of the first participant. The actual injected activity (MBq) and injection-to-scan time of each participant will be recorded in the eCRF.

Image interpretation will rely on qualitative and semi-quantitative assessments performed within each site, and comparisons with standard-of-care imaging will be made intra-individual and indication-specific, minimizing the effect from inter-scanner variability.

The route of administration is intravenous injection, delivered as a slow bolus over 5–15 seconds. Intravenous administration is the clinically established and validated route for PET radiotracer administration, providing rapid systemic distribution and reproducible biodistribution suitable for standardized PET acquisition.

3.6 Explanation for Choice of Comparator (or Placebo)

No placebo is used in this diagnostic imaging study. Instead, comparison will be made against clinically indicated, previously acquired standard-of-care imaging, such as PET/CT or PET/MR using established radiotracers and/or morphological imaging (e.g., CT or MRI). These examinations serve as the reference standard, allowing intra-individual comparison of [18F]FAPI-74 uptake with established diagnostic modalities without exposing participants to additional radiation or unnecessary procedures.

3.7 Risks / Benefits

The primary risks associated with participation in this study are those typically linked to intravenous administration of diagnostic radiotracers, including local injection-site reactions (e.g., minor irritation,

pain, or paravenous injection), and rare allergic or intolerance reactions. Adverse reactions to PET radiotracers are considered very uncommon, largely due to their significantly low molar concentrations, the molecular resemblance to endogenous compounds, and rapid systemic clearance. The formulation of [18F]FAPI-74 contains less than 10% ethanol, with an effective concentration < 3% in the injected product, which is well within the limits of standard diagnostic formulations.

All participating sites will have immediate access to emergency medical equipment and medication, including glucocorticoids, antihistamines and adrenaline to manage potential hypersensitivity reactions. Institutional experience indicates that the majority of adverse reaction in PET/CT settings are related to iodinated contrast agents, which will not be administered as part of this study. As such, the anticipated risk profile of [18F]FAPI-74 is low.

Participants will receive standard post-procedure clinical care. Since overall participation lasts approximately 2 hours and concludes with the end of the PET scan, no additional follow-up visits are required unless an adverse event (AE) occurs. Any AEs will be managed in accordance with institutional protocols and documented as required.

No immediate therapeutic benefit is expected for participants. However, potential secondary benefits include the detection of clinically relevant findings that may not be visible on standard imaging and could influence subsequent clinical decision-making. Beyond individual participants, the study is expected to contribute valuable data to expanding the clinical evidence base for [18F]FAPI-74, complementing ongoing international research thereby informing future clinical practice in both oncologic and non-oncologic disease.

3.8 Justification of choice of study population

The study population includes patients with oncologic and non-oncologic conditions who are undergoing clinically indicated standard imaging procedures. Participants that meet the inclusion criteria will be consecutively recruited from the participating study centres, ensuring a broad target population.

While a predefined gender balance will not be enforced, the study is designed to reflect the natural gender distribution observed in the epidemiology of the target diseases. Some diseases, such as prostate cancer (predominantly men), breast cancer (predominantly women), and mesothelioma (predominantly men) exhibit gender-specific prevalence. Imposing artificial gender quotas would therefore risk distorting disease-specific subgroup analyses, slow recruitment, or prevent the inclusion of participants in sex-restricted conditions. Consequently, a natural gender distribution will be achieved representing the epidemiology of the diseases under study.

No vulnerable subjects (e.g., minors, pregnant women, individual’s incapable of judgment) will be included in the study.

3.9 Patient and Public Involvement

Patient and Public Involvement (PPI) was not undertaken for this study. The research focuses on the evaluation of a novel PET radiotracer, and the study design is driven primarily by clinical, methodological, and technical considerations intrinsic to nuclear medicine. The scientific rationale, imaging procedures, and outcome measures rely on established professional standards and expert consensus rather than patient-defined preferences.

Because the study involves a single diagnostic imaging procedure, with no therapeutic intervention and minimal participant burden, PPI was not considered essential for defining the study protocol, determining feasibility, or selecting endpoints. All procedures, risk-benefit considerations, and data-collection methods were therefore developed by clinical experts in accordance with regulatory and institutional requirements.

Should future studies with broader clinical interventions or patient-reported outcomes be planned, incorporation of PPI may be considered at that time.

4. STUDY OBJECTIVES

4.1 Overall Objective

The overall objective of this study is to evaluate the clinical performance of the novel PET radiotracer [18F]FAPI-74 across a spectrum of oncologic and non-oncologic conditions, particularly in disease settings where no clinically established radiotracer exists or where current tracers offer limited diagnostic value. The study aims to characterize tracer uptake patterns, assess overall image quality, and explore the potential diagnostic utility of [18F]FAPI-74 across multiple clinical indications.

4.2 Primary Objective

The primary objective is to characterize the uptake of [18F]FAPI-74 and assess the diagnostic interpretability of the resulting PET images across diverse oncologic and non-oncologic conditions.

4.3 Secondary Objectives

- To compare [18F]FAPI-74 uptake with standard reference imaging modalities (e.g., clinically established PET radiotracers or morphological imaging such as CT or MRI)
- To evaluate the potential clinical significance of [18F]FAPI-74 findings, focusing on their contribution to diagnostic decision-making and any resulting impact on patient management.

4.4 Safety Objectives

The safety profile of [18F]FAPI-74 has been characterized in prior clinical studies, as summarized in the Investigator's Brochure. No dedicated safety endpoints are defined for this study beyond the assessment and documentation of adverse advents.

5. STUDY OUTCOMES

5.1 Primary Outcome

The primary outcome is the qualitative assessment of [18F]FAPI-74 uptake based on reader ratings, classified as either FAPI-positive or FAPI-negative in target lesions or disease-specific regions. This includes an overall evaluation of diagnostic image quality for each participant. The aim of this outcome is to determine whether [18F]FAPI-74 consistently produces diagnostically interpretable images across a range of disease settings.

5.2 Secondary Outcomes

- Qualitative and semi-quantitative comparison of [18F]FAPI-74 uptake with reference imaging (e.g., other PET radiotracer or morphological imaging techniques) using lesion-wise analyses.
- Changes in diagnostic confidence and clinical management recommendations, determined by comparing diagnostic evaluations performed before versus after [18F]FAPI-74 imaging. Outcomes may include the percentage change in diagnostic certainty and the number of participants for whom clinical management or treatment pathways are modified based on the additional information provided by [18F]FAPI-74.

5.3 Other Outcomes of Interest

Not applicable.

5.4 Safety Outcomes

No formal safety endpoints are defined. However, all safety-related events, including any AEs or SAEs temporally associated with [18F]FAPI-74 administration will be documented and evaluated according to the procedures described in Chapter 10.

6. STUDY DESIGN

6.1 General Study De sign and Justification of Design

This is an open-label, single-arm exploratory diagnostic study designed to evaluate [18F]FAPI-74 PET imaging in patients with selected oncologic and non-oncologic diseases. Each participant will receive an intravenous injection of [18F]FAPI-74, followed by one PET/CT or PET/MR acquisition. No therapeutic intervention or longitudinal follow-up is planned.

Where available, previously acquired medical imaging examinations (e.g., PET/CT or PET/MR with clinically established radiotracers) will be used as reference standards for comparative evaluation. As the comparator imaging depends on clinical indication, it may vary according to disease type and routine clinical availability.

The exploratory, single-arm, open-label design is considered both scientifically and ethically appropriate for the objectives of this study. The focus is on qualitative and semi-quantitative characterization of [18F]FAPI-74 uptake and assessing diagnostic image quality relative to existing imaging standards. Incorporating randomization, blinding or the use of a control arm would not contribute meaningfully to these descriptive endpoints, while adding unnecessary procedural complexity without corresponding scientific value.

The expected total duration of participation for each participant is approximately two hours, covering essential study procedures including informed consent, tracer administration, tracer uptake period, and PET image acquisition.

6.2 Methods of Minimising Bias

Bias is expected to be minimal because each participant undergoes only a single imaging procedure, thereby eliminating intra-individual variability associated with repeated interventions. Selection bias is reduced through consecutive enrolment of eligible patients who meet the predefined inclusion and exclusion criteria. This approach ensures systematic recruitment of patients with relevant indications and avoids convenience-based selection.

As the study employs a single, non-comparative diagnostic intervention, no randomisation nor placebo control is required. The open-label design is appropriate and does not compromise the descriptive and exploratory objectives of the study.

6.2.1 Randomisation

Not applicable. Because there is only one study arm, randomisation is neither required nor scientifically meaningful in this exploratory diagnostic context.

