Clinical Study Protocol

Study Protocol No.	FSPG-1701
Title	A pilot phase 2, open-label, non-randomized, single center study to explore diagnostic validity of (*S*)-4-(3-[^{18}F]Fluoropropyl)-L-glutamic acid ([^{18}F]FSPG) positron emission tomography (PET) for the assessment of disease activity in subjects with inflammatory bowel disease
Phase	II
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Confidentiality Statement

This protocol contains information that is confidential and proprietary to the sponsor or the investigator(s).

Document history

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Synopsis

Study title	A pilot phase 2, open-label, non-randomized, single center study to explore diagnostic validity of (*S*)-4-(3-[^{18}F]Fluoropropyl)-L-glutamic acid ([^{18}F]FSPG) positron emission tomography (PET) for the assessment of disease activity in subjects with inflammatory bowel disease (IBD)
Principal investigator, Study center, Country	Dae Hyuk Moon, Asan Medical Center, Seoul, Republic of Korea.
Study protocol number	FSPG-1701
Study phase	Phase 2
Study under IND	☑ yes ☐ no
Korea Food & Drug Administration "covered study"	☑ yes ☐ no
Study objectives	Primary • To explore the validity of [^{18}F]FSPG positron emission tomography/computed tomography (PET/CT) for the diagnosis of patients with active inflammatory bowel disease Secondary • To explore the validity of [^{18}F]FSPG PET/CT for detecting bowel segments with active inflammatory bowel disease • To assess the correlation of [^{18}F]FSPG activity with clinical, endoscopic, and biological markers of disease activity • To assess the correlation of segmental [^{18}F]FSPG PET/CT activity with segmental endoscopic and histological markers of disease activity • To assess inter-reader variability of visual [^{18}F]FSPG PET/CT interpretation • To evaluate safety of [^{18}F]FSPG PET/CT
Investigational product, dose, mode of administration, dosing schedule	[^{18}F]FSPG is a L-glutamate derivative that is specifically taken up by system x_C^- as previously demonstrated in tumor models and patients with cancer or inflammation. Radioactive dose of 200 MBq of [^{18}F]FSPG will be given intravenously by bolus injection for up to 60 seconds prior to PET/CT scanning at visit 1. The total mass of FSPG injected will be less than 100 μg.
Indication of investigational product	Diagnostic agent to image active inflammatory lesions
Study Population	Patients with ulcerative colitis (UC) or Crohn's disease (CD)
Criteria for inclusion	A subject will be enrolled if he/she meets all of the following inclusion criteria. • Subject is aged between 19 and 79 years and male or female of any race/ethnicity. • Subject has had UC or CD diagnosed by clinical, endoscopic and histologic evidence at least 3 months prior to screening. • Subject has symptoms suggestive of active disease at the time of enrollment. • Subject is scheduled to undergo sigmoidoscopy or colonoscopy for UC or CD within 7 days prior to or after the planned study with [^{18}F]FSPG administration.

Criteria for exclusion	A subject is to be excluded from the study if he/she does not fulfill the inclusion criteria or display any of the following criteria. • Subject or subject's legally acceptable representative does not provide written informed consent. • Subject displays clinical signs of ischemic colitis or has an evidence of pathogenic bowel infection. • Subject is diagnosed as having inflammatory bowel disease unclassified. • Subject has been treated with sulfasalazine or intravenous corticosteroids within the previous four weeks prior to the planned study with [^{18}F]FSPG administration. • Dose escalation of the current IBD drugs or starting a new oral aminosalicylate, corticosteroid, immunomodulator, biologics, antibiotics, probiotics, or topical preparations is scheduled from the study enrollment to the scheduled sigmoidoscopy or colonoscopy, or 24 hours after [^{18}F]FSPG administration . The dose escalation or starting a new antidiarrheal and/or analgesic drug is allowed. • Female subject is pregnant or nursing. Exclusion of the possibility of pregnancy is made by one of the following: 1) Woman is physiologically post-menopausal (cessation of menses for more than 2 years), 2) woman is surgically sterile (has had a documented bilateral oophorectomy and/or documented hysterectomy, or 3) if the woman is of childbearing potential, a serum or urine pregnancy test performed within 24 hours immediately prior to administration of [^{18}F]FSPG has to be negative and the women is advised to apply contraceptive measures during her participation in this study. • Subject has concurrent severe and/or uncontrolled and/or unstable medical disease (e.g. congestive heart failure, acute myocardial infarction, severe pulmonary disease, chronic renal or hepatic disease which could compromise participation in the study) in the judgment of the investigator. • Subject is a relative of the investigator, student of the investigator or otherwise dependent. • Subject has received any investigational drugs or devices within four weeks prior to the study enrollment. • Subject has been previously included in this study. • Subject has any other condition or personal circumstances that, in the judgment of the investigator, might make collection of complete data difficult or impossible. • Subject is allergic to hyoscine or any of ingredients of hyoscine butylbromide, or has myasthenia gravis, megacolon, closed angle glaucoma, or obstructive prostatic hypertrophy.
Study design	This open label, non-randomized, single center, single-dose explorative study is designed to obtain imaging assessments using PET with [^{18}F]FSPG in patients with UC (n = 10) and CD (n = 10).

Duration	The total amount of hours for participation in the clinical trial is approximately 5–6 hours over 3 visit days: screening visit (1 hr), [^{18}F]FSPG PET/CT imaging day (3–4 hrs), and a 24-hour follow-up safety assessment (1 hr). The expected duration of subject participation is usually less than 7 days.
Number of subjects	Patients with UC (n = 10), and CD (n = 10). If the subjects are replaced by another subject due to invalid [^{18}F]FSPG PET/CT or drop-outs, up to 24 subjects will be enrolled.
Primary variables	• Sensitivity and specificity of [^{18}F]FSPG PET/CT for the diagnosis of patients with endoscopic evidence of active disease • Sensitivity and specificity of [^{18}F]FSPG PET/CT for the diagnosis of patients with endoscopic evidence of severe disease (presence of ulceration)
Secondary variables	• Area under the receiver operating characteristic curve, sensitivity and specificity of segmental [^{18}F]FSPG PET/CT assessment for detecting bowel segments with endoscopic evidence of active disease • Area under the receiver operating characteristic curve, sensitivity and specificity of segmental [^{18}F]FSPG PET/CT assessment for detecting bowel segments with endoscopic evidence of severe disease (presence of ulceration) • Correlation of [^{18}F]FSPG activity with clinical, endoscopic, and biological markers of disease activity • Correlation of segmental [^{18}F]FSPG PET/CT activity with segmental endoscopic and histological markers of disease activity • Inter-reader variability of visual assessment of segmental [^{18}F]FSPG accumulation • Safety variables: adverse events, vital signs, physical examination and blood test
Statistical methods	Visual and quantitative assessment of [^{18}F]FSPG activity will be summarized. Frequency tables will be provided for qualitative data. Quantitative data will be described by the following summary statistics: arithmetic mean, standard deviation, median, minimum and maximum. Patient-level sensitivity and specificity of visual and quantitative assessment of [^{18}F]FSPG activity at different levels of the cut-off values. Area under the receiver operating characteristic curve using different cut-off values of visual and quantitative segmental [^{18}F]FSPG activity, and sensitivity and specificity of the optimum cut-off in detecting bowel segments with active or severe disease The correlation of [^{18}F]FSPG accumulation with the clinical, endoscopic, biologic and histologic markers of disease activity using Pearson or Spearman rank correlation coefficient Inter-reader variability of segmental [^{18}F]FSPG accumulation score measured using the kappa statistic Safety: Descriptive statistics, frequency tables
Planned study period: first enrollment – end	The date of Institutional Review Board (IRB) approval – 30 June 2018

of recruitment and study	
First participant enrollment	The date of IRB approval

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List of abbreviations and definition of terms

[^{18}F]	Isotope of fluorine
µg	Microgram
µmol	Micromole
AE	Adverse event
Bq	Becquerel
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
CDEIS	Crohn's Disease Endoscopic Activity Index of Severity
CRF	Case report form
CT	Computed tomography
DICOM	Digital Imaging and Communications in Medicine
FSPG	(2S, 4S)-2-Amino-4-(3-[^{18}F]-fluoro propyl) pentane dioic acid
g	gram
GBq	Giga-Becquerel
GCP	Good Clinical Practice
HBI	Harvey-Bradshaw Index
hCG	Human chorionic gonadotropin
IBD	Inflammatory bowel disease
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IRB	Institutional Review Board
ITF	Investigator's Trial File
IUPAC	International Union of Pure and Applied Chemistry
MBq	Megabecquerel
MIV	Metabolic inflammatory volume
mL	Milliliter

MRI	Magnetic resonance imaging
mSv	Millisievert
n.a.	Not applicable
p.i.	Post injection
PET	Positron Emission Tomography
SAE	Serious adverse event
SUSAR	Suspected Unexpected Serious Adverse Reaction
SUV	Standardized Uptake Value
TLI	Total lesion inflammation
TMF	Trial Master File
UC	Ulcerative colitis
UCEIS	Ulcerative Colitis Endoscopic Index of Severity

1. Background and rationale

1.1 Name and description of the investigational product

The name of the investigational product is (*S*)-4-(3-[^{18}F]Fluoropropyl)-L-glutamic acid ([^{18}F]FSPG). [^{18}F]FSPG is a L-glutamate derivative that is specifically taken up by system x_C^- (1). Specific transport of [^{18}F]FSPG via the x_C^- transporter was demonstrated in cell competition assays and xCT knock-down cells. This tracer is under investigation as a noninvasive diagnostic agent for assessing the system x_C^- of cancer and inflammation using positron emission tomography-computed tomography (PET/CT).

1.2 Research hypothesis

[^{18}F]FSPG PET/CT imaging can noninvasively assess disease activity status of inflammatory bowel disease (IBD).

1.3 Disease activity assessment in inflammatory bowel disease

IBD is a group of inflammatory conditions of the colon and small intestine. Ulcerative colitis (UC) and Crohn's disease (CD) are the principal types of IBD that vary in severity, extension of lesions, disease activity over time, damage progression, complications, and extraintestinal manifestations (2). Both usually involve severe diarrhea, pain, fatigue, and weight loss. IBD can be debilitating and sometimes leads to life-threatening complications. IBD is distributed world-wide and is increasing in incidence since the World War II (3). Its incidence in Korea is also increasing (4).

Although IBD is still being considered an incurable disease, various therapies have been attempted for the various clinical manifestations and complications of this disease. The goal of medical treatment is to suppress intestinal inflammation, ultimately relieving the symptoms and improving the quality of life. UC and CD are heterogeneous inflammatory bowel diseases, and therapeutic requirements vary among patients. However, we have limited capacity to predict disease progression in individual patients. Therefore, when deciding the appropriate treatment strategy for IBD one should consider the activity and distribution of IBD (5,6). Monitoring is key to identifying disease flares when symptoms are mild, the disease has a lower impact on quality of life, and is more likely to respond to new treatment interventions. Monitoring also is essential after introduction of a new therapy (7). Beyond clinical assessment, objective assessment of disease activity in IBD is important for guiding subsequent therapy as part of a 'treat to target' strategy (8). Classification based on disease severity is also clinically relevant because disease severity is a crucial aspect in most of the current therapeutic algorithms. There are multiple domains of disease activity and severity assessment in IBD (symptoms, endoscopy, histology, radiology, biomarkers and quality of life).

There are many clinical indices that evaluate symptoms of UC independently of endoscopic scoring or biological markers. They are widely used, but none have been adequately validated (9). Symptoms correlate better with endoscopic findings in UC compared with CD, though symptoms are imperfect indicators. As for CD, Crohn's Disease Activity Index (CDAI) is the most commonly used tool for assessing disease response to treatment in clinical trials (10). However, calculation of the CDAI is complex and involves eight items, including hematocrit, physical examination and a 7-day patient

diary, so it is rarely used in clinical practice (8). Determining the activity of disease may be more difficult in CD, since symptoms may be due to causes other than active disease. CDAI correlates poorly with endoscopic findings.