6.2.2 Blinding procedures

Blinding is not feasible, because all participants undergo a single imaging session, and the imaging appearance of [18F]FAPI-74 is distinct and recognisable, precluding effective masking of image interpreters. Given the descriptive nature of the study and the reliance on predefined imaging criteria, the absence of blinding is not expected to introduce meaningful bias.

6.2.3 Other methods of minimising bias

Not applicable. No additional bias-mitigation measures are required.

6.3 Unblinding Procedures (Code Break)

Not applicable. This is open-label study and does not employ blinding or randomisation codes. Therefore, no unblinding procedures are necessary.

7. STUDY POPULATION

7.1 Eligibility Criteria

Inclusion Criteria

Participants must meet all of the following criteria:

- Written informed consent obtained and documented by the participant's signature
- Age ≥18 years at the time of consent.
- Clinically established or suspected diagnosis or recurrence of an oncologic or non-oncologic disease as listed in 7.3.
- Availability of standard-of-care imaging (e.g., clinically established PET tracer or anatomical imaging such as CT/MRI) to allow comparative evaluation.

Exclusion criteria

Participants will be excluded if any of the following apply:

- Severe claustrophobia that would preclude PET imaging.
- Inability to remain still for the duration of the PET/MR examination.
- Age <18 years.
- Current pregnancy or breastfeeding; no pregnancy test is required for women who are postmenopausal for ≥12 months or have undergone surgical sterilization, bilateral oophorectomy, or hysterectomy.
- Previous hypersensitivity reactions to radiotracer administration.
- Inability to understand study information, for example due to language barriers.
- Subjects incapable of judgment (e.g individuals under legal or medical incapacity)

A qualified study physician (Investigator or Sub-Investigator) will confirm that each individual criterion is met prior to participant inclusion. The final determination of eligibility will be documented and signed by the PI or an authorized delegate before commencement of any study-specific procedures.

In line with the recommendations of the EU GCP Inspector's Working Party (web-Link) the inclusion and exclusion criteria will be mapped individually in the eCRF. An overall statement regarding a subject's eligibility in the trial such as 'Did the subject satisfy all study entry criteria?' is not accepted.

7.2 Recruitment and Screening

Participants will be recruited consecutively on a first-come-first-served basis according to the inclusion and exclusion criteria. Screening for eligible candidates will be performed through routine review of the radiological and clinical information system, as well as and by identifying potential candidates during multidisciplinary tumor boards.

Recruitment will follow standard referral pathways for diagnostic imaging and may therefore be influenced by routine clinical practice patterns, which cannot be actively controlled or modified by study personnel.

No public advertisement or active outreach campaigns are planned for the study. Participants will not receive financial compensation for participations; however, travel expenses directly related to study visit may be reimbursed.

Details of the screening procedure are provided in Section 9.3.

7.3 Assignment to Study Groups

Participants will be assigned to indication-specific subgroups according to their clinical diagnosis (numbers are envisaged patient numbers; ID: initial diagnosis, SRP: suspected recurrence/persistence):

- Thyroid Pathology: 50
- Head and neck cancer (including cancer of unknown primary): 50
- Neck node metastases from cancer of unknown primary: 30
- Sinonasal tract tumor (SNT): 50
- Sarcoidosis: 50
- Thyroid cancer (SRP): 50
- Breast cancer (ID, SRP): 50
- Hepatocellular carcinoma (ID, SRP): 50
- Gastric cancer (not: esophagogastric junction cancer) (ID, SRP): 50
- Pancreatic cancer (ID, SRP): 50
- Prostate cancer (biochemical recurrence and negative PSMA-PET): 50
- Urothelial carcinoma (ID): 50
- Multiple myeloma / plasmocytoma (ID): 20
- Mesothelioma (ID, SRP): 50
- Hepatic fibrosis (ID, SRP): 20
- Endometriosis (ID, SRP): 50
- Lung fibrosis: 50

7.4 Criteria for Withdrawal / Discontinuation of Participants

Participation in the study is voluntary. Participants may withdraw consent at any time, without providing a reason and without any negative consequences for their ongoing or future medical care. If a participant withdraws prior to administration of the radiotracer, no study-specific data will be collected or retained. If the participant withdraws after imaging, after the PET/CT or PET/MR acquisition has been completed, the data already collected may be used for analysis, provided the participant has not revoked consent for the further use of their data. Any revocation of consent will be managed in accordance with applicable data-protection regulations.

Participants who withdraw before imaging or whose imaging data are not usable for the primary endpoint will be replaced, to maintain the target sample size and subgroup representation.

8. STUDY INTERVENTION

8.1 Identity of Investigational Products

The investigational product in this study is [18F]FAPI-74, fluorine-18–labelled PET radiotracer designed to visualize fibroblast activation protein (FAP) expression in vivo. [18F]FAPI-74 is administered for diagnostic imaging purposes only.

Each participant will receive a single intravenous dose of approximately 250 MBq of [18F]-FAPI-74. The effective dose 3.5 +/- 0.5 mSv per injection (based on the administered activity of 0.014 +/- 0.002 mSv / MBq) (12).

Following tracer administration, participants will undergo a single PET/CT or PET/MR scan. For PET/CT, a low-dose CT (estimated effective dose of 3.5 mSv) will be performed for attenuation correction and anatomical localisation. The effective dose associated with the PET scan corresponds to the administered activity of the radiotracer. Total participation time, including consent, tracer administration, uptake phase, and imaging, is approximately 2 hours on a single study day.

The physical properties, specifications, manufacturing process, and quality control procedures for [18F]FAPI-74 are described in Chapter 3.2. and in detail in the Investigator's Brochure. The radiotracer is manufactured at the Radiopharmacy Unit of the University Hospital Zurich (USZ) according to GMP and site-specific Investigational Medicinal Product (IMP) standards.

8.1.1 Experimental Intervention

Generic name	[18F]FAPI-74
Brand name	n/a
Source	Precursor provided by SOFIE Biosciences; radiolabelling and final product manufacturing performed by USZ Radiopharmacy, Department of Nuclear Medicine, in accordance with the site-specific IMP dossier
Active substance	[18F] aluminium fluorine ((S)-2,2′(7-(2-(4-(3-(4-(2-(2-cyanopyrrolidin-1-yl)-2-oxoethylcarbamoyl)quinolin-6-yloxy)propyl)piperazin-1-yl)-2-oxoethyl)-1,4,7-triazonane-1,4-diyl)diacetic acid), abbreviated as [18F]FAPI-74.
Formulation / excipients	Sterile, clear, injectable solution containing phosphate buffer and ascorbate as stabiliser.
Strength / activity	Approximately 250 MBq; administered activity adjusted for radioactive decay at time of injection.
Route and mode of administration	Intravenous injection, preferably via peripheral venous catheter (alternatively central line).
Colour	Clear
Frequency	Single administration only.

8.1.2 Control Intervention (Standard/Routine/Comparator Treatment)

In this study, historical standard-of-care including imaging will serve as comparator. The comparator imaging modalities will vary depending on the indication being evaluated, as available for the respective indication (e.g., FDG-PET/CT, PSMA-PET/CT, MRI, or CT).

These imaging modalities will be employed as comparators, with their selection dependent on the

clinical indication for each participant. Since this study is an exploratory, single-arm diagnostic feasibility study, no placebo or randomized control is planned.

8.1.3 Packaging, Labelling and Supply (Re -Supply)

The investigational product, [18F]-FAPI-74, will be packaged and labelled in accordance with institutional standards and regulatory requirements. The following details describe the packaging and labelling:

Vial label:

Label dimensions: approximately 2.96 cm x 5.25 cm

18F-FAPI-74
Solution for intravenous injection
Lot: XXXXXXX
EXP: Xh after calibration time

Lead pot or tungsten pot label:

Dimensions of the label 5.41 cm x 6.45 cm

18F-FAPI-74 **XX-XX GBq/ml**
Solution for intravenous injection.
Number or name of the clinical trial
Store upright at room temperature (15-25°C).
Patient number or randomisation number
For clinical trial use only

Lot:	XXXXXXX
Activity at reference time:	XX,X GBq
Volume of the solution:	XX,X ml
Reference time:	TT/MM/JJJJ HH:MM CET
Expiry time:	TT/MM/JJJJ HH:MM CET

Name of sponsor or principal investigator or CRO

Packaging: [18F]FAPI-74 is supplied in type I borosilicate glass vials as a sterile, clear colourless solution formulated for intravenous injection. Each vial has a nominal capacity of 15mLand a maximal filling volume of 10 m. The vials are purchased closed with a rubber septum and an aluminium crimp cap, ensuring sterility and radiation safety.