Endoscopy, together with histology, is currently considered the standard of care for the evaluation of both disease activity and disease extent in patients with IBD. Simple clinical remission does not correlate well with control of the inflammatory process at the tissue level. Mucosal healing is the ultimate therapeutic goal for UC, as the disease is limited to mucosa (11). The Ulcerative Colitis Endoscopic Index of Severity (UCEIS) is the only validated endoscopic index in UC (12,13). Disadvantages of the UCEIS are that extent of disease is not documented, there is no definition of mucosal healing, and there are no validated threshold for mild, moderate or severe disease (8). The Crohn's Disease Endoscopic Activity Index of Severity (CDEIS) is the most commonly used tool in clinical trials of CD (14). Although the CDEIS is a reproducible and validated index, it is complex, requiring over 30 entries to reach the final score, which makes it cumbersome to use in clinical practice. Additionally, endoscopic evaluation may not always be feasible and there are several drawbacks related to the invasiveness, procedure-related discomfort, inconvenience of the extensive bowel cleansing required for an optimal examination, risk of bowel perforation and relatively poor patient acceptance.

Histopathology is used for diagnosis and the assessment of disease activity in UC. Microscopic features of UC can be classified into architectural features, epithelial abnormalities and inflammatory features (9). Basal plasmacytosis is a good diagnostic feature in UC. A heavy diffuse transmucosal lamina propria cell increase is a good diagnostic feature in established active disease. Robarts Histopathology Index is a new validated and reproducible index for use in patients with UC (15). The Robarts Histopathology Index incorporates four histological descriptors (severity of chronic inflammatory infiltrate, the number of lamina propria neutrophils, the number of neutrophils in the epithelium and the severity of erosions or ulceration). Histological disease activity assessment in CD is difficult because inflammation is discontinuous, transmural and can exist beyond the reach of the endoscope (16). Nevertheless, microscopic inflammation can persist in biopsy samples from tissue that appears quiescent when observed endoscopically, and some limited evidence suggests that presence of microscopic inflammation is associated with increased rates of clinical relapse, stricture formation and surgery (17).

C-reactive protein and fecal calprotectin are useful markers adjunct to endoscopy for assessing disease activity in IBD. They are noninvasive and provide objective evidence of inflammation beyond clinical assessment alone. Weaknesses are only modest correlation with endoscopic disease activity and wide variation of cut-off values for determining active versus inactive disease (18,19). Furthermore, they are not able to localize the sites of active lesions.

A non-invasive technique for the evaluation of patients with IBD would be desirable in clinical practice to reduce the risk of procedure-related complications and to ensure complete examination of all bowel segments. Imaging techniques are adjunctive to endoscopic assessment of disease activity in UC. Magnetic resonance imaging (MRI) and bowel ultrasonography demonstrate good sensitivity for evaluating disease activity and extent in UC without associated ionizing radiation, and represent the most useful techniques for assessing disease activity when endoscopic examination is not feasible (20). However, these techniques have not been validated in assessing disease activity. There is a delayed timeline as compared to clinical or endoscopic changes (20). Accuracy of each technique may vary depending on the location of the colonic segments being analyzed (21).

Given that transmural inflammation in Crohn's disease can extend beyond the reach of endoscopy, imaging has an important role in assessing disease activity (20). MRI and ultrasonography are the preferred modalities for assessing luminal disease activity. MRI has a high diagnostic accuracy for the diagnosis of suspected CD and for evaluation of disease extension and activity of CD, and is less dependent on the examiner and disease location compared with ultrasonography. The Magnetic Resonance Index of Activity is best-validated for assessment of disease activity in CD (22). The Magnetic Resonance Index of Activity correlates well with CDEIS scores assessed by ileocolonoscopy, and has been shown to be reliable in assessing disease response to therapy in CD. However, the correlation between overall CDEIS and overall Magnetic Resonance Index of Activity was not significant at baseline (23). The accuracy of MRI for the diagnosis of CD may be inferior to endoscopy for detection of mild lesions (24). MRI measures wall thickness, enhancement after contrast injection, presence of edema, and ulcerations, or even more sophisticated measures, such as diffusion weighted imaging. It remains to be determined whether the inflammatory alterations measured by MRE are responsive to anti-inflammatory therapy (25). Although, MRI is, in general, well tolerated by patients, specific preparations with oral contrast and water enema to distend small bowel and colon are required. Doppler ultrasonograpy is also helpful in assessing disease activity in CD. However, the use of ultranonography remains limited by the availability of an experienced bowel sonographer.

[^{18}F]fluorodeoxyglucose is the most widely used PET tracer and is applied in a variety of cancer types and also in inflammatory and infectious diseases. The rationale for employing this modality in IBD is an increasing recognition that inflammatory cells display similar hypermetabolic features due to an up-regulation of glucose transporters to meet the increased metabolic demands in the inflamed state. [^{18}F]fluorodeoxyglucose PET can reveal the location of disease activity and allow for measurement of its severity throughout the body in various inflammatory disorders. Although several positive results have been published on the utility of [^{18}F]fluorodeoxyglucose in IBD, a major limitation of the use in IBD is that a lot of patients present gradual physiological uptake in the bowel, especially the large bowel. There are currently no large patient studies to support the use of this imaging technique for diagnosis and therapy evaluation (26).

In conclusion, multiple domains of disease activity assessment in IBD exist, each of which has its merits, although none are perfect.

1.4 The system x_C^- in inflammation

The system x_C^- is a sodium-independent heterodimeric transporter that is composed of a light chain, xCT, and a heavy chain, 4F2hc. Its main functions in the body is mediation of cellular cystine uptake, which is intracellularly reduced to cysteine, for glutathione synthesis to protect cells from oxidative stress (27), and maintenance of a cystine:cysteine redox balance in the extracellular compartment by subsequent release of intracellular cysteine (28). Several lines of evidence suggest that system x_C^- may play a role in innate immune system. In the active phase of inflammation, neutrophils and macrophages migrate into the site of inflammation to kill the invading organisms by reactive oxygen species (29). Prominent upregulation of system x_C^- expression was observed in macrophages on activation by lipopolysaccharide (30,31) and tissue necrosis factor α (30) and in activated leukocytes (31). Induction of system x_C^- might be a mechanism for the auto-protection of activated macrophages and granulocytes from the high levels of released reactive oxygen species by fostering glutathione synthesis. System x_C^- may also modulate the adaptive immunity. Activation of T-lymphocytes by

activated macrophage and dendritic cells has been reported to involve expression of system x_C^- in antigen presenting cells (32-34). This allows lymphocytes to take up cysteine from their microenvironment as lymphocytes are the cell type where system x_C^- expression cannot be induced (35,36). Activated macrophages and dendritic cells may serve as local supplies of cysteine for proliferation and activation of lymphocytes, which might be a mechanism for fine-tuning the innate immune response. Further evidence suggests that upregulation of xCT and increased production and extracellular release of glutathione and cysteine occurs during activation and differentiation of B lymphocyte (37). On the other hand, very low or no expression of xCT was detected in peripheral leukocytes, thymus, spleen, and lymph nodes in humans (38). All of these results suggest that system x_C^- is a key player in the active phase of inflammation.

1.5 [^{18}F]FSPG for detecting inflammation

1.5.1 Findings from non-clinical studies with potential clinical significance

In vivo studies with tumor bearing mice and rats in a variety of models revealed significant accumulation of [^{18}F]FSPG with a low background signal from healthy tissues and organs leading to superior PET images. [^{18}F]FSPG accumulated in the colon of mouse models of colitis and allowed imaging of colitis in mice employing small animal PET.

Effective radiation dose for [^{18}F]FSPG were calculated from biodistribution studies in mice. Extrapolated effective dose from mice are 5.10 mSv for a male and 6.54 mSv for a female subject, assuming a patient dose of 300 MBq and a bladder voiding interval of 45 min.

A nonclinical safety summary is given in detail in the investigator brochure.

1.5.2 Radiation dosimetry study in human

Effective radiation dose for [^{18}F]FSPG were determined in five healthy volunteers (39). The absorbed dose was highest in the urinary bladder wall and kidneys, followed by the pancreas and uterus. On the basis of the distribution and biokinetic data, the determined radiation dose for [^{18}F]FSPG was calculated to be 9.5 ± 1.0 mSv at a patient dose of 300 MBq. The effective dose can be reduced to 4.5 ± 0.30 mSv (at 300 MBq), with a bladder-voiding interval of 0.75 h.

1.5.3 Previous clinical experience in cancer patients

A first in man phase I proof of mechanism trial has been completed (46 patients treated, last visit 12 Aug 2011) to assess tumor targeting potential, radiation dosimetry, safety, pharmacokinetics and metabolism of [^{18}F]FSPG following a single intravenous administration in healthy volunteers and cancer and inflammation patients. A second phase trial has been completed (30 patients treated, last subject visit 05 Oct 2011) to assess tumor accumulation and safety and tolerability of [^{18}F]FSPG following a single intravenous administration in patients with prostate cancer or other malignant tumors (40-43). A favorable biodistribution pattern and a high lesion detection rate previously seen in rodents were confirmed in these patients with different tumor types. [^{18}F]FSPG had a high *in vivo* stability without defluorination. Low uptake in small and large bowels (mean standardized uptake

value at 60 minutes after injection = 0.6 ± 0.2) was observed in comparison with blood pool (0.8 ± 0.2).

Neither serious adverse events (SAE) nor relevant safety concerns were reported by the end of both studies. There were no safety issues newly identified or re-evaluated. No risk management actions have been taken.

1.5.4 Previous clinical experience in patients with infection or inflammation

The first in man phase I study included pulmonary tuberculosis (n = 3), nontuberculous mycobacterial infection (n = 2), sarcoidosis (n = 2), pneumonia (n = 1), radiation pneumonitis (n = 1), and necrotizing granulomatous inflammation (n = 1) (44). [^{18}F]FSPG PET identified inflammatory lesions in all 10 patients and detected all 24 reference lesions (15 major and 9 minor accumulations). All five patients with available tissue samples showed positive xCT expression in histiocytes and plasma cells. Immunohistochemical staining of xCT correlated significantly with that of CD68. The maximal standardized uptake value (SUV) of [^{18}F]FSPG and CD163 were negatively correlated with a borderline significance, which may indicate that high [^{18}F]FSPG uptake might represent an active disease state by measuring xCT transporter activity of activated M1 macrophages. These results suggested the potential diagnostic value of [^{18}F]FSPG PET to assess the system x_C^- activity in patients with inflammation particularly when [^{18}F]fluorodeoxyglucose PET assessment is challenging because of the physiologic [^{18}F]fluorodeoxyglucose uptake in normal organs. The very low background, especially in the bowel, should allow for sensitive inflammation imaging in bowel. [^{18}F]FSPG PET/CT will be well tolerated by patients because of no need for colonic preparation.

1.5.5 Biodistribution of [^{18}F]FSPG in patients with infection or inflammation

In the previous phase I study, 300 MBq of the drug [18F] FSPG was administered. The SUV of [^{18}F]FSPG in normal tissues such as blood, liver, and spleen decreased gradually at 60 min, significantly lower than that of inflammatory tissue, whereas the SUV of inflammatory tissue increased to 1.4-9.7. At 105 minutes, SUV was no longer increased.

2. Study objectives

2.1 Primary objective

The primary objective for this study is:

- To explore the validity of [^{18}F]FSPG PET/CT for the diagnosis of patients with active IBD

2.2 Secondary objective

The secondary objectives for this study are:

- To explore the validity of [^{18}F]FSPG PET/CT for detecting bowel segments with active IBD

- To assess the correlation of [^{18}F]FSPG activity with clinical, endoscopic, and biological markers of disease activity
- To assess the correlation of segmental [^{18}F]FSPG PET/CT activity with segmental endoscopic and histological markers of disease activity
- To assess inter-reader variability of visual [^{18}F]FSPG PET/CT interpretation
- To evaluate safety of [^{18}F]FSPG PET/CT

3. Overview of methodology and design

3.1 Study design

This open label, non-randomized, single center, single-dose explorative study is designed to obtain imaging assessments using PET with [^{18}F]FSPG in patients with UC (n = 10) and CD (n = 10). Subjects who have symptoms suggestive of active disease and are scheduled to undergo sigmoidoscopy or colonoscopy for evaluation of IBD activity will be enrolled. The study will be conducted at a single center in Korea: Asan Medical Center.