Each vial is filled with [18F]FAPI-74 and placed inside a Type A package for radioactive materials, consisting of two containers. The first container is a lead or a tungsten transport pot, containing the labelled glass vial, providing adequate radiation shielding during shipment. The lead pot / tungsten pot is placed into a padded plastic or metal transport case (i.e., a second container), protecting the product against mechanical damage during transit.

Prior to shipment, the case is closed and sealed by an authorized operator from the USZ Zentrum für Radiopharmazie (ZRP). Upon receipt at the destination site. The seal is inspected and opened by authorised personnel.

Transport to external study sites is carried out by licensed transport companies authorized to handle radioactive materials, in compliance with Swiss radiation protection legislation.



Placement of primary packaging into secondary packaging.

Provision of supply: [18F]FAPI-74 is shipped under quarantine to the end users; this is done before completion of specified quality control procedures. Before administering the product, end users are obliged by a written commitment to await a written confirmation from ZRP ensuring product compliance (release certificate). The release certificate is signed by the ZRP official and is sent by e-mail to the end users after completion of quality control analyses and after review of batch records.

8.1.4 Storage Conditions

The substance is stored at room temperature (15–25°C) and protected from light. Storage duration is inherently limited its physical half-life (T½ =109.7 min). Consequently, the investigational product must be administered within its validated shelf life.

IMP supplies are kept in secured, access-restricted areas of the radiopharmacy or nuclear medicine department, in compliance with ClinO Art. 30 and institutional radiation protection SOPs.

8.2 Administration of experimental and control interventions

8.2.1 Experimental Intervention

See section 8.1.1. for full details on the investigational product.

Each participant receives a single intravenous injection of approximately 250 MBq [18F]FAPI-74, followed by PET/CT or PET/MR acquisition 45–60 minutes post-injection.

The administration procedure, scan protocol, and exposure levels are equivalent to those routinely used in clinical PET imaging.

8.2.2 Control Intervention

No active control intervention is performed. Historical or standard-of-care diagnostic imaging (e.g. FDG-, PSMA-, or other radiotracer PET/CT) will serve as comparators, depending on the indication.

8.3 Dose Modifications

To account for differences in scanner sensitivity and reconstruction performance across participating sites, site-specific administered activity ranges may be applied, provided they fall within the predefined range of 250 MBq (+/- 20%), and are prospectively defined before first patient is included.

The actual injected activity (MBq) will be recorded in the eCRF.

8.4 Compliance with Study Intervention

The study intervention mirrors a routine PET/CT or PET/MR examination, differing only in the use of the investigational radiotracer [18F]FAPI-74. Therefore, participant compliance is expected to be high. Non-compliance in this context refers to participants not following study-related instructions (e.g., arrival delays, failure to adhere to pre-scan requirements, early termination of the scan). Non-compliance may be identified through imaging data, such as incomplete scans, motion artefacts, or low or absent tracer uptake. These issues will be documented, and participants with non-compliance may be excluded from data analysis depending on the severity (e.g., poor image quality, failed tracer uptake).

8.5 Data Collection and Follow -up for Withdrawn Participants

All data collected up to the time of withdrawal will be retained and included in the analysis. No additional data will be collected after withdrawal, and follow-up visits are not planned for withdrawn participants.

8.6 Trial Specific Preventive Measures

As this is a non-interventional diagnostic study involving a single administration of a radiotracer, no specific behavioural or lifestyle-related preventive measures are required. Participants may continue their routine medications and follow normal daily activities. No fasting or dietary restrictions are necessary before or after the imaging procedure.

However, given that the study involves the administration of a novel radiotracer, the following precautions apply:

- Pregnancy testing: woman of childbearing age must undergo a pregnancy test during screening to confirm absence of pregnancy.
- Availability of emergency medication: in rare cases, participants may experience hypersensitivity or allergic reactions following tracer administration. Therefore, appropriate emergency medications and resuscitation equipment must be readily available on site for immediate use. A list of emergency medications is provided in Section 8.7.
- Monitoring for adverse reactions: participants will be monitored for immediate post-injection reactions according to institutional standards. Any unexpected symptoms will be documented and managed promptly.

8.7 Concomitant Interventions (Treatments)

This study does not involve any concomitant therapeutic interventions. However, in the event that the participant experiences an adverse reaction following radiotracer administration (e.g., nausea, vomiting, dizziness, or allergic/hypersensitivity reactions), appropriate rescue medication may be administered as clinically indicated. Rescue treatments include:

- Antihistamines
- Corticosteroids
- Antiemetics
- Other supportive medications according to institutional emergency protocols

All rescue medication administered will be assessed for causality, according to the adverse event reporting procedures, documented in the eCRF, and evaluated for clinical relevance, although no impact on imaging outcomes is expected due to the timing and nature of these medications.

8.8 Study Drug Accountability

A licensed transporter authorized for handling and delivering radioactive material will be used for all radiotracer shipments to study sites. Upon receipt of the vial:

- The site completes and signs a drug receipt log
- Delivery documentation and release certificates are filed at the site.
- The measured vial activity is verified against delivery records.

The radiopharmaceutical may not be administered before written confirmation from the ZRP has been received by the PET centre.

Accountability by Radioactivity Tracking

Drug accountability is based on the quantitative tracking of radioactivity. Source data include:

- Injected activity, calculated as the difference between measured syringe activity before and after injection.
- Net injected dose (in MBq) is documented in the eCRF for each participant.
- Mandatory dose reporting to the FOPH.

All handling, storage, transport and disposal will follow the regulatory and institutional procedures for radioactive materials. Site-specific accountability logs will capture physical locations, transport personnel, transporting vehicles, batch number, and received activity (MBq / GBq).

8.9 Destruction and Disposal of Study Drug

As the investigational radiotracer is a short-lived radioactive material, unused study drug cannot be returned to the manufacturer or supplier. Instead, all residual radioactivity remaining in vials, syringes or tubing will be handled in accordance with the sites internal radiation safety SOPs and the applicable FOPH regulations.

In practice, residual radioactive material will be placed in designated lead-shielded decay containers immediately after use. These containers are stored in a controlled area until the activity has decayed below the regulatory exemption limits specified for medical radionuclides. Following the decay period, the material is reclassified as non-radioactive waste and disposed of according to institutional procedures for standard medical waste.

9. STUDY ASSESSMENTS

9.1 Study flow chart(s) / table of study procedures and assessments

Please refer to study schedule (page 18.

9.2 Assessments of outcomes

Image acquisitio n:

- Tracer & activity : Participants will receive an intravenous injection of approximately 250 MBq [18F]-FAPI-74. The corresponding effective dose is 0.014 ± 0.002 mSv/MBq, resulting in a total effective dose of approximately 3.5 ± 0.5 mSv.

- Uptake / timing : Standard imaging is performed 45–60 min post-injection. Early imaging (approx. 10–20 min post-injection) is optional and performed upon PIs discretion; late imaging is mandatory. Dynamic acquisition may be performed based on indication and local SOPs. The exact time from injection to scan start will be recorded.

- Scanner & modes : Imaging will be performed using either an integrated PET/CT with low-dose CT for attenuation correction and anatomical localization (typical CT dose ≈ 3.5 mSv), or PET/MR using site-specific MR sequences.

- Acquisition duration : PET acquisition will typically last 6–12 minutes, depending on scanner sensitivity and bed coverage. Total imaging duration (PE/CT or PET/MR) is expected to be 10–15 minutes.

Image analysis

- Primary read : all images will undergo systematic visual interpretation by trained nuclear medicine physicians delegated at each site. Image quality and tracer uptake ratings will be recorded in the electronic case report form (eCRF).

- Data format / Data handling : all imaging data will be stored in DICOM format within each institution's PACS. Source data, including injected activity, injection-to-scan time, and scanner parameters will be automatically encoded in the DICOM metadata.

The clinical chart, i.e., patient record must note that [18F]FAPI-74 is investigational and that study images are not to be used to guide patient treatment decisions. Incidental findings will be communicated to the participant as described in the informed consent form, unless the participant explicitly wishes not to be informed.

9.2.1 Assessment of primary outcome

The primary outcome is the qualitative assessment of [18F]FAPI-74 uptake based on reader ratings, classified as either FAPI-positive or FAPI-negative in target lesions or disease-specific regions.

In addition, the overall diagnostic image quality will be evaluated using a 4-point scale: fully diagnostic; almost fully diagnostic; diagnostically limited; non-diagnostic.

9.2.2 Assessment of secondary outcomes

The [18F]FAPI-74 uptake will be compared with historical standard-of-care imaging (e.g., FDG-PET, PSMA-PET, MRI, or CT) based on qualitative ratings of the diagnostic value and information gain.

- Overall more relevant information (classified as positive)
- Overall comparable relevant information (equivalent)
- Overall less relevant information (classified as negative)

In addition, a rating of overall [18F]FAPI-74 uptake will be performed with respect to its clinical significance, and potential impact on patient management. This will be rated as:

- Major impact: changes in diagnosis or additional findings requiring a change in patient management)
- Minor impact :additional findings not altering overall management);
- No impact: No change in patient management

9.2.3 Assessment of other outcomes of interest

Not applicable, as no questionnaires or biosamples are involved in this study.

9.2.4 Assessment of safety outcomes

9.2.4.1 Adverse events

Adverse events will be recorded directly after the PET scan and at discharge. Information to be collected includes time of onset, duration, resolution, action taken, severity (mild/moderate/severe), and relationship to the investigational product.

9.2.4.2 Laboratory parameters

No laboratory parameters will be assessed for this study.

9.2.4.3 Vital signs

Vital signs will not be assessed as part of this study.

9.2.5 Assessments in participants who prematurely stop the study

Not applicable.

9.3 Procedures at each visit

9.3.1 Pre-**screening visit (≤30 days)**

Potential participants will be identified through institutional clinical information systems, radiological information systems and multidisciplinary tumour board meetings, based on the inclusion and exclusion criteria outlined in Chapter 7.1. Recruitment will primarily depend on factors outside the control of the study team (e.g., timing of diagnosis, treating physician's referral for standard imaging).

Eligible individuals may be approached either in person during routine clinical appointments or standard imaging visits, or by telephone, to provide a brief overview of the study and assess initial interest in participation. If the participant expresses interest, an appointment will be arranged for an in-person consenting process. Following provision of written informed consent, inclusion and exclusion criteria will be formally verified, and demographic information and relevant medical history will be recorded.

9.3.2 Baseline / Study Visit (Day 0)

This visit constitutes the single study visit, during which all imaging procedures will be performed.

Upon arrival of the participant, the investigator will reconfirm eligibility and verify that written informed consent is on file. Any contraindications will be assessed in accordance with institutional guidelines. An intravenous line will be placed for radiotracer administration. The participant will receive approximately 250 MBq of [18F]-FAPI-74; the administered activity and calibration time will be documented in the eCRF. Following a 45–60-minute uptake period, the participant will either undergo PET/CT or PET/MR imaging. The imaging procedure includes a low-dose CT or MR for attenuation correction and anatomical correlation, and a PET scan. After completion of image acquisition, the intravenous line will be removed, and the participant will be assessed for any adverse events or post-procedural symptoms. Once all study procedures are completed and the participant is clinically stable, they may be discharged.

9.3.3 Split into subtitles by type of visit

Not applicable. This is a single-visit study, no additional follow-up visits are planned.

10. SAFETY

In this imaging study, no severe or clinically significant side effects are expected. [18F]FAPI-74 has been well-tolerated in previously published clinical studies.

10.1 Drug studies

The Sponsor's SOPs provide further details on safety documentation and reporting.

All adverse events (AEs) and serious adverse events (SAEs) occurring during the study will be collected, assessed and documented in the source data and eCRF. For this study, study duration is defined as the period from the moment when the participant signs the informed consent form until completion of the last protocol-specific procedure and has been evaluated for any AEs, which corresponds to the participants discharge from the PET centre.

Definition and assessment of (serious) adverse events and other safety related events

An Adverse Event (AE) is any untoward medical occurrence in a patient or a clinical investigation participant administered a pharmaceutical product and which does not necessarily have a causal relationship with the study procedure. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory findings), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the investigational product. [ICH E6 1.2]

A Serious Advers e Event (SAE) is classified as any untoward medical occurrence that:

- Results in death,
- Is life-threatening,
- Requires in-patient hospitalization or prolongation of existing hospitalisation,
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect.

Additionally, important medical events that may not be immediately life-threatening or result in death, or require hospitalisation, but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed above are also considered serious. [ICH E2A]

Participants with ongoing SAEs after completion of study procedures will continue to be followed until recovery or stabilisation. These follow-ups are part of the safety obligations but do not extend the participant's study duration (i.e., they are not additional study visits).

Assessment of Causality

Both the Investigator and Sponsor-investigator will assess the causality of the event to the study drug based on the criteria outlined in the ICH E2A guidelines:

Relationship	Description
Definitely related	Temporal relationship; improvement after de-challenge; recurrence after re-challenge or other proof of drug causality
Probably related	Temporal relationship; improvement after de-challenge; no other cause evident
Possibly related	Temporal relationship; alternative cause possible
Unlikely related	Temporal relationship not convincing; other cause more likely
Not related	Causal relationship can be ruled out

Unexpected Adverse Drug Reaction

An unexpected adverse drug reaction is an adverse reaction, the nature or severity of the reaction is not consistent with the applicable product information (e.g. Investigator's Brochure for drugs not yet approved or Product Information for approved drugs) [ICH E2A].

Suspected Unexpected Serious Adverse Reactions (SUSARs)

Any SAE assessed as related to the investigational product and both serious and unexpected will be classified as a SUSAR. The Sponsor-Investigator evaluates any SAE reported regarding its seriousness, causality and expectedness.

Assessment of Severity

Severity will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 6.0 https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm).

10.1.1 Reporting of serious adverse events (SAE) and other safety related events

Reporting o f SAEs

All SAEs must be reported immediately, and no later than 24 hours, to the Sponsor-Investigator. The Sponsor-Investigator will review the SAE report, confirm or reassess seriousness, causality and expectedness, determine whether the event qualifies as a SUSAR, and provide feedback to the site.

Reporting of SUSARs

A SUSAR must be reported to the Ethics Committee via BASEC and to Swissmedic within 7 days if the event is fatal, or 15 days for all other SUSARs. The Sponsor-Investigator must also inform all participating investigators of the SUSAR occurrence.

The reporting obligations of SUSAR also apply if the investigator or the sponsor becomes aware of a suspected case that has arisen in Switzerland after termination of the clinical trial, or if the investigator or the sponsor only becomes aware of such a suspected case after termination of the clinical trial.

Reporting of immediate safety and protective measures

Any new safety information requiring urgent protective measures must be reported to the Sponsor-Investigator within 24 hours. The sponsor-investigator will then notify the ethics committee and Swissmedic within 7 days in accordance with swiss legislation.

Reporting and Handling o f Pregnancies

Pregnant participants are excluded from the study. Pregnancy testing is performed prior to the administration of [18F]FAPI-74 according to local institutional practice.

Periodic reporting of safety and general progress of the clinical trial

Once a year, the investigator submits to the CEC a list of the safety events including the severity of the events, their causality to the intervention and the safety of the study participants. The investigator also informs the CEC about the general progress of the clinical trial.

The safety report / general study progress report will be submitted once a year to the CEC via Investigator and to Swissmedic via Sponsor-Investigator.

The start date for the safety report is the date is the sponsor's first authorisation to conduct a clinical trial in any country worldwide.

The safety report / general study progress report is submitted to the CEC and to Swissmedic throughout the duration of the clinical trial, and the last submission of the safety report will cover the Last Patient Last Visit.

10.1.2 Follow up of (Serious) Adverse Events

Participants experiencing AEs or SAEs will be followed up approximately 24 hours after the event, either via telephone contact with the participant or treating physician, or through review of the participant's electronic medical record.

Follow-up will continue until the AE/SAE has resolved, stabilized, or a final medical diagnosis has been established.

In case of loss to follow-up, the date of last contact and the last available clinical information will be recorded.

10.2 Assessment, Notification and Reporting on the Use of Radiation Sources

If at any point the permitted dose guidance value is exceeded, the Investigator must notify Swissmedic within 7 working days of it becoming known.

Within one year of study completion or discontinuation, the sponsor will submit a final radiological protection report to the Federal Office of Public Health (FOPB), including retrospective participant dose estimations.

In clinical trials involving therapeutic products capable of emitting ionising radiation, and in investigations using radiation sources, the sponsor shall assess compliance with the dose guidance value in accordance with Article 45 of the Radiological Protection Ordinance of 26 April 2017. The

dose guidance values for clinical trials without expected direct benefit for the participants is 5 mSv effective dose per year.