[^{18}F]FSPG is the investigational medical product in this study. [^{18}F]FSPG is a new PET tracer that accumulates in inflammatory sites, as has been shown in nonclinical and clinical studies. It may also have a potential in discriminating active inflammation from inactive lesions.

This study is designed to explore the validity of [^{18}F]FSPG PET in the diagnosis of active IBD. This study includes endoscopic assessment of disease activity as a valid reference standard of disease activity and disease extent of IBD. This study also evaluates the correlation of [^{18}F]FSPG activity with clinical, biological and histological assessment of IBD activity. [^{18}F]FSPG activity will be assessed visually and quantitatively by two experienced readers. Inter-reader variability of visual assessment will be assessed.

The study comprises 3 periods: screening, treatment, and follow-up. The screening period starts with the subject's signature on the informed consent form and ends with assignment to treatment that is inclusion of the subject for treatment. The treatment period starts with baseline measurements, and ends with the last measurement/procedure on the day following injection of 200 MBq of [^{18}F]FSPG. The follow-up period contains the end-of-study interview. Key measurement is the PET/CT image acquisition about one hour after the single injection of [^{18}F]FSPG. For evaluation of safety, adverse events (AE) will be monitored and recorded during the study period.

3.2 Justification of the design

Initial clinical results indicate that [^{18}F]FSPG may be a useful PET tracer for detecting inflammation. This study will explore the clinical feasibility of [^{18}F]FSPG in patients with IBD for the first time. Only a limited numbers of adult IBD patients will be examined. Given heterogeneous nature of IBD, this study will enroll patients with either UC or CD. Due to increased co-morbidity, patients ≥80 years will be excluded.

[^{18}F]FSPG is a diagnostic PET tracer. The PET technology allows obtaining diagnostic images with very low doses of, for example, [^{18}F]-labeled tracers. In this study the required total quantity to obtain an image (as extrapolated from non-clinical studies) is ≤ 100 μg and this dose is by a factor of >100 below a pharmacological active dose. Therefore the study with [^{18}F]FSPG falls under the scope of the microdosing concept. The safety pharmacology and toxicology studies were performed in accordance with International Conference for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guideline M3 on recommended non-clinical studies to support exploratory clinical trials demonstrated that the safety margin calculated for this study is even considerably wider than required by the microdosing concept. From the No-Observed-Effect-Level determined in non-clinical studies in toxicology and safety pharmacology, the human equivalent dose was calculated. The total quantity of PET tracer to be applied is by a factor >1,000 smaller than this human equivalent dose. In addition to results of nonclinical studies, results of initial human experiences identified none of any AEs. Therefore, reduced human safety monitoring including collection of AEs is appropriate for safety assessment.

3.3 Administration of [^{18}F]FSPG and imaging time

In the phase 1 study, [^{18}F]FSPG uptake of inflammatory lesions after administration of 300 MBq was the highest at 60 minutes post-injection and ranged from 1.4-9.7 SUV. Converting this uptake kBq/cc in 50-100 kg adults, the SUV of 1.4 is 2.9-5.8 kBq/cc and the SUV of 9.4 is 19.9-39.9 kBq/cc. The detection sensitivity of [^{18}F] for PET/CT is usually 7 cps/kBq/cc, and PET/CT was taken for 2 min as in the phase 1 study. Therefore, [^{18}F] FSPG PET/CT radioactivity counts in inflammatory lesions were 2417-4835 for SUV of 1.4 and 16750-33500 for SUV 9.7.

If the administered dose is 200 MBq, the count of SUV 1.4 will be 1611-3223 and that of SUV 9.7 will be 11166-22333. Therefore, even with adults weighing 100 kg, the measured radioactivity is well above the reliable measurement of 400. Furthermore, PET / CT imaging is limited to the pelvis in the abdomen, and the PET/CT scan duration will be increased to more than 3 minutes per lesion. Even with 200 MBq, it is possible to obtain more radioactivity than that of 300 MBq for whole body scan. Therefore, the optimal dose is 200 MBq. As a result of the first Phase 1 study, [^{18}F] FSPG uptake in inflamed lesions peaked at 60 minutes, so optimal imaging time is 60 minutes after injection. At 120 minutes after injection, the measured radioactivity is reduced to 68.5% of 60 minutes or less, even if the intake is kept at its maximum.

3.4 Protocol adherence

Strict adherence to all specifications laid down in this protocol is required for all aspects of the study conduct; the investigator may not modify or alter the procedures described in this protocol. If protocol modifications are necessary, all alterations that are not solely of an administrative nature require a formal protocol amendment.

If an investigator has deviated from the protocol in order to eliminate an immediate hazard to subjects for other inevitable medical reasons, the investigator shall document all such deviations, including the reasons thereof, and submit the document to the sponsor and the responsible person at the medical institution (if the latter is applicable).

Hospitalization or prolongation of hospitalization for purely logistical or reasons or the comfort of the subject will not be considered a protocol violation, nor will it be reported as a SAE.

3.5 Risk-Benefit Evaluation

3.5.1 Exposure to the investigational product

As indicated above, the safety pharmacology and toxicology studies followed ICH guideline M3. The very low total quantity applied, the large safety margin observed and the fact that [^{18}F]FSPG is not a high-risk compound allow applying the microdosing concept. The total quantity of ≤100 µg [^{18}F]FSPG to be used in this study is below the starting dose of a conventional dose escalation and even by a factor of >1,000 below the No-Observed-Effect-Level. [^{18}F]FSPG is a fluorine-18 labeled amino acid that is a substrate for amino acid transporters. It does not bind to central nervous glutamate receptors, as could be shown in a MDS Lead Profiling Screen on a broad panel of receptors, ion channels and transporters. This screen was performed to evaluate the potential of [^{18}F]FSPG to cause adverse side effects. The screen did not show any relevant binding, nor did any other safety pharmacology or toxicology study give rise to concerns.

Previous clinical studies employing [^{18}F]FSPG have been published. A dose of 300 MBq was found to be well-tolerated in all subjects during their participation in the clinical trials and none experienced any AEs (39-42,44). The kinetic data showed rapid clearance of the investigational product from the blood pool and most organs, except the pancreas (42).

3.5.2 Radiation exposure

Effective dose for [^{18}F]FSPG will be 3.0 ± 0.2 mSv at a subject dose of 200 MBq. Deviations of 10% will not be considered protocol violations. Additional radiation dose from CT part of the [^{18}F]FSPG PET/CT will not exceed 1 mSv. The total effective dose of study subjects will maximally be as summarized in Text Table 1.

Text Table 1 Expected study related radiation exposure in subjects

[^{18}F]FSPG Dose	Max. radiation exposure* (mSv)	Radiation exposure from CT of [^{18}F]FSPG PET/CT (mSv)	Total max. study related radiation exposure (mSv)*
200 MBq	3.4	≤ 1	4.4
220 MBq	3.8	≤ 1	4.8

* As extrapolated from clinical data for [^{18}F]FSPG

The effective radiation doses following [^{18}F]FSPG as listed in Text Table 1 are based on an assumed voiding interval of 45 minutes. Study participants can opt for a bladder catheterization in order to prevent movements during the imaging period. The effective radiation doses will be lower in those subjects volunteering to have a bladder catheter and thus a constant urine flow.

3.5.3 Benefit

The results of this study will have no direct impact on the subjects' further treatment. However, subjects may benefit as lesions newly seen with [^{18}F]FSPG will be followed-up with established routine measures. This new information may be clinically important especially when evaluation of disease extent by conventional colonoscopy is not feasible.

4. Study population

4.1 Eligibility

4.1.1 Inclusion criteria

A subject will be enrolled if he/she meets all of the following inclusion criteria.

- Subject is aged between 19 and 79 years and male or female of any race/ethnicity.
- Subject has had UC or CD diagnosed by clinical, endoscopic and histologic evidence at least 3 months prior to screening.
- Subject has symptoms suggestive of active disease at the time of enrollment.
- Subject is scheduled to undergo sigmoidoscopy or colonoscopy for UC or CD within 7 days prior to or after the planned study with [^{18}F]FSPG administration.

4.1.2 Exclusion criteria

A subject is to be excluded from the study if he/she does not fulfill the inclusion criteria or display any of the following criteria.

- Subject or subject's legally acceptable representative does not provide written informed consent.
- Subject displays clinical signs of ischemic colitis or has an evidence of pathogenic bowel infection.
- Subject is diagnosed as having inflammatory bowel disease unclassified.
- Subject has been treated with sulfasalazine or intravenous corticosteroids within the previous four weeks prior to the planned study with [^{18}F]FSPG administration.
- Dose escalation of the current IBD drugs or starting a new oral aminosalicylate, corticosteroid, immunomodulator, biologics, antibiotics, probiotics, or topical preparations is scheduled from the study enrollment to the scheduled sigmoidoscopy or colonoscopy, or 24 hours after [^{18}F]FSPG administration. The dose escalation or starting a new antidiarrheal and/or analgesic drug is allowed.

- Female subject is pregnant or nursing. Exclusion of the possibility of pregnancy is made by one of the following: 1) Woman is physiologically post-menopausal (cessation of menses for more than 2 years), 2) woman is surgically sterile (has had a documented bilateral oophorectomy and/or documented hysterectomy, or 3) if the woman is of childbearing potential, a serum or urine pregnancy test performed within 24 hours immediately prior to administration of [^{18}F]FSPG has to be negative and the women is advised to apply contraceptive measures during her participation in this study.

- Subject has concurrent severe and/or uncontrolled and/or unstable medical disease (e.g. congestive heart failure, acute myocardial infarction, severe pulmonary disease, chronic renal or hepatic disease which could compromise participation in the study) in the judgment of the investigator.

- Subject is a relative of the investigator, student of the investigator or otherwise dependent.

- Subject has received any investigational drugs or devices within four weeks prior to the study enrollment.

- Subject has been previously included in this study.

- Subject has any other condition or personal circumstances that, in the judgment of the investigator, might make collection of complete data difficult or impossible.

- Subject is allergic to hyoscine or any of ingredients of hyoscine butylbromide, or has myasthenia gravis, megacolon, closed angle glaucoma, or obstructive prostatic hypertrophy.

4.2 Recruitment

Potential subjects for inclusion in this study will be identified through the investigators in the referring clinics of Asan Medical Center, Seoul, Korea.

4.3 Withdrawal of study subjects from study participation or medication

4.3.1 Withdrawal

Withdrawal from study participation

A study subject must be withdrawn from the study prior to administration of the study medication under the following circumstances:

- Withdrawal of consent: Every subject has the right to refuse further participation in the study at any time and without providing reasons. A study subject's participation is to be terminated immediately upon his/her request. The investigator should seek to obtain the reason and record this in the case report form (CRF).

- Participation in any other clinical trial involving administration of an investigational drug

- Any intercurrent conditions, or safety concerns that preclude administration of study treatment

A study subject may be withdrawn from the study after the administration of the study medication under the following circumstances:

- Apparent inability of the study subject to comply with the protocol for any reason
- Development of an SAE that is classified as drug related

The reason for withdrawal should be fully documented in the CRF.

Follow-up of withdrawn subjects

For all subjects having received the investigational product attempts should be made to perform and document the safety evaluations and measures planned for the follow-up visits.

Subjects who discontinue due to a study-related SAE must be followed until resolution or stabilization. Investigational product-related AEs will be followed-up for a maximum of 28 days after the follow up telephone contact. If they have not resolved by this time, they will be classified and reported as "ongoing at study end" and reported as such in the CRF.

Withdrawal from assessment

Subjects with a major protocol deviation, rendering the analysis of [^{18}F]FSPG PET/CT imaging data impossible, or negatively affecting their comparability to the remaining study subjects, will be withdrawn from assessment. The sponsor will make the decision on whether a subject is considered an invalid case in mutual agreement with the clinical investigators on a case by case basis.

4.3.2 Replacement

Study subjects will be replaced under the following conditions.

Invalid cases:

- Subjects who completed the PET/CT image acquisition but whose images cannot be evaluated due to technical reasons (e.g., artifacts from movements of study subjects, technical problems of [^{18}F]FSPG PET/CT).

Drop-outs (post treatment):

- Subjects who did receive the study medication, but in which the acquisition of [^{18}F]FSPG PET/CT imaging data is not adequately possible, e.g. due to an intercurrent AE, requirement of priority treatment, or withdrawal of consent during imaging will be replaced by an additional subject. Subjects will be replaced with subjects with the same disease group.

Drop-outs (prior treatment):

- Subjects who did not receive the study medication due to withdrawal of consent after assignment to treatment or any intercurrent medical reason that is not merely transient in nature or that present an exclusion criterion will be replaced by an additional subject. The selection of replacements will follow the same rules as outlined in the paragraph above.

4.4 Subject identification

Upon signing the informed consent form, each subject will be assigned the unique subject number by the CRF for unambiguous identification.

The subject number will have three digits:

First digit = indication (1 = UC, 2 = CD)

Second and third digits = consecutive number of subject for a specific indication including replacements

5. Investigational product

5.1 [^{18}F]FSPG - Identity

IUPAC name: (S)- 4-(3-[^{18}F]Fluoropropyl)-L-glutamic acid

Chemical name: (2S, 4S)-2-Amino-4-(3-[^{18}F]-fluoro propyl) pentane dioic acid

Empirical formula: $C_8H_{14}FNO_4$

Molecular weight: 206.2 g/ mol

The active pharmaceutical ingredient for PET/CT imaging is the compound [^{18}F]FSPG that is labeled with the radioactive fluoride isotope ^{18}F (Text Table 2).

^{18}F has a half-life of 110 minutes. The radioactive drug substance and the final drug product are produced on-site at Asan Medical Center, Seoul, according to the radiolabeling and purification procedure described in the investigator brochure and the respective investigational medicinal product dossiers.

Each batch of [^{18}F]FSPG produced must meet criteria listed in the specification for identity, purity, concentration of [^{18}F]FSPG, specific activity and pH before being released. Manufacturing and quality control testing will be checked by the responsible person of the manufacturer and will be documented accordingly. Sterility tests will be conducted as control of the validated production process after release of the product according to the established procedures.

Text Table 2 Identity of investigational product [^{18}F]FSPG

Text Table 3 [^{18}F]FSPG-Composition of drug product (raw batch)

The final product will be formulated as sterile solution for intravenous injection (Text Table 3). The radioactivity of the final product will be verified before injection using a suitable counter, as established on site.

For traceability, the manufacturing site will allocate individual batch numbers to all [^{18}F]FSPG production runs. A complete batch documentation, detailing manufacturing, quality control, analytical results and the batch release for humans use will be generated according to established standards. These documents will be archived on site. A complete record of batch numbers and expiry dates of all study medication will be maintained by the manufacturer.

5.2 Dosage and administration

5.2.1 [^{18}F]FSPG

5.2.1.1 Administration of a microdose of [^{18}F]FSPG

The drug specification of the investigational medicinal product dossier and the limited volume of drug product provided by the manufacturer will ensure that only a dose of [^{18}F]FSPG can be applied to the subjects that fulfill the criteria of the microdosing concept.

5.2.1.2 Radioactive dose – radiation exposure

In nuclear medicine imaging, it is important to record sufficient numbers of events (here: counts per pixel/voxel) in the regions of interest in order to produce statistically reliable images. The number of recorded events increases with the duration of the acquisition period. Furthermore, for a given duration of image acquisition and for a given imaging time post injection (p.i.), image quality increases with the administered radioactivity over a wide range of radioactivity doses. Therefore, the

injected radioactivity should be sufficiently high in order to spare the subject a cumbersome long imaging time. On the other hand, higher radioactivity doses cause higher radiation exposure to the subjects, which is to be avoided. The optimum radioactivity dose is typically defined as the lowest dose that provides high image quality and diagnostic confidence for a reasonably short given duration of image acquisition and for a defined imaging time after injection.

Pre-clinical and clinical data as well as the large and experience with other routinely used ^{18}F-labeled tracers suggest that the optimum radioactivity dose for [^{18}F]FSPG imaging of whole body is about 300 MBq. [^{18}F]FPSG PET imaging in this investigation will cover only the abdomen and pelvis to assess activity of small and large bowel. 200 MBq will allow to record PET/CT images of sufficient diagnostic quality in subjects. Given a urinary bladder voiding interval of 45 minutes p.i., such a dose of [^{18}F]FSPG would result in a radiation exposure of less than 5 mSv in all subjects.

Subjects will be asked to void the bladder after about 45 minutes. The radiation applied in this study will not produce any immediate harmful effects, although there is no known minimum level of radiation exposure considered to be totally free of the risk of causing genetic defects or cancer. The risk associated with the amount of radiation exposure participants receive in this study is considered low and comparable to every day risks.

The treatment period will last 1 day for subjects followed by a 24-hour follow-up safety assessment. A detailed treatment schedule is available in section 7.

5.3 Treatment assignment

Subjects who meet the entry criteria will be sequentially assigned to a unique subject identification number. See section 4.4.

5.4 Blinding

n/a

5.5 Packaging and labeling of [^{18}F]FSPG

[^{18}F]FPSG will be provided by the manufacturer (Asan Medical Center) in injection vials, containing the specified radioactive dose and total quantity of the investigational product. Vials will be shielded by secondary lead containers for radiation protection purposes. The injection vials will be labeled according to the standards of the manufacturer and the specifications of the respective Korean regulations in the national language. Labels will be in accordance with all requirements of Good Clinical Practice (GCP). The label for the vial will have a tear-off part that can be transferred to the investigator trial file (ITF). A sample copy of the labels will be filed in the Trial Master File (TMF). If a filled syringe has to be transported through the clinic, it will be the responsibility of the study site to label the syringe in a way to make sure that the right subject receives the investigational product.

For [^{18}F]FPSG, a system of medication numbering (batch numbers) in accordance with all requirements of Good Manufacturing Practice will be used. This will ensure that for each subject, any dose of i can be identified and traced back to the production run.

5.6 Drug logistics and accountability

5.6.1 Supply, storage, dispensation and return

Precursor and reference standard for [^{18}F]FSPG will be stored at 2–8 °C temperature (refrigerator). Protection against light is not needed during transport. At the manufacturer, starting material supplies will be stored in a secure storage area to which only authorized personnel will have access.

The investigational product, [^{18}F]FSPG, will be manufactured in individual batches sufficient for 1 to 2 study subjects, on the day of intended imaging. Following manufacturing and batch release, the investigational product will be directly handed to the investigator for institutional administration at the respective study site. The manufacturers must not dispense the investigational product to the investigator before the approvals of the Institutional Review Board (IRB) and competent authorities are available in written form.

The quality control of the manufacturing procedure for [^{18}F]FSPG lies in the responsibility of the nuclear medicine department of Asan Medical Center. Documentation of the shipments including controlled transport conditions, substance accountability, all other manufacturing procedures and collaboration will be filed.

5.6.2 Drug accountability

The study medication [^{18}F]FSPG will be manufactured by the responsible radiochemist at the institution. The investigator (or designated personnel) will confirm receipt of the investigational product in writing and will use the investigational material only within the framework of this clinical study and in accordance with this study protocol.

The investigator will keep records of the investigational materials used. For each study subject he / she will keep a printout providing relevant parameters of synthesis and formulation of the investigational product [^{18}F]FSPG.

The investigational materials will be protected from unauthorized access.

The residual contents of the vials may be disposed of at the study site. Receipt, distribution, disposal and / or return of the investigational materials must be properly documented on the forms supplied by the study sites giving the following information: Study protocol number, sender, receiver, date, mode of transport, quantity, batch number and expiration or retest date, if applicable.

5.7 Treatment compliance

Monitoring of compliance will not be necessary, because it is a single application and the investigational product will be administered by the investigator or designated site personnel, who ascertain and document, that subjects receive treatment according to this study protocol. The clinical research associate will check the source data against entries into the CRFs. All deviations will be documented on the protocol deviation log.

6. Therapies other than investigational product

6.1 Prior and concomitant therapy

Prior medication (or medication history) refers to medication taken before first injection of the investigational product. In this study prior medication for subjects will be, for example, aminosalicylates, corticosteroids, immunomodulators, or biologics. A detailed recording of prior medication will be recorded for a period of 4 weeks prior to treatment with the investigational product.

Concomitant medication refers to medication received by the subject from the time point of injection of the investigational product.

Study participants may receive concomitant medications during the study with the following exceptions:

- Dose escalation of the current IBD drugs
- Initiation of a new oral aminosalicylates, corticosteroids, immunomodulators, biologics, antibiotics, probiotics, or topical preparations from the study enrollment to the scheduled sigmoidoscopy or colonoscopy, or 24 hours after [^{18}F]FSPG administration
- Administration of sulfasalazine or intravenous corticosteroids
- The dose escalation or starting a new antidiarrheal and/or analgesic drug is allowed.

Any prior and concomitant medication taken will be recorded on the CRF.

6.2 Post-study therapy

n/a

6.3 Contraception of women of childbearing potential

Women of childbearing potential have to be required that contraceptive measures are to be strictly applied during the participation in this study (until follow-up contact). The investigator will discuss with the woman the acceptable forms of contraception: Oral contraceptives, diaphragm, intrauterine device, spermicides (cream, jelly, film, suppository, sponge), sexual abstinence.

7. Schedule of evaluations and visit description

7.1 Schedule of evaluations

Evaluations will be performed over a period of 2 days plus a screening period as indicated in Text Table 4. Details of screening examination are given in Text Table 5. Subjects will stay in the hospital on the day of treatment with [^{18}F]FSPG (Day 1). Screening period may be combined with Day 1. Activities during this period include PET/CT scanning, blood sampling and safety examinations as indicated in Text Table 6, and Text Table 7. Follow up safety assessment will be performed on the next day (Day 2) after treatment with [^{18}F]FSPG according to Text Table 8.

Text Table 4 Schedule of evaluations

Period	**General overview of procedures**	**Up to 14 days pre Day 1**	**Day 1**	**Day 2**
Screening	Screening examination (see Text Table 5)	X	X	
Pre-dose and treatment	Pre-dose (baseline) (see Text Table 6)		X	
	Injection of [^{18}F]FSPG		X	
	PET/CT acquisition (see Text Table 6 and Text Table 7)		X	
	and safety (see Text Table 8)		X	
Follow-up	Safety and end of study (see Text Table 8)			X

X: (measure/action) to be done at the time point indicated

Text Table 5 Screening examination

Parameter	**Day 0 (up to 14 days pre Day 1)**
Informed consent	X
Allocation of unique screening number	X
Check of in-/exclusion criteria	X
Demographic data	X
Medical and surgical history	X
Confirmation of evidence for clinical condition - Current symptoms of UC or CD	X
Prior and concomitant medication	X

Documentation of clinical, endoscopic and histologic evidence of UC or CD	X
Recording and documentation of disease activity of UC or CD [a]	X
Recording of laboratory examinations [b]	X
Examination of vital signs (blood pressure, heart rate, and body temperature), height, and body weight, and calculation of body mass index	X
Physical examination for safety	X
AEs prior to treatment [c]	X
Serum or urine pregnancy test in fertile women	X
Blood sampling and/or providing a clean container for biological assessment of disease activity [d]	X

X: (measure/action) to be done at the time point indicated
a Can be assessed during the study period.
b Can be recorded from Medical History (data obtained maximally within 7 days before the planned study with [^{18}F]FSPG)
c Recorded continuously from time of informed consent
d If not done within 7 days before the planned study with [^{18}F]FSPG

Text Table 6 Pre-dose and treatment

Parameter	**Pre-dose** [a]	**Treatment**			
Relative time (day)	01	01	01	01	01
Relative time (hour)	00	00	01	01	03
Relative time (min)	Pre-administration	00	00	15 [h]	00
Final check in-/exclusion criteria	X				
Check fasting state	X				
Assignment to treatment	X				
Stay in clinic	→	→	→	→	→
Prior medication [b]	→				
Concomitant medication [b]		→	→	→	→
AEs [c]	→	→	→	→	→
Vital signs	X				X
Physical examination	X				X
Determination of weight	X				
Serum or urine pregnancy test (females of childbearing potential, only) [d]	X				
Blood sample for safety [e]	X				X
Blood/stool sampling for hemoglobin, hematocrit, white blood cell and platelet count, erythrocyte sedimentation rate, C-reactive protein, and fecal calprotectin [f]	X				
[^{18}F]FSPG administration for up to 60 seconds		X			
Intravenous administration of hyoscine butylbromide [g]			X		
PET/CT acquisition [h]	See Text Table 7				
Subject leaves clinic [i]					X