For each application of ionising radiation, the investigator documents all information relevant to radiation protection in the final study report, and includes a retrospective participant dose estimation.

Within a year of the completion or premature termination of the clinical trial which included investigations involving radioactive sources, the investigator submits to the FOPH the final study report including all information of relevance for radiological protection. The final study report is submitted to the FOPH, if the FOPH has issued an opinion in accordance with ClinO Art. 36 or 36a.

10.3 Exemption from the Documentation Requirements of AE

N/A

11. STATISTICAL METHODS

This exploratory study will primarily employ descriptive statistics and qualitative and semi-quantitative analyses to summarize tracer uptake, image quality, and diagnostic interpretability. Estimates will be presented with 95% confidence intervals (CIs) where applicable. Unless otherwise specified, all statistical tests will be two-sided, and an exploratory significance level of $\alpha = 0.05$ will be applied. No formal confirmatory statistical claims will be made.

11.1 Hypothesis

The primary endpoint is to assess the presence or absence of FAPI uptake, and to determine whether the observed uptake pattern is diagnostically interpretable.

Primary endpoint : Proportion of participants with diagnostically interpretable [18F]FAPI-74 imaging (rating ≥ pre-specified threshold, e.g., ≥3 on 1–5 scale), evaluated per indication.

Hypothesis (per indication):

H0: $p \leq p^*$ (non-inferiority/adequacy margin; commonly $p^*=0.70–0.80$)

H1: $p > p^*$

(If no formal hypothesis is desired, report estimates with CIs only.)

Secondary endpoint alternative hypothesis will explore whether FAPI PET provides additional diagnostic information compared to standard-of-care imaging. Specificity, sensitivity and positive predictive value will be estimated per indication and compared with the reference standard.

11.2 Determination of Sample Size

As this is an open-label, exploratory study, no formal hypothesis-based sample size calculation was performed. The sample size determination was based on (i) prior experience with patient numbers from comparable diagnostic imaging studies, (ii) published data in the relevant literature, and (iii) feasibility considerations, including anticipated rates of eligibility and case volumes across the targeted indications. These considerations informed the planned number of participants per indication (as outlined in Chapter 7.3.), ensuring that the study provides sufficient data to characterize tracer uptake patterns, image interpretability, and potential diagnostic utility.

11.3 Statist ical criteria of termination of trial

This exploratory study does not include formal statistical stopping rules (e.g., interim analyses with predefined futility or efficacy boundaries), as no confirmatory hypothesis testing is planned. Consequently, no statistical criteria for early termination of the overall study are defined.

The study will proceed as planned unless:

- operational feasibility becomes compromised,
- safety concerns arise that require intervention by the Sponsor or EC/Swissmedic, or
- external factors necessitate early discontinuation.

Any decisions to terminate the study prematurely will therefore be based on administrative or safety-related considerations, and not statistical criteria.

11.4 Planned Analyses

Descriptive statistics and qualitative or semi-quantitative measures will be used for all analyses, unless otherwise specified.

11.4.1 Primary Outcome analysis:

The primary analysis will compute the proportion of participants with diagnostically interpretable [18F]FAPI-74 scans, including 95% CI (Wilson), reported per indication and pooled across indications.

Sensitivity Analyses:

- Unreadable/indeterminate scans are treated as not interpretable (primary).
- Reader-consensus vs. reader-majority will be compared.

- Ordinal model: a proportional-odds cumulative logit mixed model will be applied to the raw 4–/5-point rating, including random reader and random site (if applicable), fixed effect for indication; report common OR and 95% CI and test proportional-odds assumption (score test).
- Inter-reader agreement: Weighted Cohen's κ (quadratic weights) with 95% CI per indication, ICC(2,k) as supportive.

Precision note:

For n=50 a proportion of 0.80 corresponds to a 95% CI half-width of ~±0.11, i.e., CI width (≈22 percentage points per indication. Pooled analysis improves precision.

11.4.2 Secondary Outcome Analysis

Lesion -wise Detection (Qualitative):

- Define the reference standard (per indication: histopathology when available; otherwise composite imaging/clinical follow-up).
- Endpoints include sensitivity, PPV, lesion-level agreement, and Cohen's κ (lesion-level).

Patient Management:

- Diagnostic confidence (Reader-reported 0–100 or ordinal scale pre- vs post-FAPI-74 per case).
- Management plan: Binary indicator of change in management (yes/no) after FAPI-74; categorize type of change (e.g., additional biopsy, therapy switch).

Confidence (Paired):

- If continuous/approximately normal: paired t-test, mean change with 95% CI.
- If ordinal/non-normal: Wilcoxon signed-rank, median change with Hodges–Lehmann 95% CI.
- Mixed model with random reader and fixed indication for pooled estimate; adjusting for baseline confidence.
- Management change (paired binary): McNemar's test (within-participant before/after), report risk difference and 95% CI. For pooled and indication-specific effects, fit mixed-effects logistic regression with random reader (if reader-specific), fixed indication; report OR and 95% CI.

11.4.3 Gain Statistical Methods for Descriptive Analyses

- Chi-square or exact Fisher test to compare FAPI-positive vs. FAPI-negative cases against standard clinical imaging .
- Per-indication estimated of sensitivity, specificity and positive predictive value.

11.4.4 Gender Analysis

Where feasible, outcomes such as uptake, lesion detectability, and diagnostic confidence will be analysed by sex/gender; if gender stratification is not feasible, this will be documented in the final report.

11.4.5 Datasets to be Analysed and Analysis Populations

Analysis will focus on all PET/CT or PET/MR datasets acquired with [18F]-FAPI-74.

Subgroup analyses will be performed by disease/indication, depending on participant numbers available within each subgroup.

11.4.6 Interim Analyses

A subgroup-specific preliminary analysis will be conducted after approximately 50% of participants per indication have been enrolled. The results will be reviewed to determine whether recruitment should continue or be stopped for any subgroups.

11.4.7 Safety Analysis

No dedicated safety analyses are planned, as [18F]FAPI-74 is administered in tracer-level diagnostic doses. Unexpected adverse events will be recorded and reported according to Chapter 10.

11.4.8 Deviation(s) from the Statistical Plan

Any deviations from the statistical analysis procedures described in this protocol will be documented justified and reported in the final study report.

If observed data distributions differ substantially from expectations, appropriate non-parametric tests (e.g., Mann-Whitney U test) or alternative descriptive methods may be employed to ensure valid and interpretable analysis.

11.5 Handling of Missing Data and Drop -Outs

As the primary endpoint is based on PET/CT and PET/MR image interpretability, missing data cannot be imputed using methods such as multiple imputation or carried-forward techniques. Participants who withdraw consent will be classified as dropouts and may be replaced to maintain the required sample size for each subgroup.

12. QUALITY ASSURANCE AN D CONTROL

The Sponsor is responsible for implementing and maintaining a quality assurance and quality control system to ensure that the study is conducted, and data are generated, documented, and reported in compliance with the protocol, GCP, and applicable Swiss regulations. Written SOPs and Working Instructions (WI), govern trial conduct at all participating sites. Each local investigator is responsible for ensuring that all delegated study personnel are adequately trained and qualified before performing study-specific tasks. Training records are maintained in the Investigator Site File (ISF).

12.1 Data handling and record keeping / archiving

The Trial Master File (TMF) will be managed by the Sponsor-Investigator. Each site will maintain its own Investigators Site File (ISF) containing essential documents (e.g protocol, regulatory documents, training records), correspondence and source data location lists in accordance with GCP.

12.1.1 Case Report Forms

Study data will be recorded in electronic Case Report Forms (eCRF) within REDCap ®. The CRF is maintained for every enrolled participant and updated regularly to reflect their current status. Participants will be identified in the CRF using coded identifiers. The identifier consists of a site-specific acronym (e.g., USZ), followed by a consecutive number (e.g., USZ-007). The PI and authorized delegated investigators have personal logins for data entry, with an automatic audit trail recording all entries, changes, and validations.

12.1.2 Specification of Source Documents

Source data must be available at the site to verify the existence of study participants and to substantiate all information documented in the eCRF. Source data include both original documents and certified copies related to the participant's clinical status, medical history, imaging procedures, and study-specific assessments.

Source documents include, but are not limited to:

• Adverse Event / Serious Adverse Event (AE / SAE) documentation

• Dose accountability logs

• DICOM imaging data

• Relevant sections of participant's medical record, including prior imaging reports

• Participant demographic information (e.g. age, sex)

• Eligibility documentation (inclusion / exclusion criteria)

• Signed and dated informed consent forms

The location of all source documents will be recorded in the ISF at each site.