X : (measure/action) to be done at the time point indicated
→: (measure/action) to be done continuously
a Pre-dose procedures may be repeated in case of failure of synthesis of [^{18}F]FSPG or failure of PET/CT system.
b Prior / concomitant medication will be recorded continuously
c AEs will be recorded continuously
d To be performed within 24 hours prior to treatment
e Can be recorded from Medical History if performed within 72 hours prior to the administration of [^{18}F]FSPG
f Can be recorded from Medical History if performed within 7 days prior to the planned study with [^{18}F]FSPG
g To be performed just before scanning, infusion of 20 mg slowly followed with a flush of normal saline, repeated after half an hour if necessary.
h One imaging period (60-75 minutes, p.i.) is planned. However, the investigator may vary timing and length of the imaging periods, see 8.3.3. The PET/CT will cover the abdomino-pelvic cavity.
h If the imaging window is changed, the measures and actions planned for this time point should be done shortly after the end of the [^{18}F]FSPG PET/CT
i Subjects may leave later, if investigators modify timing of image windows

Text Table 7 Timing of [^{18}F]FSPG PET/CT in subjects

[^{18}F]FSPG PET Imaging window [a] [minutes p.i.]	**Duration [minutes]**	**PET/CT procedure**
60–75	15	Abdominopelvic scan [b]

a The investigator may vary timing and length of the imaging periods, see 8.3.3. PET/CT should be acquired for at least 3 minutes or more per bed.
b For the subjects the total radiation exposure due to the CT scan will be less than 1 mSv

Text Table 8 Follow up safety assessment (direct or telephone contact), end of study

Parameter	**Follow-up (Day 2)**
Patient contact directly or through telephone	X
Urine pregnancy test (fertile female subjects only, done at home)	X
Concomitant medication	→ X
AEs	→ X

X : action to be done at the time point indicated
→: action to be done continuously

7.2 Visit description

7.2.1 Screening

The screening visit will take place as close as possible (but not longer than 14 days) before the injection of the investigational product. Signed, dated, and timed informed consent must be obtained from all subjects before any study-specific procedures are performed.

The screening visits will comprise the following procedures / assessments. The data will be collected and documented on the study-specific CRF. The examinations will be performed by or under the supervision of an investigator nominated as responsible for the screening examinations.

- Date and time of signed informed consent
- Allocation of unique screening number
- Start check of inclusion and exclusion criteria
- Recording of demographic data
- Interview asking for the following subject-specific characteristics – Current symptoms of UC (stool frequency and rectal bleeding) or CD (general well-being, abdominal pain, and liquid or soft stool), medical and surgical history, and prior or concomitant medication
- Documentation of endoscopic and histological evidence of UC or CD

- Recording and documentation of disease activity of UC or CD assessed at the time of enrollment or during the study period. (See Attachment 1, 2, 3); partial Mayo score for UC and CDAI and Harvey-Bradshaw Index (HBI) score for CD

- Recording of laboratory examinations comprising hemoglobin, hematocrit, while blood cell and platelet count, erythrocyte sedimentation rate, C-reactive protein, and fecal calprotectin within 7 days before the planned study with [^{18}F]FSPG

- Examination of vital signs (blood pressure, heart rate, body temperature), height, and body weight and calculation of body mass index

- Physical examination for safety

- AEs before treatment (e.g. results of physical examinations)

- Serum or urine pregnancy test in fertile women

- Blood sampling for laboratory examinations for complete blood count, erythrocyte sedimentation rate and C-reactive protein if not done within 7 days prior to the planned study with [^{18}F]FSPG

- Providing a clean container for fecal calprotectin measurement before endoscopy if not done within 7 days before the planned study with [^{18}F]FSPG

7.2.2 Pre-dose

The pre-dose procedures / assessments are described below. See also Text Table 6. The examinations will be performed on day 1 before administration of the investigational product by or under the supervision of an investigator nominated as responsible for the pre-dose examinations. Scheduled sigmoidoscopy or colonoscopy should not be performed on Day 1, and will preferably be performed after Day 1. If sigmoidoscopy or colonoscopy is scheduled one day after [^{18}F]FSPG PET/CT, bowel cleansing solution or medication should be given after acquisition of [^{18}F]FSPG PET/CT imaging.

- Final check of in-/exclusion criteria. All inclusion criteria have to be answered with yes, all exclusion criteria have to be answered with no.

- Check fasting state

- Assignment to treatment

- Prior medication (update)

- Concomitant medication

- AEs before treatment (update)

- Examination of vital signs (blood pressure, heart rate, body temperature)

- Physical examination

- Blood sampling for safety laboratory examination (see Text Table 6). Blood can be taken after the insertion of the indwelling catheter for treatment
- Determination of body weight for calculation of SUV of [^{18}F]FSPG
- Serum or urine pregnancy test in fertile women

All signs / symptoms emerging after signing the Informed Consent will be recorded as AEs. Recent findings are recorded as "Medical History" on the corresponding CRF, see section 8.1.2.

Signs/symptoms which fulfill the criteria of SAEs will be recorded on the corresponding AE-page and the Complementary SAE-Page, see section 8.6.1.5.

If technical problems (for example regarding manufacturing of drug or the PET camera) do not allow treatment as planned, pre-dose procedures may be repeated.

7.2.3 Treatment

The treatment for subjects is described below. See also Text Table 6.

- Intravenous administration of [^{18}F]FSPG
- PET/CT acquisition (for details see Text Table 7)
- Documentation of concomitant medication and AEs

The following procedures are to be performed right after [^{18}F]FSPG PET/CT

- Documentation of concomitant medication and AEs
- Injection site monitoring

About 3 hours after investigational product administration

- Concomitant medication (update)
- AEs (update)
- Examination of vital signs (blood pressure, heart rate, body temperature)
- Physical examination for safety
- Blood sampling for safety laboratory examination (see Text Table 6)

- Subject leaves the clinic. For safety reasons the study subjects should not be discharged from hospital immediately after the last study related measure. They may leave only after being under observation for 3 hours after treatment.

7.2.4 Follow-up safety assessment

The following information has to be collected at 24 hours after treatment. All subjects will be contacted directly or through the telephone.

- Urine pregnancy test in women of childbearing potential (can be done by subject at home)
- Concomitant medication (retrospective update)
- AEs (retrospective update)

7.3 End of the study

The follow-up safety assessment marks the end of study for the individual study participant. In case of ongoing AEs after the telephone contact, the individual end of the study will be set to the time when the last investigational product-related AEs resolved, or up to a maximum of 28 days after the follow-up visit (see also section 4.3.1, Follow-up of withdrawn subjects). End of trial is defined as database closure.

8. Study procedures and assessments

8.1 Population characteristics

Upon study entry, the following subject characteristics will be recorded on the CRF according to the in-/exclusion criteria defined in section 4.1.

8.1.1 Demographic data

The following data will be collected and documented on the study-specific CRF:

- Date of birth (day, month, year)
- Sex: female or male
- Ethnicity: Hispanic or Latino; or Not Hispanic or Latino
- Race: American Indian or Alaska Native; Asian; Black or African American; Native Hawaiian or other pacific islander; or White

For collecting race and ethnicity data, subjects will be asked the following questions. Subject will self-report race and ethnicity information. When the collection of self-reported designations is not feasible (e.g., because of the subject's inability to respond), the information be requested from a first-degree relative or other knowledgeable source. Race and ethnicity should not be assigned by the study team conducting the trial.

- Question 1 (answer first): Do you consider yourself Hispanic/Latino or not Hispanic/Latino?
- Question 2 (answer second): Which of the following five racial designations best describes you: American Indian or Alaska Native; Asian; Black or African American; Native Hawaiian or other pacific islander; or White? Asian race category will be further asked to comment on more detailed information as follows: Asian Indian, Chinese, Filipino, Japanese, Korean, Vietnamese, or Other Asian. One or more categories may be selected

8.1.2 Medical and surgical history

The Medical History CRF collects relevant conditions which started before or are ongoing at signing the informed consent. It must be updated at every visit during the study in order to capture the end dates of the conditions.

All findings that are found or worsened thereafter should be documented on the AE CRF.

Clinically relevant conditions that are being stabilized by some treatment at the time of the informed consent should also be documented on this CRF.

Detailed instructions on the differentiation between Medical History and AEs can be found in section 8.6.1.

Medical and surgical history will be recorded for the following on the study-specific CRFs: subject age at endoscopic diagnosis of UC or CD (year), disease duration at inclusion (months), smoking history, family history of UC or CD (yes/no), and prior abdominal surgery (name of surgery and date)

Smoking history will be classified into 4 categories: (1) Never smoker: a person who has never smoked, or who has smoked less than 100 cigarettes in his or her lifetime. (2) Former smoker: a person who has smoked at least 100 cigarettes in his or her lifetime but who had quit smoking at the time of interview. (3) Some days smoker: a person who has smoked at least 100 cigarettes in his or her lifetime, who smokes now, but does not smoke every day. (4) Every day smoker: a person who has smoked at least 100 cigarettes in his or her lifetime, and who now smokes every day.

8.1.3 Prior and concomitant medication

Any prior medication used within the last 4 weeks before first injection of the investigational product or concomitant medication (as defined in Section 6.1) received by the subjects is to be documented on the CRF by brand or generic name, indication, total daily dosage, unit, frequency, route of administration and start/stop time periods with particular attention paid to aminosalicylate, corticosteroid, immunomodulator or biologic therapy.

Flushes with saline (0.9% sodium chloride) to check the correct localization of an inserted cannula are not to be documented as concomitant medication.

8.2 Clinical assessment of disease activity

Clinical disease activity will be assessed using the partial Mayo Clinic Index for UC and CDAI and HBI for CD (Appendices). If not given previously, subjects will be provided with a paper diary that is routinely used in practice at screening visit in order to record the information related to UC or CD. Diary data will be assessed at the time of enrolment or on day 1 before [^{18}F]FSPG PET/CT. The information extracted will be used for calculation of clinical disease activity of UC or CD.

8.3 Investigational product injection and [^{18}F]FSPG PET/CT

8.3.1 Preparation of study subjects

Fasting of food is required for at least 4 hours before the administration of [^{18}F]FSPG. After a high-protein diet, subjects will fast for at least 8 hours. Oral hydration with water is encouraged. Preparation of subjects consists of inserting a suitable indwelling intravenous catheter into a large vein (e.g. antecubital vein), preferably of the subject's non-dominant arm. Correct localization of the indwelling cannula must be ensured by test injection of normal saline prior to injection of the investigational product. If the investigator cannot locate/insert an indwelling intravenous catheter, other veins may be used. Implanted venous access ports, central venous catheters and similar devices that subjects may present with should not be used.

8.3.2 Injection of the investigational product and measurement of the injected radioactivity

Study staff will measure the ^{18}F radioactivity in the syringe prior to injection using a suitable counter. A radioactive dose of 200 MBq of the investigational product with a total quantity of ≤ 100 µg will be administered as slow intravenous bolus injection for up to 60 seconds. Deviations of ± 10% of the 200 MBq to be administered will not be considered protocol violations. After injection of the investigational product, the cannula and injection system must be flushed with 3 to 5 mL of normal saline.

The precise administered ^{18}F net radioactivity must be calculated from the difference of radioactivity measured in the syringe/injection system prior to and after injection. For radioactivity measurement a suitable counter system has to be used.

The following data will be documented:

- Batch number
- Date and time of injection
- Duration of injection (seconds)

- Volume of injection (mL)
- Tracer mass injected (µg, calculated as the product of tracer mass per volume and volume of injection)
- Radioactivity in syringe prior to injection (MBq, measured) and time of measurement
- Radioactivity in syringe and injection system after injection (MBq, measured) and time of measurement
- Radioactivity injected (MBq), calculated as difference of the radioactivity of the syringe measured prior to and the syringe and injection system measured after the injection. In addition, the injected radioactivity as a function of decay and injection time will later be calculated.

8.3.3 [^{18}F]FSPG PET/CT acquisition and image reconstruction

The site can use any state of the art PET/CT. PET/CT examinations will be performed approximately 60 minutes after injection of [^{18}F]FSPG. The investigators may vary timing and length of the imaging window. In any case, the total time for PET/CT will not exceed 30 minutes. The PET/CT will cover the abdomen and pelvis. One very low dose CT will be performed at about 1.0 mSv or less. Scan direction is usually craniocaudal. A urinary bladder voiding interval will be maintained at approximately 45 minutes or less p.i. Hyoscine butylbromide will be given through a cannula before or during the PET/CT to slow down peristaltic movement and improve the quality of PET/CT images.

The following data will be documented:

- Onset time of image acquisition
- Stop time of image acquisition
- Comments (free text) (technical problems, subject movement, others)

For reconstruction of the PET/CT raw data, an iterative algorithm will be used. Procedures will follow the respective hospital's routine. Images will be assessed by the investigator. Overall technical image quality will be graded as technically adequate or inadequate. All images deemed inadequate will have reasons specified.

PET images and raw data will be forwarded to the sponsor for quality control and storage. The preferable image format used will be digital imaging and communications in medicine (DICOM). Raw data or DICOMS sent to the sponsor have to be anonymized, that is should neither bear the study subject's name, initials or full birth date (only month and year is allowed).

8.3.4 Assessment of [^{18}F]FSPG PET/CT

8.3.4.1 Visual assessment of images with scores: [^{18}F]FSPG accumulation score

[^{18}F]FSPG PET/CT images will be interpreted independently by two board-certified nuclear medicine physicians who do not have any knowledge of clinical and endoscopic data. Reader will be completely unaware of findings of the other reader (including findings of other blind reader and onsite investigators) and not influenced by the findings of the other reader. However, the readers will be aware of particular elements of subject-specific information, inclusion and exclusion criteria for enrollment and other details of the protocols. The particular elements which will be provided to the reader will be defined in the image interpretation format.

Readers evaluate image in a random sequence. For this purpose, anonymized image data are merged to fullest degree that is practical and then images in this merged set are presented to the readers in a random sequence. Only protocol images are evaluated by the readers. Any nonprotocol images are not provided to readers. Readers assess images of all enrolled subjects (intention-to-diagnose principle) regardless of the image quality unless subjects were already excluded from the study assessment. Readers review all images to determine whether [^{18}F]FSPG PET/CT image quality is adequate for interpretation. The study is defined as technically inadequate when misregistration of >1 cm or other sources of errors can affect the accuracy of qualitative or quantitative assessment of images. If overall image quality is determined to be uninterpretable or if the study is technically inadequate, the reader must record the reason on the source document. Characteristics of physical findings and other imaging modalities are not informed.

Readers will assess objective image features which include the location (the number of axial, sagittal and coronal plane), and intensity of [^{18}F]FSPG activity. PET intensity results will be scored per each five bowel segment (rectum, sigmoid and left colon, transverse colon, right colon, and ileum) with the help of the CT images for a precise localization. The maximal intensity in each segment (segmental [^{18}F]FSPG score) will be graded according to a five-point scale as follows.

- Score 1: no uptake above background
- Score 2: uptake is less than or equal to blood pool
- Score 3: uptake is greater than blood pool but less than or equal to liver
- Score 4: uptake moderately increased compared to the liver
- Score 5: uptake markedly increased compared to the liver

Maximum [^{18}F]FSPG score is the highest value among segmental scores. Global [^{18}F]FSPG score will be calculated as the average of summing segmental [^{18}F]FSPG score.

8.3.4.2 Quantitative assessment of images

[^{18}F]FSPG PET/CT images will be assessed quantitatively by two board-certified nuclear medicine physicians who visually assess images. Readers will also be blind to clinical and endoscopic data and the result of the other reader. Multiple three-dimensional volume of interests will be placed around

each bowel segment Standard body weight = (height in cm – 100) x 0.9 with significant [^{18}F]FSPG avid lesions. [^{18}F]FSPG uptake will be assessed quantitatively by SUV as follows.

SUV = activity (Bq/g)/[injected activity (Bq)/ body weight (g)]

Single-pixel maximum SUV of each segment is defined as the segmental SUV. Maximum SUV is the highest value among segmental SUVs. Global SUV is defined as the average of the summing all segmental SUV.

In each bowel segment, isoactivity contours will be automatically drawn using a margin threshold (SUV = 1.0). Segmental metabolic inflammatory volume (MIV), mean SUV of the MIV and total lesion inflammation (TLI) is calculated by adding measures of all volume of interests in each segment. Global MIV and TLI are the sum of MIV and TLI of all segments, respectively. Global mean SUV is calculated via dividing global TLI by global MIV.

8.3.4.3 Consensus image assessment

In case of discrepancies, readers will review the images together in order to reach a consensus. Their consensus interpretation will be used for efficacy analysis.

8.4 Sigmoidoscopy or colonoscopy

Sigmoidoscopy or colonoscopy will be performed by experienced gastroenterologists in IBD following the standard protocol used in clinical practice. The severity and extent of inflammatory lesions will be evaluated using the UCEIS for UC (13) and CDEIS for CD (14). UCEIS or CDEIS will also be applied to five bowel segments (rectum, sigmoid and left colon, transverse colon, right colon, and ileum) to obtain a segmental UCEIS or CDEIS.

For segmental CDEIS, the score for ulcerated or non-ulcerated stenosis will be imputed to the affected segment. Endoscopic evidence of active disease is defined as UCEIS score of ≥ 2 for UC and CDEIS of ≥ 3 for CD. The same criteria will be used to categorize each bowel segment as inactive or active. In addition, bowel segments with superficial or deep ulcer will be considered as having severe disease. Investigators reporting the endoscopic lesions will be blinded to subject's symptoms and to the results of other laboratory and imaging studies. For accuracy of endoscopic data collection, endoscopists will complete the UCEIS or CDEIS on a predefined scoring sheet immediately after finishing the procedure.

Histological assessment of biopsied samples will be done following the standard protocol in clinical practice. Biopsies from different segments will be handed in such a way that the segment of origin can be identified. Disease activity will be assessed by experienced pathologists using the Robarts Histopathology Index for UC (15) and for the Colonic and Ileal Global Histologic Disease Activity Score for CD (45). Investigators reporting endoscopic lesions and histology will be blinded to the results of [^{18}F]FSPG PET/CT.

8.5 Biological markers of disease activity

Erythrocyte sedimentation rate, C-reactive protein and fecal calprotectin will be used as biological markers of disease activity.

8.6 Safety assessment

8.6.1 Adverse events

8.6.1.1 Definition of adverse event

The definition below follows ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting E2A.

AE is defined as any untoward medical occurrence in a volunteer or clinical investigation subject administered with a investigational product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product.

By definition, for this study, all untoward medical occurrences after signing the informed consent are to be regarded as AEs. AEs are regarded as "treatment emergent" if started or worsened after start of treatment. This means, AEs already present before treatment but worsened after start of treatment will be documented twice, in the phase before and after start of treatment.

8.6.1.2 Categories for adverse event assessment

All AEs will be assessed and documented by the investigator according to the categories detailed below.

Seriousness

For each AE, the seriousness and the reason for seriousness must be determined according to the criteria given in Section 8.6.1.5.

Intensity

The intensity of an AE is classified according to the following categories, taking into account the possible range of the intensity of the event:

Mild
Moderate
Severe

Investigational product action

Any potential investigational product action to resolve the AEs is to be documented as follows:

Drug withdrawn
Dose reduced
Dose not changed
Other action (entered in free text, e.g., 'dose interrupted', 'dose interrupted and re-started')

Investigational product treatment
Documentation of drug treatment of AE

Non-drug treatment

Documentation of non-drug treatment of AE.

Causal relationship to investigational product

The possible causal relationship between the AE and the administration of the investigational product is classified according to the following definitions:

The assessment of a possible causal relationship between the AE and the administration of the investigational product is based on the following question:

“Is there a reasonable likelihood that the event was caused by the investigational product?”

Possible answers are “yes” or “no.”

Causal relationship to study conduct

The assessment of a possible causal relationship between the AE and the administration of the investigational product is based on the following question:

“Is there a reasonable likelihood that the event was caused by the study conduct?”

Possible answers are “yes” or “no.”

Outcome

The outcome of the AE is to be documented as follows:

Recovered / resolved
Recovering / resolving
Not recovered / not resolved
Recovered / resolved with residual effects
Fatal
Unknown.

8.6.1.3 Assessments and documentation of AEs

AEs observed, mentioned upon open questioning by a member of the investigator team or spontaneously reported by the volunteer will be documented. The observation phase for AEs will start with signing the Informed Consent and will end with the last visit of follow-up. Investigational new drug-related AEs still present at the end of the observation phase will be followed-up for a maximum of 28 days after the follow up telephone contact.

AEs will be documented event based without change documentation. The investigator is responsible for the grading of each category mentioned. The sponsor has to carry out a separate assessment for expectedness, seriousness and causal relationship to investigational product.

8.6.1.4 Expected adverse events

Expected disease-related adverse events

AEs typically occurring in patients with IBD are considered as expected AEs.

Expected conduct-related adverse events

The use of an indwelling venous cannula for the purpose of blood sampling and administration of investigational product may be accompanied by mild bruising and also, in rare cases, by transient inflammation of the vessel wall. After initial irritation, the presence of an indwelling cannula is usually painless and hardly noticeable. The same applies to single vein punctures for blood sampling.

The total amount of blood withdrawn during the study is displayed in the Text Table 9.

Text Table 9 Amount of blood withdrawn

Laboratory examination *	**Amount of blood**
Hemoglobin, hematocrit, white blood cell and platelet count	2 mL
Erythrocyte sedimentation rate	2 mL
C-reactive protein	4 mL
Blood sampling for safety	10 mL
Total	**18 mL**

* May be omitted if available from medical history

Expected adverse drug reactions

The definition below follows ICH Guideline for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting E2A.

In the pre-approval clinical experience with a new medicinal product or its new usages, all noxious and unintended responses to a medicinal product related to any dose should be considered as adverse drug reaction. The phrase 'responses to a medicinal product' means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

Unexpected adverse drug reactions

An unexpected adverse drug reaction is defined as an adverse reaction which in nature and severity is not consistent with the applicable product information (e.g. Investigator's Brochure).

Any adverse experience that is not listed in the current Investigator's Brochure or which is with regard to the specificity or severity not consistent with the risk information shall be regarded as unexpected.

Examples would be (a) acute renal failure listed in the Investigator's Brochure with a subsequent new report of interstitial nephritis and (b) hepatitis with a first report of fulminant hepatitis. "Unexpected" as used in this definition refers to an adverse drug experience that has not been previously observed and included in the product information, rather than from the perspective of such experience not being anticipated from the pharmacological properties of the investigational product.

8.6.1.5 Serious adverse events

Definition of serious adverse events

The following SAE definition is based on ICH guidelines and the final rule issued by the Food and Drug Administration and effective from 06 Apr 1998. See section 8.6.1.2.

An SAE is classified as any untoward medical occurrence that at any dose

- Results in death, or
- Is life threatening, or
- Requires inpatient hospitalization or prolongation of existing hospitalization, or
- Results in persistent or significant disability / incapacity, or
- Is a congenital anomaly / birth defect
- Is another medically important serious event or reaction

Hospitalization or prolongation of hospitalization for purely logistical or reasons or the comfort of the subject will not be considered an SAE.

The term ‘life threatening’ in the definition refers to an event in which the subject was at risk of death at the time of the event, it does not refer to an event which hypothetically might have caused death if it were more severe.

Medical and scientific judgment should be exercised in deciding whether it is appropriate to report an AE as serious also in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the volunteer or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in volunteer hospitalization; or development of drug dependency or drug abuse.

Actions and reporting obligations in case of serious adverse events

The investigator must submit a complete SAE Report for all SAEs, regardless of a possible causal relationship, to the sponsor’s respective Medical Safety Surveillance function within 24 hours of having gained knowledge of the event. This report to be sent is the related AE-page and the Complementary SAE-page provided by the sponsor. The investigator is required to document in full the course of the SAE and any therapy given, including any relevant findings / records in the report. The investigator will also inform the sponsor of the relevant follow up information and the outcome of the SAE as soon as possible using the Complementary SAE-page. For fatal or life-threatening SAEs, this follow up report is to be provided within 8 calendar days.