Direct data entry into the eCRF is used for study-specific evaluations where the electronic entry itself constitutes the source data (e.g., imaging reads).

The following are considered direct data entries in this study:

- Uptake pattern ratings of nuclear medicine physicians
- Presence or absence of FAPI uptake
- Number of lesions visible with [18F]-FAPI-74
- Number of lesions on reference imaging
- Visual uptake pattern classification
- Diagnostic image quality rating
- Comparison assessment between [18F]FAPI-74 and reference imaging
- Clinical impact assessment of FAPI findings
- Assessment of increased diagnostic confidence or changes in management based on the tracer

<u>Source Data:</u>

Screening

- Site code
- Subject ID

- Screening date
- Informed consent signed
- Eligibility confirmed by Investigator
- Sex
- year of birth
- Weight (kg)
- Height (cm)
- pregnancy test result
- Clinical diagnosis / indication
- Eligibility inclusion met
- ->Written Informed Consent
- ->Age >18
- ->Confirmed diagnosis of one of the listed indications
- Eligibility exclusion met
- -> Inability to lie still during PET examination
- -> Age <18
- -> Unable to understand study information (e.g language barrier)
- -> Subjects incapable of judgment (e.g. legal or medical incapacitation)
- Screening result

Visit

- Visit date
- Time of injection
- Injected activity (MBq)
- PET scan start time
- Imaging completed successfully
- Deviation from protocol
- Imaging centre / scanner ID

Image Assessment (Primary & Secondary Outcomes)

- Reference imaging modality available
- Reference modality type
- Would this result change overall staging / assessment
- Comments

End of Study

- Participant status
- Reason for withdrawal
- Date of withdrawal
- Data usable for analysis
- AE occurrence
- Follow-up AE required

A full description each variable, including definitions and permitted values, is provided in the “eCRF List” appendix.

12.1.3 Record Keeping / Archiving

All essential trial documents, including TMF and ISFs, will be archived for a minimum of 20 years after study completion or premature termination, in accordance with the new ClinO Art. 45. ISF’s will be stored in designated archive rooms of the respective hospitals following institutional archiving procedures. Information regarding the final storage location of each ISF will be documented in the TMF, which will be archived in a locked, access-controlled institutional archive room following departmental and institutional archiving policies.

12.2 Data Manageme nt

All study data will be entered into the eCRF and verified for completeness and accuracy by the local PI or delegated study team member. Range checks will be implemented to ensure the plausibility of data, for example to validate injected activity values for [18F]-FAPI-74.

Health-related personal data will be handled confidentially and processed in accordance with applicable data-protection regulations. Data are initially recorded with identifiers (non-coded) as part of routine clinical documentation and subsequently entered into the study database in coded

(pseudonymised) form for analysis.

Each participant will be assigned a unique study identification code, consisting of a site-specific acronym (e.g., USZ) followed by a consecutive number (e.g., USZ-007). The master list linking participant identities with their study codes will be stored separately at the site, accessible only to authorized personnel.

12.2.1 Data Management System

All participant data will be collected and managed in REDCap®, a secure, web-based application for research data capture. The system is hosted on secure institutional servers at the University Hospital Zurich.

Prior to study initiation, user roles are configured according to institutional SOPs, database functions are tested, and audit trails are activated to record all data entry and modifications.

Image analysis will be performed on clinically approved CE-marked clinical workstations using certified medical-grade software. Imaging data remain stored in institutional PACS systems under standard access restrictions.

12.2.2 Data security, access and back -up

Access to study data in REDCap is restricted to authorized study personnel, with role-based permissions granted by the Sponsor-Investigator or a delegated data / project manager.

Source Data (e.g., medical records, PACS images, DICOM metadata) remain stored in clinical information systems under institutional access rules. For monitoring, auditing, or inspection purposes, source data will be made available to authorised monitors, auditors, and representatives of the EC or Swissmedic according to regulatory requirements.

Regular system backups will be supplemented by local data exports archived in the TMF. Backup and archiving procedures are overseen by the Sponsor-Investigator or an authorized delegate.

12.2.3 Analysis and archiving

Data will be exported from the eCRF using standard REDCap export functions in pseudonymized form. Statistical analysis will be conducted using validated software such as SPSS, SAS or R.

Following database lock, the final coded dataset will be archived on secure institutional servers for a t least 20 years. The master code list will be archived separately, under restricted access, for the same duration.

12.2.4 Electronic and central data validation

Centralised data validation and on-site Source Data Verification (SDV) will be performed in accordance with the Monitoring Plan and CTC SOPs. To support data quality, eCRF fields will employ predefined input formats and range limits, mandatory fields will reduce missing critical data, drop-down menus and coded response categories will be used where appropriate, and queries generated through monitoring or central reviews must be addressed by site personnel before database lock.

12.3 Monitoring

Regular monitoring visits will be conducted at each investigator site throughout the study, following a risk-based monitoring approach. The Sponsor-Investigator will ensure independent monitoring in collaboration with the Clinical Trials Center (CTC), University Hospital Zurich.

In accordance with the CTC's monitoring SOP, the scope, frequency and method of monitoring are defined in a study-specific monitoring plan reflecting the exploratory diagnostic design and the low-risk profile of the study.

In brief, monitors will review essential study documents, verify eCRF data entries against source documents (SDV), confirm proper execution and documentation of informed consent, verify participant eligibility based on inclusion/exclusion criteria, assess relevant clinical source information, and ensure general adherence to the protocol ICH-GCP guidelines, and applicable regulations.

For this purpose, all original records required to substantiate study data (e.g., source documents, imaging records, consent forms, eligibility documentation) must be made accessible to the monitor during visits or remote checks

12.4 Audits and Inspections

Study documentation and source data will remain accessible to auditors and inspectors, including representatives from the EC, Swissmedic and other competent authorities. Investigators and study staff will be required to provide access to relevant documents and respond to queries in a timely manner. All parties involved in audits and inspections are bound to keep participant data confidential.

12.5 Confidentiality, Data Protection

Access to source documents will be permitted exclusively for purposes of monitoring (Section 12.3), and audits or regulatory inspections (Section 12.4), in accordance with applicable data-protection regulations and ICH-GCP E6 (6.10).

The Principal Investigator and authorized personnel will have access to the study protocol and coded data sets during the conduct of the study and after its completion for purposes of analysis, publication and dissemination of results. All participant data entered into the eCRF will be handled in pseudonymized form. Direct identifiers (e.g. name, date of birth) will be stored separately from the pseudonymized data.

12.6 Storage of biological material and related health data

No biological samples will be collected as part of this study. Imaging data from the PET/CT and PET/MR scans will be stored in institutional Picture Archiving and Communication System (PACS) at each study site in accordance with local institutional policies and applicable legal retention requirements. Imaging data retained in PACS remain part of the clinical source documentation and will be accessible only to authorized personnel under standard institutional access controls.

13. PUBLICATION AND DISS EMINATION POLICY

The results of the study will be disseminated to the scientific community through publication in peer-reviewed journals. If gender specific effects are observed, these will be explicitly reported in the final study report. If no such effects are observed, this absence will also be documented.

Each participating site retains the right to publish data collected at its own site. Any publications involving pooled data from multiple sites will require prior agreement that defines the authorship, particularly the first three authors (including potential shared first authorship) and the last author(s) including the possibility of shared authorship. This agreement must be finalized before manuscript drafting begins.

Requests for secondary use of study data will be considered upon reasonable request. Approval for secondary data use requires authorization by the Sponsor-Investigator and the local Principal Investigator(s) of the contributing sites. Furthermore, if the proposed case falls outside the scope of the protocol, an amendment or a new protocol must be prepared and approved by the responsible ethics committee.

14. FUNDING AND SUPPORT

14.1 Funding

Each study site will cover its own operational costs associated with study conduct, including but not limited to PET scanner usage, technical personal, and tracer production. Institutional funds at the Sponsor site will support study management activities, including monitoring, study coordination and data-management oversight.

Applications for external funding support will be submitted to industry partners and relevant national and international research foundations. At present, no external funding has been secured. Should external funding be obtained during the course of the study, this will be disclosed to the responsible ethical committee and Swissmedic and communicated via protocol amendment.

14.2 Other Support

The company SOFIE will provide the precursor required for production of [18F]FAPI-74 under a contractual agreement (see appendix). Any additional material contribution or infrastructural resources obtained during the study will be reported to the responsible ethical committee via an amendment.