The investigator should take appropriate diagnostic and therapeutic measures to minimize the risk to the subject. Where appropriate he / she should take diagnostic measures to collect evidence for clarification of the relationship between the SAE and the investigational product.

The primary contact person at the sponsor will be:

Jae Eun Kim at 010-5308-8628 or via Email: kje0216@amc.seoul.kr

SAEs emerging after signing the Informed Consent will be documented on the Complementary Page as described above.

Notification of the Institutional Review Board

All SAEs which are regarded as at least unexpected and “possibly” investigational product related (suspected unexpected serious adverse reaction = SUSARs) will be promptly reported to the IRBs concerned by local pharmacovigilance. For life threatening cases the IRB is informed within 7 days, for follow up information within an additional 8 days. All other SAEs which are unexpected and at least possibly investigational product related are notified within 15 days. IRB will be informed on a single case basis.

The sponsor will process and report all relevant events (e.g. SAEs, SUSARs) to the authorities according to all applicable regulations. Irrespective of the time elapsed after the completion of the study, all SAEs which may be attributed to the clinical research must be reported to the authority as

soon as the sponsor is informed, unless a cause other than research can be identified. This is done by pharmacovigilance.

Sponsor's notification of the investigators

The sponsor will inform all investigators about reported relevant events (e.g. SAEs, SUSARs*)* within the same timelines.

8.6.1.6 The type and duration of the follow-up of subjects after adverse events

Any SAE that has not resolved or returned to baseline after study treatment will be followed and recorded in the CRF for a maximum of 28 days after the follow up telephone contact. AEs continuing beyond this time should be followed by the investigator or treating physician in accordance with standard medical practice.

8.6.2 Vital signs

Blood pressure, heart rate

Systolic/diastolic blood pressure and heart rate will be measured repeatedly under the following conditions:

Posture	supine position for at least 3 min
Site	upper arm, same side for all measurements in one subject

Blood pressure, heart rate

Body temperature will be recorded.

8.6.3 Physical examination

A qualified physician who is certified by National law to perform physical examinations will conduct physical examinations at the following time points: screening, pre-dose period and 3 hours after [^{18}F]FSPG administration. The limited physical examination will comprise: general appearance, skin, neck, lungs, heart, abdomen, and a limited neurological examination (mental status, motor strength and sensor perception).

Information about the physical examination must be present in the source documentation at the study site. Significant findings that are present prior to the start of [^{18}F]FSPG administration be included in the relevant medical history/current medical conditions on the CRF. Significant findings made after the start of [^{18}F]FSPG, which meet the definition of an AE must be recorded on the CRF.

8.6.4 Blood test

Blood samples for the evaluation of clinical laboratory safety parameters will be obtained following study participation. For exact timing of the blood and urine collections, see Text Table 6.

The clinical laboratory safety parameters to be assessed are as follows: glutamate pyruvate transaminase (GPT/ALAT), glutamate-oxaloacetate transaminase (GOT/ASAT), alkaline phosphatase, total bilirubin, creatinine, potassium, sodium, total protein, blood urea nitrogen (BUN), albumin

The laboratory at the study site will be used for the analysis of all blood samples in this study.

Blood samples will be taken, processed and analyzed in the standard way. The laboratories will provide a list of normal ranges prior to the start of the study, this will be filed in ITF and TMF. The consumables routinely used at the study sites will be used for the collection, processing and analysis of blood and urine samples within this study.

Any clinically significant changes in laboratory values are to be followed up with repeated tests at appropriate intervals (as determined by the investigator and the Study Team Lead) until the values return to baseline level or until the abnormality is explained by the investigator. Such additional tests should be done at the same laboratory that did the first analysis, and results will be entered into the database.

All laboratory reports must be promptly reviewed by the investigator, and upon review, initialed and dated by the investigator. Change(s) in post-dose test values considered clinically significant, which would require either additional control or therapy, must be specified on the evaluation of laboratory test page of the CRF and, in case of disturbing or influencing factor(s) on values/samples, details of the appropriate value(s) and the source of disturbance or influence (e.g., quality of sample, co-medication etc.) are to be recorded.

Safety laboratory samples obtained for this study will be used only for this study; samples obtained in this study will not be retained or used for any other purposes.

Any change in laboratory value which results in a change of patient management (additional controls or treatment required) will be reported as a clinically significant change. Clinically significant changes in laboratory parameters which are not the result of laboratory error are to be recorded as AEs.

8.7 Other procedures and variables

Procedures of urine pregnancy tests

A commercially available test will be used based on the (qualitative) detection of beta unit of human chorionic gonadotropin (beta-hCG) in urine samples. The test will be performed by a member of the investigator's team at the study site at the following time points: screening, pre-dose and at follow-up.

Positive serum or urine pregnancy test results before start of treatment

A positive pregnancy test is an exclusion criterion.

Positive serum or urine pregnancy test results after start of treatment

In case of a positive test result after administration of [^{18}F]FSPG the woman is to be asked to agree to further follow-up examinations. By participating in this study the woman agrees to provide information on course and outcome of a pregnancy.

Pregnancy reporting

Documentation and reporting of the pregnancy will follow the current SOP. The investigator has to submit to Local Pharmacovigilance and the sponsor a complete report for any pregnancy detected during the study (i.e., after informed consent) or which might have been exposed to the treatment (i.e., detected after the end of the study) immediately, at the latest within 24 hours of having gained knowledge of the pregnancy (within the same time frame as reporting of an SAE).

The investigator will be responsible for confirmation of the initial test result by e.g. a quantitative hCG test in serum and further diagnostic measures. The investigator should provide - as far as possible - the following information: date of last menstrual period, expected date of delivery, the course of pregnancy and any applied diagnostic measures. The final outcome of both mother and child will be followed. For reports and documentation purposes the Pregnancy Monitoring Forms provided by the sponsor are to be used.

In case of a pregnancy with an **abnormal outcome** both an AE and SAE page have to be filled out. Pregnancy reports with an abnormal outcome must be submitted to the authorities together with the relevant spontaneous report or SAE-report within 7 calendar days (fatal/life-threatening) or 15 calendar days (all other serious).

8.8 Appropriateness of procedures / measurements

All methods used (apart from [^{18}F]FSPG PET/CT) are standard methods.

9. Statistical methods and determination of sample size

9.1 List of variables and population characteristics

9.1.1 Population characteristics

Population characteristics comprise:

- Number of subject with UC or CD enrolled
- Number of subjects included in the safety analysis
- Number of subjects included in the efficacy analysis
- Number of subjects withdrawn from the study and the reason for withdrawal
- Demographic data
- Medical and surgical history
- Prior and concomitant medication
- Height, weight and body mass index
- Clinical disease activity assessment: partial Mayo score for UC; and CDAI and HBI score for CD
- Results of laboratory examinations: hemoglobin, hematocrit, while blood cell and platelet count, erythrocyte sedimentation rate, C-reactive protein, and fecal calprotectin

9.1.2 Injected investigational product data

- Tracer mass injected (μg)
- Radioactivity injected (MBq)

9.1.3 Endpoints

The primary endpoints for this study are:

- Sensitivity and specificity of [^{18}F]FSPG PET/CT for the diagnosis of patients with endoscopic evidence of active disease
- Sensitivity and specificity of [^{18}F]FSPG PET/CT for the diagnosis of patients with endoscopic evidence of severe disease (presence of ulceration)

The secondary endpoints for this study are:

- Area under the receiver operating characteristic curve, sensitivity and specificity of segmental [^{18}F]FSPG PET/CT assessment for detecting bowel segments with endoscopic evidence of active disease
- Area under the receiver operating characteristic curve, sensitivity and specificity of segmental [^{18}F]FSPG PET/CT assessment for detecting bowel segments with endoscopic evidence of severe disease (presence of ulceration)

- Correlation of [^{18}F]FSPG activity with clinical, endoscopic, and biological markers of disease activity
- Correlation of segmental [^{18}F]FSPG PET/CT activity with segmental endoscopic and histological markers of disease activity
- Inter-reader variability of visual assessment of segmental [^{18}F]FSPG accumulation
- Safety variables: AEs, vital signs, physical examination and blood test

9.2 Statistical and analytical plans

9.2.1 General considerations

This study is explorative in nature.

The statistical evaluation will be performed by using the statistical analysis systems software package. All data will be listed and trial summary tables will be provided.

All descriptions will be done for the total population and separated by indication strata groups (UC and CD).

9.2.2 Analysis sets

Safety analysis set: All subjects who received any amount of [^{18}F]FSPG will be included in the safety analysis set.

Full analysis set: All subjects who received any amount of [^{18}F]FSPG and have PET/CT images available, but may have major deviations from the protocol will be included into the full analysis set.

Per protocol set: All subjects in the full analysis set who received [^{18}F]FSPG as planned in the protocol, have PET/CT images and valid data available, and have no major protocol deviation will be included in the per protocol set.

9.2.3 Statistical analyses

The statistical evaluation will be performed under the supervision of the responsible study biometrician.

Demographic and other characteristics

Summary statistics (arithmetic mean, standard deviation, median, minimum and maximum for quantitative variables) will be presented for all analysis sets. Frequency tables will be provided for qualitative data. Medical history findings will be summarized using MedDRA terms.

Efficacy data

As a principle, efficacy analysis will be performed in the full analysis set and additionally in the per protocol set. Visual and quantitative assessment of [^{18}F]FSPG activity will be summarized. Frequency tables will be provided for qualitative data. Quantitative data will be described by the following summary statistics: arithmetic mean, standard deviation, median, minimum and maximum.

Patient-level sensitivity and specificity of maximum and global [^{18}F]FSPG score, maximum and global SUV, global MIV and TLI will be calculated.

The cut-off values for diagnosis is visual [^{18}F]FSPG accumulation score of 3. Sensitivity is calculated as the probability of [^{18}F]FSPG activity will be positive when the active or severe disease is present. Specificity is the probability of [^{18}F]FSPG activity will be negative when the disease is not present.

Area under the receiver operating characteristic curve using cut-off values of all segmental [^{18}F]FSPG score, SUV, MIV and TLI will be determined. Sensitivity and specificity of the optimum cut-off in detecting bowel segments with active or severe disease will be defined.

The correlation of [^{18}F]FSPG accumulation with the clinical, endoscopic, biologic and histologic markers of disease activity will be assessed using Pearson or Spearman rank correlation coefficient.

Inter-reader variability of segmental [^{18}F]FSPG accumulation score will be measured using the kappa statistic to assess the reproducibility of the visual assessment of [^{18}F]FSPG accumulation.

Safety parameters

Safety analysis will be performed by using descriptive statistics and frequency tables in the safety analysis set. Individual listings of AEs (including age, weight, height, gender, AE as reported, start, duration, severity, relation to investigational product) in the safety analysis set will be provided. The incidence of treatment-emergent AEs and drug-related AEs, respectively, will be summarized by treatment using MedDRA.

Interim analysis

No formal statistical interim analysis will be performed.

9.3 Determination of sample size

The study is explorative in nature. Therefore, the numbers of subjects examined should be as low as possible for ethical reasons, in particular in view of the radiation exposure. On the other hand, choice of too few subjects might lead to inconclusive results of the study. The chosen numbers of subjects appear to be a reasonable compromise to get sufficient information on PET/CT imaging following application of [^{18}F]FSPG while avoiding unnecessary exposure to of ionizing radiation. Minimally 10 subjects with UC and 10 subjects with CD will be enrolled in the study (plus replacements for

drop-outs). If the subjects are replaced by another subject due to invalid [^{18}F]FSPG PET/CT or drop-outs, up to 24 subjects will be enrolled.

Study subjects will be replaced under the following conditions.
Invalid cases:

- Subjects who completed the PET/CT image acquisition but whose images cannot be evaluated due to technical reasons (e.g., artifacts from movements of study subjects, technical problems of [^{18}F]FSPG PET/CT).

Drop-outs (post treatment):

- Subjects who did receive the study medication, but in which the acquisition of [^{18}F]FSPG PET/CT imaging data is not adequately possible, e.g. due to an intercurrent AE, requirement of priority treatment, or withdrawal of consent during imaging will be replaced by an additional subject. Subjects will be replaced with subjects with the same disease group.