15. INSURANCE

Insurance coverage is provided through the Sponsors institution' insurance certificate from the Baloise Versicherung AG, which covers all clinical research activities conducted at the University Hospital Zurich (USZ). The insurance policy guarantees compensation for any study-related harm, with policy values set in accordance with ClinO Annex 2, and extends to damage occurring up to 10 years after trial completion.

A copy of the insurance certificate is filed in the investigator site file at each participating site and in the TMF.

16. REFERENCES

1. Declaration of Helsinki, Version October 2013, (http://www.wma.net/en/30publications/10policies/b3/index.html)
2. International Conference on Harmonization (ICH, 1996) E6(R2) Guideline for Good Clinical Practice. (http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2__Step_4.pdf)
3. International Conference on Harmonization (ICH, 1997) E8 Guideline: General Considerations for Clinical Trials (http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E8/Step4/E8_Guideline.pdf)
4. International Conference on Harmonization (ICH, 2010) E2F Development Safety Update Report. (https://database.ich.org/sites/default/files/E2F_Guideline.pdf)
5. Humanforschungsgesetz, HFG Bundesgesetz über die Forschung am Menschen (Bundesgesetz über die Forschung am Menschen, HFG) vom 30. September 2011/ Loi fédérale relative à la recherche sur l'être humain (loi relative à la recherche sur l'être humain, LRH) du 30 septembre 2011 / Legge federale concernente la ricerca sull'essere umano (Legge sulla ricerca umana, LRUm) del 30 settembre 2011
6. Verordnung über klinische Versuche in der Humanforschung (Verordnung über klinische Versuche, KlinV) vom 20. September 2013 / Ordonnance sur les essais cliniques dans le cadre de la recherche sur l'être humain (Ordonnance sur les essais cliniques, OClin) du 20 septembre 2013. Ordinanza sulle sperimentazioni cliniche nella ricerca umana (Ordinanza sulle sperimentazioni cliniche, OSRUm) del 20 settembre 2013
7. Heilmittelgesetz, HMG Bundesgesetz über Arzneimittel und Medizinprodukte (Heilmittelgesetz, HMG) vom 15. Dezember 2000 / Loi fédérale sur les médicaments et les dispositifs médicaux (Loi sur les produits thérapeutiques, LPT) du 15 décembre 2000 / Legge federale sui medicamenti e i dispositivi medici (Legge sugli agenti terapeutici, LATer)
8. WHO, International Clinical Trials Registry Platform (ICTRP) (http://www.who.int/ictrp/en/)
9. Strahlenschutzverordnung (StSV) vom 26. April 2017 / Ordonnance sur la radioprotection (ORaP) du 26 avril 2017 / Ordinanza sulla radioprotezione (ORaP) del 26 aprile 2017.
10. Giesel FL, Kratochwil C, Schlittenhardt J, Dendl K, Eiber M, Staudinger F, Kessler L, Fendler WP, Lindner T, Koerber SA, Cardinale J, Sennung D, Roehrich M, Debus J, Sathekge M, Haberkorn U, Calais J, Serfling S, Buck AL. Head-to-head intra-individual comparison of biodistribution and tumor uptake of 68Ga-FAPI and 18F-FDG PET/CT in cancer patients. Eur J Nucl Med Mol Imaging. 2021 Dec;48(13):4377-4385.
11. Kratochwil C, Flechsig P, Lindner T, Abderrahim L, Altmann A, Mier W, Adeberg S, Rathke H, Röhrich M, Winter H, Plinkert PK, Marme F, Lang M, Kauczor HU, Jäger D, Debus J, Haberkorn U, Giesel FL. 68Ga-FAPI PET/CT: Tracer Uptake in 28 Different Kinds of Cancer. J

Nucl Med. 2019 Jun;60(6):801-805.
12. Giesel FL, Adeberg S, Syed M, Lindner T, Jiménez-Franco LD, Mavriopoulou E, Staudinger F, Tonndorf-Martini E, Regnery S, Rieken S, El Shafie R, Röhrich M, Flechsig P, Kluge A, Altmann A, Debus J, Haberkorn U, Kratochwil C. FAPI-74 PET/CT Using Either 18F-AlF or Cold-Kit 68Ga Labeling: Biodistribution, Radiation Dosimetry, and Tumor Delineation in Lung Cancer Patients. J Nucl Med. 2021 Feb;62(2):201-207. doi: 10.2967/jnumed.120.245084. Epub 2020 Jun 26. PMID: 32591493; PMCID: PMC8679591.
13. Bundesamt für Gesundheit (BAG): Strahlenexposition der Schweizer Bevölkerung (https://www.bag.admin.ch/de/strahlenexposition-der-schweizer-bevoelkerung)
14. Mori Y, Haberkorn U, Giesel FL. 68Ga- or 18F-FAPI PET/CT-what it can and cannot. Eur Radiol. 2023 Nov;33(11):7877-7878.
15. Chandekar KR, Prashanth A, Vinjamuri S, Kumar R. FAPI PET/CT Imaging-An Updated Review. Diagnostics (Basel). 2023 Jun 9;13(12):2018.
16. Fitzgerald AA, Weiner LM. The role of fibroblast activation protein in health and malignancy. Cancer Metastasis Rev. 2020 Sep;39(3):783-803.
17. Loktev A, Lindner T, Mier W, Debus J, Altmann A, Jäger D, Giesel F, Kratochwil C, Barthe P, Roumestand C, Haberkorn U. A Tumor-Imaging Method Targeting Cancer-Associated Fibroblasts. J Nucl Med. 2018 Sep;59(9):1423-1429.
18. Chen H, Pang Y, Wu J, Zhao L, Hao B, Wu J, Wei J, Wu S, Zhao L, Luo Z, Lin X, Xie C, Sun L, Lin Q, Wu H. Comparison of [68Ga]Ga-DOTA-FAPI-04 and [18F] FDG PET/CT for the diagnosis of primary and metastatic lesions in patients with various types of cancer. Eur J Nucl Med Mol Imaging. 2020 Jul;47(8):1820-1832.
19. Shi X, Xing H, Yang X, Li F, Yao S, Zhang H, Zhao H, Hacker M, Huo L, Li X. Fibroblast imaging of hepatic carcinoma with 68Ga-FAPI-04 PET/CT: a pilot study in patients with suspected hepatic nodules. Eur J Nucl Med Mol Imaging. 2021 Jan;48(1):196-203.
20. Shi X, Xing H, Yang X, Li F, Yao S, Congwei J, Zhao H, Hacker M, Huo L, Li X. Comparison of PET imaging of activated fibroblasts and 18F-FDG for diagnosis of primary hepatic tumours: a prospective pilot study. Eur J Nucl Med Mol Imaging. 2021 May;48(5):1593-1603.
21. Guo W, Pang Y, Yao L, Zhao L, Fan C, Ke J, Guo P, Hao B, Fu H, Xie C, Lin Q, Wu H, Sun L, Chen H. Imaging fibroblast activation protein in liver cancer: a single-center post hoc retrospective analysis to compare [68Ga]Ga-FAPI-04 PET/CT versus MRI and [18F]-FDG PET/CT. Eur J Nucl Med Mol Imaging. 2021 May;48(5):1604-1617.
22. Deng M, Chen Y, Cai L. Comparison of 68Ga-FAPI and 18F-FDG PET/CT in the Imaging of Pancreatic Cancer With Liver Metastases. Clin Nucl Med. 2021 Jul 1;46(7):589-591.
23. Shou Y, Xue Q, Yuan J, Zhao J. 68Ga-FAPI-04 PET/MR is helpful in differential diagnosis of pancreatitis from pancreatic malignancy compared to 18F-FDG PET/CT: a case report. Eur J Hybrid Imaging. 2021 Jun 15;5(1):12.
24. Röhrich M, Naumann P, Giesel FL, Choyke PL, Staudinger F, Wefers A, Liew DP, Kratochwil C, Rathke H, Liermann J, Herfarth K, Jäger D, Debus J, Haberkorn U, Lang M, Koerber SA. Impact of 68Ga-FAPI PET/CT Imaging on the Therapeutic Management of Primary and Recurrent Pancreatic Ductal Adenocarcinomas. J Nucl Med. 2021 Jun 1;62(6):779-786.

25. Fotsitzoudis C, Koulouridi A, Messaritakis I, Konstantinidis T, Gouvas N, Tsiaoussis J, Souglakos J. Cancer-Associated Fibroblasts: The Origin, Biological Characteristics and Role in Cancer-A Glance on Colorectal Cancer. Cancers (Basel). 2022 Sep 9;14(18):4394.
26. Pang Y, Zhao L, Luo Z, Hao B, Wu H, Lin Q, Sun L, Chen H. Comparison of 68Ga-FAPI and 18F-FDG Uptake in Gastric, Duodenal, and Colorectal Cancers. Radiology. 2021 Feb;298(2):393-402.
27. Lin R, Lin Z, Chen Z, Zheng S, Zhang J, Zang J, Miao W. [68Ga]Ga-DOTA-FAPI-04 PET/CT in the evaluation of gastric cancer: comparison with [18F]FDG PET/CT. Eur J Nucl Med Mol Imaging. 2022 Jul;49(8):2960-2971.
28. Gege Z, Xueju W, Bin J. Head-To-Head Comparison of 68Ga-FAPI PET/CT and FDG PET/CT for the Detection of Peritoneal Metastases: Systematic Review and Meta-Analysis. AJR Am J Roentgenol. 2023 Apr;220(4):490-498.
29. Qin C, Liu F, Huang J, Ruan W, Liu Q, Gai Y, Hu F, Jiang D, Hu Y, Yang K, Lan X. A head-to-head comparison of 68Ga-DOTA-FAPI-04 and 18F-FDG PET/MR in patients with nasopharyngeal carcinoma: a prospective study. Eur J Nucl Med Mol Imaging. 2021 Sep;48(10):3228-3237.
30. Röhrich M, Syed M, Liew DP, Giesel FL, Liermann J, Choyke PL, Wefers AK, Ritz T, Szymbara M, Schillings L, Heger U, Rathke H, Kratochwil C, Huber PE, von Deimling A, Debus J, Kauczor HU, Haberkorn U, Adeberg S. 68Ga-FAPI-PET/CT improves diagnostic staging and radiotherapy planning of adenoid cystic carcinomas - Imaging analysis and histological validation. Radiother Oncol. 2021 Jul;160:192-201.
31. Kömek H, Can C, Güzel Y, Oruç Z, Gündoğan C, Yildirim ÖA, Kaplan İ, Erdur E, Yıldırım MS, Çakabay B. 68Ga-FAPI-04 PET/CT, a new step in breast cancer imaging: a comparative pilot study with the 18F-FDG PET/CT. Ann Nucl Med. 2021 Jun;35(6):744-752.
32. Elboga U, Sahin E, Kus T, Cayirli YB, Aktas G, Uzun E, Cinkir HY, Teker F, Sever ON, Aytekin A, Yilmaz L, Aytekin A, Cimen U, Mumcu V, Kilbas B, Çelen YZ. Superiority of 68Ga-FAPI PET/CT scan in detecting additional lesions compared to 18FDG PET/CT scan in breast cancer. Ann Nucl Med. 2021 Dec;35(12):1321-1331.
33. Backhaus P, Burg MC, Roll W, Büther F, Breyholz HJ, Weigel S, Heindel W, Pixberg M, Barth P, Tio J, Schäfers M. Simultaneous FAPI PET/MRI Targeting the Fibroblast-Activation Protein for Breast Cancer. Radiology. 2022 Jan;302(1):39-47.
34. Eshet Y, Tau N, Apter S, Nissan N, Levanon K, Bernstein-Molho R, Globus O, Itay A, Shapira T, Oedegaard C, Gorfine M, Eifer M, Davidson T, Gal-Yam E, Domachevsky L. The Role of 68 Ga-FAPI PET/CT in Detection of Metastatic Lobular Breast Cancer. Clin Nucl Med. 2023 Mar 1;48(3):228-232.
35. Perugino CA, Stone JH. IgG4-related disease: an update on pathophysiology and implications for clinical care. Nat Rev Rheumatol. 2020 Dec;16(12):702-714.
36. Luo Y, Pan Q, Zhang W. IgG4-related disease revealed by 68Ga-FAPI and 18F-FDG PET/CT. Eur J Nucl Med Mol Imaging. 2019 Nov;46(12):2625-2626.
37. Luo Y, Pan Q, Yang H, Peng L, Zhang W, Li F. Fibroblast Activation Protein-Targeted PET/CT with 68Ga-FAPI for Imaging IgG4-Related Disease: Comparison to 18F-FDG PET/CT. J Nucl

Med. 2021 Feb;62(2):266-271.
38. Windisch P, Zwahlen DR, Giesel FL, Scholz E, Lugenbiel P, Debus J, Haberkorn U, Adeberg S. Clinical results of fibroblast activation protein (FAP) specific PET for non-malignant indications: systematic review. EJNMMI Res. 2021 Feb 19;11(1):18.
39. Wang Y, Wang R, Geng L, Li Q, Qi E, Shi Y, Wang Y, Zheng Q, Zhang G, Chen J, Tian J. Different uptake patterns of 68Ga-FAPI in aseptic loosening and periprosthetic joint infection of hip arthroplasty: A case series and literature review. Front Med (Lausanne). 2022 Nov 24;9:1014463.
40. Lindner T, Altmann A, Giesel F, Kratochwil C, Kleist C, Krämer S, Mier W, Cardinale J, Kauczor HU, Jäger D, Debus J, Haberkorn U. 18F-labeled tracers targeting fibroblast activation protein. EJNMMI Radiopharm Chem. 2021 Aug 21;6(1):26.
41. Dendl K, Finck R, Giesel FL, Kratochwil C, Lindner T, Mier W, Cardinale J, Kesch C, Röhrich M, Rathke H, Gampp H, Ristau J, Adeberg S, Jäger D, Debus J, Haberkorn U, Koerber SA. FAP imaging in rare cancer entities-first clinical experience in a broad spectrum of malignancies. Eur J Nucl Med Mol Imaging. 2022 Jan;49(2):721-731.
42. Lang M, Spektor AM, Hielscher T, Hoppner J, Glatting FM, Bicu F, Hackert T, Heger U, Pausch T, Gutjahr E, Rathke H, Giesel FL, Kratochwil C, Tjaden C, Haberkorn U, Röhrich M. Static and Dynamic 68Ga-FAPI PET/CT for the Detection of Malignant Transformation of Intraductal Papillary Mucinous Neoplasia of the Pancreas. J Nucl Med. 2023 Feb;64(2):244-251.
43. Glatting FM, Hoppner J, Kauczor HU, Huber PE, Kratochwil C, Giesel FL, Haberkorn U, Röhrich M. Subclass Analysis of Malignant, Inflammatory and Degenerative Pathologies Based on Multiple Timepoint FAPI-PET Acquisitions Using FAPI-02, FAPI-46 and FAPI-74. Cancers (Basel). 2022 Oct 28;14(21):5301.
44. Giesel FL, Kratochwil C, Lindner T, Marschalek MM, Loktev A, Lehnert W, Debus J, Jäger D, Flechsig P, Altmann A, Mier W, Haberkorn U. 68Ga-FAPI PET/CT: Biodistribution and Preliminary Dosimetry Estimate of 2 DOTA-Containing FAP-Targeting Agents in Patients with Various Cancers. J Nucl Med. 2019 Mar;60(3):386-392.
45. Johannes Siebermair, Lukas Kessler, Jana Kupusovic, Tienush Rassaf, Christoph Rischpler. 68Ga-FAPI PET/CT: Cardiac fibroblast activation detected by 68Gallium-FAPI-46 positron emission tomography–magnetic resonance imaging as a sign of chronic activity in cardiac sarcoidosis. European Heart Journal - Case Reports (2022) 6(1), 1–2.
46. Kim M Pabst · Manuel M Weber · Christina Laschinsky · Patrick Sandach · Timo Bartel, · Alina T Küper · Lukas Kessler · Marija Trajkovic-Arsic · Markus Eckstein · Elena Gilman, · Michael Nader · Francesco Barbato · Lars E Podleska · Prof Boris A Hadaschik · Rainer Hamacher · David Kersting · Nicola von Ostau · Prof Bastian von Tresckow · Hans-Peter Kaelberlah · Prof Claudia Kesch · Prof Sherko Kuemmel · Prof Anke Reinacher-Schick · Prof Martin Schuler · Prof Jens T Siveke · Prof Viktor Grünwald · Prof Ken Herrmann · Prof Wolfgang P Fendler [68Ga]Ga-FAPI-46 PET accuracy for cancer imaging with histopathology validation: a single-centre, single-arm, interventional, phase 2 trial

17. APPENDICES

The following documents are provided separately:

- List of Study Sites and Principal Investigators
- Patient Information and Informed Consent Form
- Case Report Form / eCRF List
- Monitoring Plan
- Contract with SOFIE
- Investigator’s brochure (IB) for [18F]FAPI-74
- IMPD