Drop-outs (prior treatment):
Subjects who did not receive the study medication due to withdrawal of consent after assignment to treatment or any intercurrent medical reason that is not merely transient in nature or that present an exclusion criterion will be replaced by an additional subject. The selection of replacements will follow the same rules as outlined in the paragraph above.

10. Data handling and quality assurance

10.1 Data recording

The investigator will document the items that are required to evaluate the study in the subject files (hospital files).

Data required according to this protocol are to be recorded on the CRFs as soon as possible.

If corrections on printed material are necessary, they will be entered by an authorized member of the investigator's staff in the following manner: The wrong entry will be crossed out, although it must remain legible, and the correct entry will be placed next to it. Corrections will be initialed and dated. For corrections concerning AEs or the primary variables, a reason for any alteration must be provided.

Results from laboratory tests will either be entered manually on the CRF or electronically imported. Images have to be anonymized, i.e. is the name of the study participant has to be deleted and should preferably be replaced with the randomization number.

Data of ‘only screened subjects’ will be recorded at least as raw data, as far as the reason for the premature discontinuation is identifiable. At least screening number, date of birth (month, year) and the reason for premature discontinuation have to be recorded on the CRF. Only screening number (if available) and the reason for premature discontinuation will be transferred to the clinical database, because they will be described in the report.

In case the subject withdraws consent, she/he may require that her/his human material (such as blood samples) that has not been analyzed yet will be destroyed. Additionally, no new information may be

collected on the CRF and added to the existing database without the subject's agreement. As the study data should be as complete as possible, the subject will be asked whether she/he agrees to sign a corresponding consent form, so that analysis and data collection can be performed as originally planned.

Any documents related to the study must be archived at the study site or in a central archive. This includes the careful listing of the identities of the subject involved in the study. This list and the signed informed consent statements are key documents in the files to be stored by the investigator.

10.2 Monitoring

This study will be monitored regularly by a clinical research associate from the sponsor or a designated contract research organization. Data quality and study integrity will be assessed. During monitoring, the clinical research associate will check for completion of the entries on the CRFs, their compliance with the study protocol and with Good Clinical Practice, and will compare the CRF entries with the source data.

10.3 Auditing

This study may be evaluated by auditors designated by the sponsor or the contract research organization, and government inspectors. The investigator will allow them to access to CRFs, source documents, other study files, and studies facilities.

10.4 Archiving

The sponsor and the investigator / medical institution shall, in every case, retain the complete documentation relating to this study (as ITF or TMF) for 15 years after its completion. Essential documents shall be archived in such a way that ensures that they are readily available upon authorities' request.

Study subjects' hospital files will be archived according to local regulations and in accordance with the maximum period of time permitted by the hospital, institution or private practice. The ITF is not to be destroyed without the sponsor's approval. The investigator's contract will contain all regulations relevant for the study center

11. Premature termination of the study

At the discretion of the sponsor, the entire study may be cancelled for medical reasons, such as safety concerns. In addition, the sponsor retains the right to end the study for medical-scientific or GCP-relevant reasons.

12. Ethical and legal aspects

12.1 Ethical and legal conduct of the study

12.1.1 Institutional Review Board

The study will commence only after the protocol has been approved by the IRB and a notification of the approval has been received. The investigator is committed in accordance with local requirements to inform the IRB of any emergent problem, SAEs, and/or protocol amendments.

The investigator may not modify or alter this protocol without first obtaining the written agreement of the sponsor. All substantial alterations require a formal protocol amendment and must be approved by the IRB prior to implementation, except where immediate implementation in order to eliminate an imminent hazard to the volunteer is necessary.

12.1.2 Good clinical practice

The planning and conduct of this clinical study are subject to national laws. Only when all of the requirements of the appropriate regulatory authority have been fulfilled will the study begin. The study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the ICH Guideline Good Clinical Practice E6 of June 1996. The study will be conducted in compliance with the protocol. All potential serious breaches must be reported to the sponsor immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

As required by local law, current safety-relevant information will be provided to the IRB and the regulatory authorities by the sponsor. The sponsor will also inform all investigators about relevant safety events according to the applicable regulations.

12.2 Subject information and consent

All relevant information on the study will be summarized in an integrated information and consent sheet provided by the sponsor or the study center. A sample subject information and informed consent form is provided as a document separate to this protocol.

Based on this subject information sheet, the investigator will explain all relevant aspects of the study to each subject, before his / her entry into the study (i.e., before examinations and procedures associated with selection for the study are performed).

The investigator will also mention that written approval of the IRB has been obtained.

Each subject will have ample time and opportunity to ask questions and will be informed about the right to withdraw from the study at any time without any disadvantage and without having to provide reasons for this decision.

Following this informative discussion, the subject will be asked if he / she is willing to sign and personally date a statement of informed consent, which includes consenting to the processing of his / her data as explained in the subject and information sheet. Only if the subject agrees to sign the informed consent form and has done so, may he / she enter the study. Additionally, the investigator will personally sign and date the form, too. The will receive a duplicate of the signed and dated form.

The signed informed consent statement is to remain in the ITF.

The investigator will document on the CRF the time and date of obtaining informed consent. In the event that informed consent is obtained on the date that baseline study procedures are performed, the study record or volunteer's clinical record must clearly show that informed consent was obtained prior to these procedures.

The informed consent form and any other written information provided to subject will be revised whenever important new information becomes available that may be relevant to the subject's consent, or there is an amendment to the protocol which necessitates a change to the content of the subject information and / or the written informed consent form. The investigator will inform the subject of changes in a timely manner and will ask the subject to confirm his / her participation in the study by signing the revised informed consent form. Any revised written informed consent form and written information must receive the IRB's approval / favorable opinion in advance of use.

A sample of the integrated volunteer information and consent sheet is provided as a separate document.

12.3 Financial disclosure

Each investigator (including principle and/ or any subinvestigators) who is directly involved in the treatment or evaluation of research subjects has to provide a financial disclosure according to all applicable legal requirements. If applicable, the financial disclosure signed by the investigator also has to apply to the investigator's spouse and dependent children. All relevant documentation will be filed in the TMF and/or ITF, as appropriate.

12.4 Publication policy

The sponsor is interested in the publication of the results of every study it performs. As some of the information concerning the investigational product and the sponsor's development activities may be strictly confidential, any publication manuscript (including conference contributions, etc.) must first be reviewed by the sponsor before its submission or presentation

Publication of subgroup data shall not be performed until the complete study has been published.

All relevant aspects regarding publication will be part of the contract between the sponsor and the investigator / institution.

12.5 Compensation to subjects

Insurance of subjects against health impairment occurring as a result of participation in the study will be set up in accordance with laws and regulations. All relevant documentation regarding such insurance will be filed as appropriate.

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Attachments

Attachment 1. Mayo scoring system for ulcerative colitis (Mayo score)

The Mayo Score evaluates ulcerative colitis stage, based on four parameters. Each parameter of the score ranges from zero (normal or inactive disease) to 3 (severe activity). Sum of Mayo score defines disease severity as follows: 0-2: remission; 3-5: mild activity; 6-10: moderate activity; > 10: severe activity. The partial Mayo score uses the three noninvasive components eliminating the scores for the endoscopic findings (<2: remission; 2-4: mild; 5-7: moderate; >7 severe).

Descriptor	Sore and description	
Stool frequency*	0	Normal number of stools
	1	1-2 stool/day more than normal
	2	3-4 stools/day more than normal
	3	≥5 stools/day more than normal
Rectal bleeding**	0	No blood seen
	1	Streaks of blood with stool less than half the time
	2	Obvious blood with stool most of the time
	3	Blood alone passed
Mucosal appearance at endoscopy	0	Normal or inactive disease
	1	Mild disease (erythema, decreased vascular pattern, mild friability)
	2	Moderate disease (marked erythema, absent vascular pattern, friability, erosions)
	3	Severe disease (spontaneous bleeding, ulceration)
Physician global assessment†	0	Normal
	1	Mild disease
	2	Moderate disease
	3	Severe disease
Mayo score	Sum of all above items	

*Each patient served as his or her own controls to establish the degree of abnormality of the stool frequency.

**The daily bleeding score represented the most severe bleeding of the day.

†The physician's global assessment acknowledged the three other criteria, the patient's daily record of abdominal discomfort and general sense of well-being, and other observations, such as physical findings and the patient's performance status.

Reference: Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. N Engl J Med 1987;317:1625-1629.

Attachment 2. Crohn's Disease Activity Index (CDAI)

The Crohn's Disease Activity Index or CDAI is frequently used to assess disease severity. It gives a score ranging from 0 to over 600, based on a diary of symptoms kept by the patient for 7 days, and other measurements such as the patient's weight and hematocrit. The CDAI score is calculated by summation of the score for each parameter multiplied by the corresponding weighting/multiplication factor. A CDAI score of less than 150 is considered to be remission, and a score of 150 or greater indicates active disease. Mild active disease is defined as a score between 150 and 219 points, moderate active disease as a score between 220 and 450 points, and severe disease is defined as a CDAI score > 450 points.

Clinical or laboratory variable	Weighting factor
Number of liquid or very soft stools each day over the last 7 days*	Sum x 2
Abdominal pain (0=none, 1=mild, 2=moderate, 3=severe) each day over the last 7 days*	Sum x 5
General well being, subjectively assessed (0=generally well, 1=slightly under par, 2=poor, 3=very poor, 4= terrible) each day over the last 7 days*	Sum x 7
Presence of symptoms or findings presumed to related to Crohn's disease**	Score x 20
Taking loperamide, diphenoxylate (Lomotil), or opiates for diarrhea (0=none, 1=yes)	Value x 30
Presence of an abdominal mass (0=none, 2=questionable, 5=definite)	Value x 10
Anemia (male: 47–hematocrit; female: 42-hematocrit)	Value x 6
Percentage deviation from standard body weight (wt)†	100 x (1-current wt/standard wt)
CDAI score	Sum of all above

* Sum of 7 days

** One point each is added for each set of symptoms or findings

- Arthritis or arthralgia
- Iritis or uveitis
- Skin/mouth lesions (erythema nodosum, pyoderma gangrenosum, aphthous stomatitis)
- Peri-anal disease (anal fissure, fistula, or perirectal abscess)
- Other bowel-related fistula
- Febrile (fever) episode over 37.8ºC (100ºF) degrees in the last weak

† Skip this section if weight changes related to Crohn's disease are unknown. Standard body weight = (height in cm – 100) x 0.9

Reference: Best WR, Becktel JM, Singleton JW, Kern F Jr. Development of a Crohn's disease activity index. National Cooperative Crohn's Disease Study. Gastroenterology 1976;70:439-44.

Attachment 3. Harvey-Bradshaw Index (HBI) for Crohn's disease

The Harvey-Bradshaw index is a simpler version of the Crohn's disease activity index (CDAI). It consists of only clinical parameters: The first three items are scored for the previous day. A score of less than 5 is generally considered to represent clinical remission. Mild disease is defined as a score between 5 and 7, moderate disease as a score between 8 and 16, and severe disease is defined as a HBI score > 16.

General well-being (yesterday)	0	Very well
	1	Slightly below par
	2	Poor
	3	Very poor
	4	Terrible
Abdominal pain (yesterday)	0	None
	1	Mild
	2	Moderate
	3	Severe
Number of liquid or soft stools per day (yesterday)	Score 1 per movement	
Abdominal mass	0	None
	1	Dubious
	2	Definite
	3	Definite and tender
Complications (score 1 per item)	1	Arthralgia
	1	Uveitis
	1	Erythema nodosum
	1	Aphthous ulcers
	1	Pyoderma gangrenosum
	1	Anal fissure
	1	New fistula
	1	Abscess
Harvey-Bradshaw Index score	Sum of all above items	

Reference: Harvey RF, Bradshaw JM. A simple index of Crohn's-disease activity. Lancet 1980;1:514.

■ 임상시험계획서 승인

임상시험제목: 염증성 장질환 환자에서 [^{18}F]FSPG 양전자단층촬영술의 안전성, 인체 내 분포 및 진단능에 대한 탐색적 2상, 라벨공개, 비무작위, 단일기관 임상시험

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Principal investigator

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Sponsor's legal representative

Date: Signature: