Statistical Analysis Plan: 18FFAPI-2023P2

Study Title:	A Phase 2, Multicenter, Single Arm, Open Label, Non-Randomized Study of [^{18}F]FAPI-74 PET in Patients with Gastrointestinal Cancers
Study Number:	18FFAPI-2023P2
Study Phase:	Phase 2
Sponsor:	Sofie Biosciences, Inc 21000 Atlantic Boulevard Suite 730 Dulles, VA 20166
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Version History		
Version	**Date**	**Description of Changes**
Original (v1.0)	05AUG2024	Initial version
Amendment [1 (v2.0)]	07OCT2025	Updated Section 5.2 to exclude analyses not specified by the protocol objectives
		Removal of Isotope Used for AUC with Decay from PK parameters in Section 6.4, as it was neither provided nor defined in the data transfer agreement
		Section 10.6.4.1 has been updated to clarify the analysis method used to compute correlations, with the removal of generalized linear models
		The generalized linear approach has been removed from the SAS code presented in Appendix 9

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2 SIGNATURE PAGE

Study Title: A Phase 2, Multicenter, Single Arm, Open Label, Non-Randomized Study of [18F]FAPI-74 PET in Patients with Gastrointestinal Cancers

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3 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	adverse event
ATC	Anatomic Therapeutic Chemical
BMI	body mass index
CFB	change from baseline
CI	confidence interval
CRF	case report form
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DBP	diastolic blood pressure
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
ECOG	Eastern Cooperative Group
eCRF	electronic case report form
EDC	electronic data capturing
EFFS	Efficacy Analysis Set
FAP	fibroblast-activation-protein
FAPI	fibroblast-activation-protein inhibitor
FDG	Fluorodeoxyglucose
GI	Gastrointestinal
IHC	Immunohistochemistry
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
PD	protocol deviation
PET	positron emission tomography
PG	performance goal
PK	Pharmacokinetic
PPV	positive predictive value
PPS	Per Protocol Population Set
PT	preferred term
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SAP	statistical analysis plan

SAS	Safety Analysis Set
SBP	systolic blood pressure
SE	standard error
SOC	system organ class
SUV	standardized uptake value
SUV_{max}	maximum standard uptake value
TBR	tumor-to-background ratio
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
TLF	tables, listings, and figures
WHO	World Health Organization

4 INTRODUCTION

The purpose of this SAP is to describe the framework for the reporting, summarization, and statistical analysis methodology of the safety and efficacy parameters measured throughout the study. It is based on Protocol 18FFAPI-2023P2, Version 5.0, dated 13 Sep 2024.

5 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives and Endpoints

Table 1. Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the PPVs of [^{18}F]FAPI-74 PET images, to detect FAP-expressing cells using IHC	PPV will be determined on a per-lesion basis for all lesions with tissue available for FAP analysis. • Lesions positive for FAP as detected by IHC • Lesions positive for FAP as detected by [^{18}F]FAPI-74 PET imaging
Secondary	
To evaluate PPVs of [^{18}F]FAPI-74 PET images, to detect cancer cells using histopathology as truth standard	PPV will be determined on a per-lesion basis for all lesions with tissue available for histopathology. • Malignant lesions as detected by histopathology • Lesions positive for FAP as detected by [^{18}F]FAPI-74 PET imaging
To further characterize the safety profile of [^{18}F]FAPI-74 PET in subjects utilizing CTCAE Version 5.0	Incidence and severity of TEAEs occurring within 24 hours of [^{18}F]FAPI-74 administration
Exploratory	
[redacted]	

5.2 Estimands

Table 2. Objectives and Estimands

Objectives	Estimand
Primary	
To evaluate the PPV of [18F]FAPI-74 PET images to detect FAP-expressing cells, using IHC as gold standard	a) **Population**: EFFS1 b) **Endpoint**: Positive/negative status according to [18F]FAPI-74 PET and positive/negative status according to IHC for the same lesion (See Section 10.6.1 for instruction on determination of positive/negative status) c) **Population-level summary measure**: • PPV; point estimate, SE, and 95% asymptotic normal CI • Sensitivity; point estimate, SE, and 95% asymptotic normal CI • Specificity; point estimate, SE, and 95% asymptotic normal CI d) **Intercurrent event(s):** There are no intercurrent events.
Secondary	
To evaluate the performance of [18F]FAPI-74 PET imaging to detect FAP-expressing cells, using histopathology as truth standard	a) **Population**: EFFS2 b) **Endpoint**: Positive/negative status according to [18F]FAPI-74- PET and positive/negative status according to histopathology (See Section 10.6.1 for instruction on determination of positive/negative status) c) **Population-level summary measure**: • PPV; point estimate, SE, and 95% asymptotic normal CI • Sensitivity; point estimate, SE, and 95% asymptotic normal CI d) **Intercurrent event(s):** There are no intercurrent events.
To further characterize the safety profile of [18F]FAPI-74 in patients with confirmed GI cancer utilizing CTCAE Version 5.0	a) **Population**: SAS/PKS b) **Endpoint**: Incidence and severity of AEs c) **Population-level summary measure**: Frequency and percentages of patients with each type of AE • TEAEs • Serious TEAEs • TEAEs by maximum severity • Study drug relatedness to TEAEs • TEAEs leading to discontinuation of study • Fatal TEAEs d) **Intercurrent event(s):** There are no intercurrent events.

Exploratory
[redacted]

6 STUDY DESIGN CONSIDERATIONS

6.1 Study Design

This is a prospective, multi-center, single-arm, open-label, non-randomized study to assess the efficacy of administering [18F]FAPI-74 to detect FAP-expressing cells in patients diagnosed with GI cancers, including hepatocellular carcinoma, cholangiocarcinoma, gastroesophageal, pancreatic, and colorectal cancer. The [18F]FAPI-74 PET scans will be acquired in patients with proven GI cancer confirmed after initial staging using institutional standard methods. The results will then be compared to FAP IHC (primary objective) and histopathology (as the secondary objective) of the biopsied or resected tissue. An expanded PK profile of [18F]FAPI-74 will also be obtained in a group of healthy volunteers.

Experimental Design: Phase 2, prospective, multi-center, single-arm, open-label, non-randomized study

Allocation of treatment: Open-label, non-randomized, single-dose intervention

Number of subjects planned: The study will be conducted in 2 cohorts. Cohort A consists of the evaluation of patients with cancers of the GI tract with the goal of establishing efficacy parameters of [18F]FAPI-74. Cohort B consists of an evaluation of the PK parameters and additional safety profile of [18F]FAPI-74 in healthy volunteers.

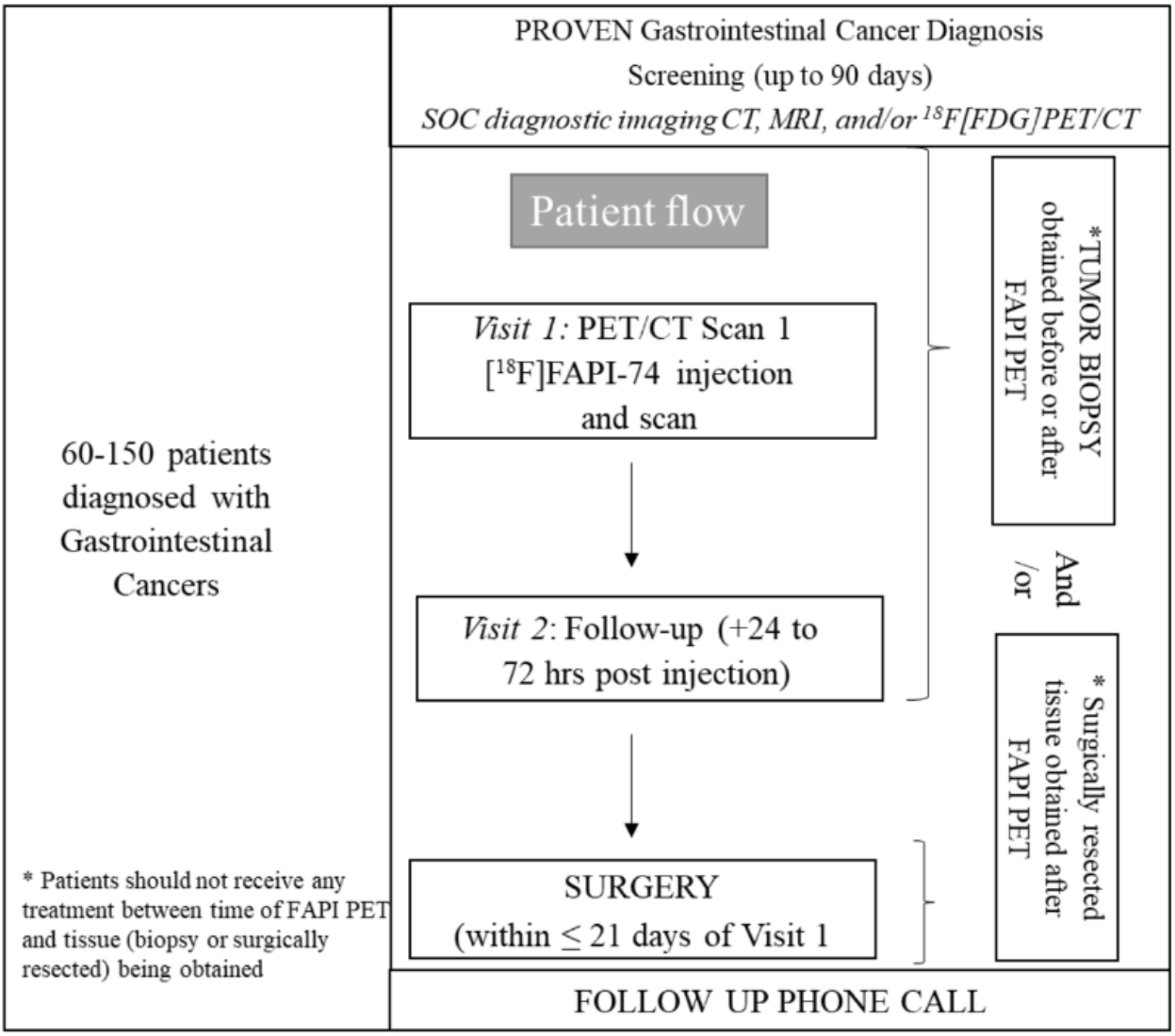
A. Investigational Cohort: 60 to 150 cancer patients in support of the clinical protocol in cancers of the GI tract.

B. Healthy Cohort: Up to 6 healthy volunteers to assess PK, cardiac metrics, and TEAEs in subjects unburdened with known malignancy.

Note applicable to A: In order to have an appropriate number of each cancer type, there will be a minimum of 10 patients enrolled per cancer type. Due to the high incidence rate of colorectal cancer, and to ensure appropriate sampling of various GI cancers, the maximum number of patients of any cancer type in this study will be capped at 60. Enrollment will stop when each tumor type includes at least 10 patients, and the total number of patients is at least 60, with a maximum of 150 patients. Due to low incidence rate of Cholangiocarcinoma, the analysis for Cholangiocarcinoma and Hepatocellular carcinoma will be combined under hepatobiliary cancer with minimum of 10 subjects total.

Summary of Study Visits and Data Collection: Refer to the Schedule of Activities (Appendix 1) for each visit's full requirements as defined for the Investigational Cohort and the Healthy Cohort. The Schema (Figure 1) provides a graphical representation of the study visits for the Investigational Cohort.

Figure 1. Schema for Investigational Cohort



CT = computed tomography; FAPI = fibroblast protein inhibitor ; FDG = fluorodeoxyglucose; hrs = hours; MRI = magnetic resonance imaging; PET = positron emission tomography; SOC = standard of care

Investigational Cohort

Study Day 1 refers to the day the (first) [18F]FAPI-74 PET occurs, Day 2 is the following calendar day, etc. Tissue is obtained from subjects through biopsy and/or surgical resection. Subjects are not to receive any treatment between [18F]FAPI-74 PET acquisition and tissue obtainment.

Screening: Screening assessments can be conducted at multiple visits provided they are within 90 days prior to Study Day 1, including anatomic imaging. Tests performed for standard of care may be used for screening purposes

provided they are within the window. Tissue biopsy may be obtained during the screening period, and standard of care imaging includes MR, CT and/or [18F]FDG PET.

Visit 1: Defines Study Day 1. [18F]FAPI-74 PET scan obtained

Visit 2: 24 to 72 hours after [18F]FAPI-74 injection. Safety assessment with safety labs and, if needed, a symptom-directed physical examination.

Surgery: Surgical resection to occur within 21 days after [18F]FAPI-74 PET scan. Resected tissue should be collected as per laboratory manual. Surgical and pathology reports will be collected. Biopsy tissue obtained within 6 months of [18F]FAPI-74 PET, without any treatment performed between the 2 events, can be accepted for analysis. At the discretion of the sponsor, with additional justification, tissue beyond 6 months can be considered for inclusion. Tissue samples will be assessed for FAP expression and by histopathology analysis.

Surveillance Period: Passive follow-up through chart review to collect information about postsurgical imaging, planned treatment, and outcomes for 14 days postsurgery (or 14 days after Visit 2 for those not receiving surgery).

Healthy Cohort

Screening: Screening assessments can be conducted at multiple visits to assure that the healthy volunteer meets all inclusion and exclusion criteria.

Visit 1: [18F]FAPI-74 PET scan along with PK and ECG assessment performed.

Follow-up: A phone call will occur within 24 - 48 hours to perform a wellness check on the subject to ensure that they have had no AEs. If AEs are reported, they will be captured for the study and reported appropriately.

6.1.1 Safety Review Committee/Data Monitoring Committee

Safety oversight will be under the direction of a DSMB composed of individuals with appropriate expertise. The DSMB will meet at least semi-annually to assess the safety of the study. The DSMB will operate under the scrutiny of an approved charter to be written and reviewed at the organizational meeting of the DSMB.

6.1.2 Justification of Sample Size

The sample size for the Investigational Cohort will be between 60 and 150 subjects in order to provide adequate testing properties overall [redacted]. Six additional healthy volunteers will be enrolled in support of the PK and ECG study.

For this study, the primary efficacy endpoint is PPV by comparing the results from [18F]FAPI-74 PET and IHC in detecting FAP-expressing cells.

For determination of the PPV, a test with appropriate levels of sensitivity is appropriate. This will be demonstrated by the hypothesis test for sensitivity:

H0: Sensitivity ≤ PG

H1: Sensitivity > PG

The minimum sample sizes necessary to achieve desired power for sensitivity were computed for the hypothesis test above utilizing a one-sided significance level of 0.05 and assuming a prevalence of 75.0% of FAP-expressing cells using IHC (gold standard) and the following parametric assumptions:

- PG = 0.75
- True Sensitivity = 0.90

In a one-sided test for sensitivity, a sample size of 60 subjects achieves 84.15% power at the 0.05 one-sided significance level when the sensitivity under the null hypothesis is 0.75 and the sensitivity under the alternative hypothesis is 0.9, assuming a condition prevalence of 75.0%.

It is expected that the sample size will be larger than 60 based on the goal of having 10 subjects for each cancer type, with a maximum of 150 total subjects. Due to low incidence rate of Cholangiocarcinoma, the analysis for Cholangiocarcinoma and Hepatocellular carcinoma will be combined under hepatobiliary cancer with minimum of 10 subjects total.

6.2 Efficacy Measures

Refer to Section 10.6 for a complete description of the efficacy analyses.

6.2.1 Primary Efficacy Measures

The primary efficacy endpoints will compare on a per-lesion basis the results from the [18F]FAPI-74 PET performed at Visit 1 and the IHC performed at Screening.

The Positive/Negative status according to [18F]FAPI-74 PET and Positive/Negative status according to IHC will be determined based on a prespecified cut-off value for each appropriate test (see Appendix 7) as determined by the clinician.

The primary analysis of PPV will be summarized using frequency counts and percentages as well as 95% asymptotic normal CIs.

6.2.2 Secondary Efficacy Measures

The secondary efficacy endpoint will compare on a per-lesion basis the results from the [18F]FAPI-74 PET performed at Visit 1 with the histopathology performed at Screening, instead of IHC. This will be conducted on a per-lesion basis in the same manner as the primary analysis, where in this case histopathology will be considered the gold standard.

6.2.3 Exploratory Efficacy Measures



6.3 Safety Measures

All subjects who receive any amount of [18F]FAPI-74 will be included in the final summaries and listings of safety data (SAS).

The safety endpoints to be analyzed include:

- Frequency of TEAEs from injection to 24 hours postinjection
- Frequency of TESAEs from injection to 24 hours postinjection
- Frequency of TEAEs by maximum severity

- Frequency of TEAEs related to study drug
- Frequency of TEAEs among subjects who discontinued study early
- Frequency of fatal TEAEs
- Clinical laboratory results, including hematology and serum chemistry
- Vital signs, including body temperature, respiratory rate, SBP, DBP, and heart rate
- Physical examination results where necessary

6.4 Pharmacokinetic Measures/Parameters

A cohort of up to 6 healthy volunteers will undergo PK and ECG assessments as outlined below. Details are provided in the PK and ECG Manual. This design has been adopted from the PK and ECG assessment performed by Progenic Pharmaceuticals (2021).

A 4.5 mL blood sample will be collected at the following 9 time points: predose; 5 ± 2 minutes; 15 ± 2 minutes; 30 ± 5 minutes; 1 ± 0.25 hours; 2 ± 0.25 hours; 4 ± 0.25 hours; 6 ± 0.25 hours; and 8 ± 0.25 hours postdose. Urine samples will be collected over the following intervals: 0 to 2 hours, 2 to 4 hours, and 4 to 8 hours postdose. Whole body PET/CT scans will be collected at 3 timepoints: up to 17 minutes after [^{18}F]FAPI-74 injection and prior to voiding; 1 ± 0.25 hours; and 4 ± 0.25 hours postdose.

PK parameters to be included are as follows:

Blood

- Distribution Half-Life
- Elimination Half-Life
- Max Concentration
- Elimination Volume of Distribution
- Central Volume of Distribution
- AUC Total
- AUC t-infinity
- AUC data
- AUC Total including isotope decay
- AUC t-infinity including isotope decay
- AUC data including isotope decay
- Blood clearance rate

Urine

- Total radiation activity in the urine volume collected over the collection interval

- Cumulative radiation activity in urine collected up until each timepoint

A 12-lead ECG will be taken at 2 intervals on the day of dosing. The predose ECG should be evaluated prior to dosing by the investigator or delegated team member. In the absence of clinically significant symptoms, the postdose ECG may be reviewed by the investigator, delegated team member, or per the site's usual clinical practice. If either ECG is machine-interpreted as other than normal and clinically significant, the ECG must be evaluated by a cardiologist or qualified site designee for subject safety at a turn-around time chosen at the investigator's discretion. Refer to Appendix 2 for a Schedule of Assessments and Procedures for the PK analysis.

ECG parameters to be included are as follows:

- Heart Rate
- PR Interval
- QRS Interval
- QT Interval
- QTcB Interval
- QTcF Interval
- RR interval

7 STUDY POPULATIONS

7.1 Analysis Populations

7.1.1 All Enrolled Subjects

All subjects who provide informed consent and meet all eligibility criteria will be included under the All Enrolled Subjects population.

Of the enrolled subjects, individual listings will be created, presenting which analysis populations one is included in and the reasons for exclusion from the ones they are not a part of.

7.1.2 Safety Analysis Set (SAS)

All subjects who received any amount of [18F]FAPI-74. The SAS will be used for all safety evaluations.

7.1.3 Efficacy Analysis Sets

Subjects with invalid [18F]FAPI-74 PET data will be excluded from the efficacy analyses. Thus, to be included in the efficacy populations, subjects must have a response of "Yes" to the FAPI Imaging CRF question that reads "Is Image of technical quality for interpretation". Subjects with missing or invalid IHC (standard of truth) data will also be excluded.

7.1.3.1 Efficacy Analysis Set 1 (EFFS1)

All subjects who received [18F]FAPI-74 with interpretable FAPI-74 PET image results (positive or negative) for at least 1 lesion with corresponding IHC results (positive or negative). For subjects with multiple PET scans, only 1 PET scan will be considered for analysis, where the most recent 1 performed prior to surgery will take precedence.

7.1.3.2 Efficacy Analysis Set 2 (EFFS2)

All subjects who received [18F]FAPI-74 with interpretable FAPI-74 PET image results (positive or negative) for at least 1 lesion with corresponding histopathology results (positive or negative).



7.1.4 Per Protocol Analysis Set (PPS)

All subjects in the SAS who complete the study according to the protocol with no critical or major protocol deviations. The decisions regarding critical and major protocol deviations, and the definition of the analysis set, will be finalized prior to database lock.

7.1.5 Pharmacokinetic Analysis Set (PKS)

This population consists of all subjects enrolled in the Healthy Cohort, with at least 1 available postdose drug concentration for the purpose of delineating the PK and cardiac metrics of [18F]FAPI-74.

7.2 Subgroups

No formal subgroup analyses will be conducted for this study.

8 CHANGES IN CONDUCT OR PLANNED ANALYSES FROM THE PROTOCOL

Protocol	SAP	Description
Section 1.1; Section 1.4, Section 6.1, and Section 6.2	Section 5.2; Section 6.1; Section 6.4; Section 7.1.5; Appendix 2	Protocol amended to incorporate inclusion of a Healthy Cohort of 6 subjects to allow for PK analysis and to further assess safety.
Section 6.1 and Section 6.2.1	Section 6.1.2.	Due to low incidence rate of cholangiocarcinoma, the analysis for cholangiocarcinoma and hepatocellular carcinoma will be combined under hepatobiliary cancer with a minimum of 10 subjects total needed to fulfill study's recruitment requirements.
Section 8.3.2	Section 10.6.3	Due to there being only a single reader, intra- and inter-reader agreement analyses are no longer to be conducted

PK = pharmacokinetics.

9 OVERALL STATISTICAL CONSIDERATIONS

9.1 General Conventions

Statistical testing for PPV and sensitivity will be one-sided and performed at the 0.05 level.

Summary statistics will be presented for categorical data as number and percentage (n [%]) where the percentage is displayed to 1 decimal point (eg, 98.1).

Descriptive statistics will be presented for continuous data with applicable decimal precision as follows in relation to the source data (indicated as N + x), with a maximum of 3 decimals to be displayed:

Number (n)

Mean, (N + 1)

SD, (N + 2)

Median, (N + 1)

Minimum, (N + 0)

Maximum, (N + 0)

9.2 Adjustment for Multiplicity

No alpha adjustment is required in this study for statistical testing.

9.3 Baseline Definition

Baseline for a given parameter is defined as the last non-missing evaluation before the first dose of [18F]FAPI-74.

9.4 Handling of Partial Dates

There will be no imputation for missing data unless explicitly specified. Rules for partial and missing dates for AEs and medications are given in Appendix 4.

9.5 Interim Analysis

No formal interim analysis is planned for this study.

9.6 Pooling Strategy for Study Sites

Subject data will be reported under the site recorded into the EDC database and then pooled for analysis purposes.

9.7 Visit Windows/Unscheduled Visits

The study date and corresponding study visits will be captured on each eCRF. Safety analyses will use the nominal visits as collected in the study database; therefore, such analyses will not utilize visit windows.

Unscheduled visits will not be included in by-visit summaries or analyses but may contribute to baseline and worst postbaseline assessments.

The following visit convention will be used for by-visit efficacy TLFs. Refer to Section 6.1 for an extensive description of each visit.

Table 3. Visit Windows by Cohort

Investigational Cohort	
Visit Description/Window	**Visit Format Within TLFs**
≤ 90 days of Day 1	Screening*
Study Day 1	Visit 1*
+ 24 to 72 hours postinjection	Visit 2
≤ 21 days of PET scan	Surgery
14 days following surgery	Surveillance
Any unscheduled visit	Unscheduled
End of study assessments	End of Study
Healthy Cohort	
Visit Description/Window	**Visit Format Within TLFs**
≤ 30 days of Day 1	Screening*
Study Day 1	Visit 1*

TLF = tables, listings, and figures
*Depending on the assessment, if considered a baseline value at that visit, then the visit will be renamed to "Baseline" for statistical summaries.

10 STATISTICAL ANALYSIS METHODS

Note: All pertinent summaries and listings in this study will be presented separately by cohort.

10.1 Subject Disposition

All screened subjects who provided informed consent will be accounted for in the study. The frequency and percentage will be summarized for subjects in the following disposition categories:

- Subjects who were screened, enrolled, and completed the study
- Subjects in each analysis population
- Subjects who discontinued prematurely along with reason for study discontinuation (progressive disease; AE; death; protocol deviation; physician decision; sponsor request; withdrawal by subject; lost to follow-up; study terminated by sponsor; subject non-compliance; or other)

A listing of all the screened subjects, indicating date of eligibility, reason for screen failure, date of study completion or discontinuation, and reason for discontinuation will be provided.

10.2 Protocol Deviations

Summary statistics including frequency and percentage of subjects in the SAS with major PDs for each deviation category will be provided. A subject with multiple occurrences of a major PD in the same deviation category will only be counted once in that category. A listing of PDs will be provided for all subjects in the SAS, including the PD classification (major or minor).

10.3 Demographics and Baseline Characteristics

The list below enumerates the demographic and baseline characteristic variables that will be summarized for subjects in the SAS.

- Age (years): Age will be used as calculated in the database.
- Sex (Female, Male, Unknown, Declined)
- Childbearing potential among females
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Unknown, Declined)
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Not Reported, Unknown, Multiracial, Declined, Other)
- Height (cm) at screening
- Weight (kg) at screening
- BMI (kg/m^2) at screening. BMI will be derived by using the following formula:

$$BMI = Weight\ (kg)/[Height\ (m)]^2$$

- Childbearing potential (Yes, No)
- ECOG performance status at baseline (0, 1, 2, 3, 4, 5)
- Cancer diagnosis type

For continuous parameters, mean, standard deviation, median, minimum, and maximum will be displayed. Categorical data will be presented using numbers and percentages. The denominators for percentages will be the number of subjects in the SAS, with non-missing data for the variable of interest. A listing for subject demographics based on the SAS will also be produced.

10.3.1 ECOG Performance Status

ECOG performance status scale (Table 9) will be used to evaluate subject performance at screening (pretreatment) and on the day of administration (pretreatment).

ECOG performance status will be included in the aforementioned listing designated for demographic and baseline characteristics.

The data for these presentations will be obtained from the ECOG performance status eCRF.

10.3.2 Medical and Surgical History

Medical history, including surgical history, will be coded using MedDRA Version 25.1. Medical history will be listed individually by SOC and PT for the SAS.

No imputation of partial or missing dates will be performed for medical history and study days will not be presented for these cases.

10.4 Prior and Concomitant Medications and Procedures

Prior and concomitant medications will be coded using Version B3, Mar 2022 of the WHO Drug Dictionary. Prior medications are defined as any treatment whose use started before the day of first study treatment administration. Concomitant medications are defined as any therapy used on or after the same day as the first dose of treatment, including those that started before the first dose of study intervention. A medication may be considered both prior and concomitant.

Partial and missing dates for medications will be imputed using the guidance in Table 7. The recorded partial/missing dates will be displayed in the listings, and study days will not be presented for these cases.

Prior and concomitant medications will be listed separately by subject for the SAS.

Concomitant non-pharmacologic treatments/procedures will be coded using MedDRA Version 25.1 and will be listed by subject for the SAS. The listing will include procedure

number, SOC, PT, procedure name, primary reason for treatment/procedure, medical history number, AE number, indication, treatment/procedure date, and concomitant medication number (if applicable).

10.5 Study Drug [18F]FAPI-74 Administration and PET Scan

The proportion and percentage of subjects receiving dose and corresponding image quality will be summarized for the SAS.

A listing displaying each dose of [18F]FAPI-74, including the date and time of study drug administration, dose (mCi), date of image, imaging start time, and image quality will be provided for the SAS.

PET Visual Assessment

Image quality will be presented using numbers and percentages for each category (optimal, readable but not optimal, not readable). The denominators for percentages will be the number of subjects with non-missing imaging data.

10.6 Efficacy

Efficacy analyses will be presented overall and by tumor type.

10.6.1 Primary Analysis

The primary analysis will evaluate the performance (measured by PPV) of [18F]FAPI-74 PET images to detect FAP-expressing cells, using IHC as the gold standard.

The primary efficacy endpoints will compare positive/negative status from [18F]FAPI-74 PET and IHC, and the analysis will be based on the EFFS1, as defined in Section 7.1.2. Positive and negative PET and IHC status will be determined using the client-provided criteria found in Appendix 7.

The table below presents a visualization of how PPV and sensitivity are calculated. In a traditional 2 x 2 table the IHC column would be comprised by the health outcome in question; but here it is replaced by IHC since IHC is considered the truth standard for GI cancer diagnosis, allowing it to be equated to disease status.

Table 4. [18F]FAPI-74 PET vs IHC

		IHC		
		Positive	Negative	Total
[18F]FAPI-74 PET	Positive	A	B	A + B
	Negative	C	D	C +D
	Total	A + C	B + D	N
A = true positive; B = false positive; C = false negative; D = true negative; IHC = immunohistochemistry; PET = positron emission tomography. N indicates the number of patients with FAPI-74 and corresponding IHC results.				

The PPV is defined as the probability that one is indeed positive for an outcome given that they test positive for the outcome and is calculated as follows:

$$PPV = A / (A + B)$$

The sensitivity, the probability that one tests positive for a given outcome given that they indeed are positive for the outcome, is calculated as follows:

$$Sensitivity = A / (A + C)$$

The specificity, the probability that one tests negative for a given outcome given that they indeed are negative for the outcome, is calculated as follows:

$$Specificity = D / (B + D)$$

The point estimate, SE, and both the 90% and 95% asymptotic normal CIs will be presented for PPV, sensitivity, and specificity. Furthermore, these estimates will be presented overall for all positive IHC results, as well as by positive results with stricter cutoffs categorized as moderate to high and high according to the reference ranges found in Appendix 7.

Inference for the primary hypotheses will be conducted utilizing a one-sample binomial proportion test with a normal approximation, a one-sided significance level of 0.05, and assumed null proportion/performance goal of 0.75 for sensitivity. Success for the primary efficacy analysis will be defined as demonstrating that the PPV is greater than that of IHC. The one-sided asymptotic p-value will be provided for sensitivity. Refer to Appendix 9 for SAS code to determine estimates and CIs.

10.6.2 Key Secondary Analysis

The first secondary analysis will determine the PPV and sensitivity of [18F]FAP-74 PET imaging using histopathology as the truth standard. Similar to the method employed to determine

positive/negative status for IHC, the PPV and sensitivity will be calculated by using the same logic as Table 4, and the analysis will be based on the EFFS2.

The point estimate, SE, as well as the 95% asymptotic normal CI will be presented for PPV and sensitivity.

Inference for the secondary analyses will be conducted utilizing a one-sample binomial proportion test with a normal approximation, a one-sided significance level of 0.05, and assumed null proportion/performance goal of 0.75 for sensitivity. Success for this secondary analysis will be defined as demonstrating that the PPV is greater than that of histopathology. The one-sided asymptotic p-value will be provided for sensitivity. Refer to Appendix 9 for SAS code to determine estimates and CIs.

10.6.3 Other Secondary Analyses

Refer to Section 10.8 for the safety analyses .

10.6.4 Exploratory Analyses

10.6.4.1 Exploratory Analysis #1

[redacted]

10.6.4.2 Exploratory Analyses #2

[redacted]

10.6.4.3 Other Exploratory Analyses

[redacted]



10.6.5 Efficacy Analysis Listings

For the myriad diagnostic techniques employed to the end of this study's efficacy objectives, listings will also be provided to enumerate individual results for the given parameters associated with each technique The analysis set that these will be presented for depends on the listing and the associated diagnostic test.

10.6.6 Interim Analysis

No formal interim analysis is planned for this study.

10.7 Pharmacokinetics

A PK assessment including a 12-lead ECG will be performed for the Healthy Cohort. Summary tables will be constructed presenting CFB by timepoint for PK plasma concentrations, along with separate ones for PK and ECG parameters. Accompanying subject listings will also be presented. Individual line plots displaying concentrations by timepoint will also be displayed for the plasma samples, both on a linear and a semi-log scale.

10.8 Safety and Tolerability

All safety analyses will be based on the SAS for the Investigational Cohort.

Safety variables will be summarized by visit, overall, and by tumor type, where applicable.

10.8.1 Adverse Events

AE assessment is designated for the Investigational Cohort only. The verbatim terms used in the eCRF to identify AEs will be coded using MedDRA Version 25.1. AE severity will be evaluated utilizing the CTCAE Version 5.0 [Appendix 6])

For the purposes of this study, the AE collection window is from the time of [18F]FAPI-74 administration through minimum 10 half-lives or 24 hours postinjection. If the 24-hour window ends on a holiday or nonclinic day (or the subject cannot return to clinic due to unforeseen circumstances, such as weather), the window may be extended until 72 hours postinjection. AE summaries will be limited to AEs collected 24 hours postinjection.

A TEAE overview table containing the frequency and percentage of subjects, as well as the number of reported events in each of the following categories, will be presented:

- TEAEs
- TEAE by maximum toxicity grade (CTCAE Version 5.0)
- Serious TEAEs
- Study drug related TEAEs
- Serious study drug related TEAEs
- TEAEs leading to study discontinuation
- Fatal TEAEs

Additionally, the following will be summarized by SOC and PT:

- TEAEs
- Serious TEAEs
- TEAEs by maximum toxicity grade (CTCAE Version 5.0)
- Study drug related TEAEs
- TEAEs leading to study discontinuation
- Fatal TEAEs

Summaries of TEAEs by SOC and PT will be sorted alphabetically by SOC and by decreasing frequency of PT overall. If a subject has more than 1 TEAE at a given level (eg, SOC and/or PT), the subject will only be counted once within that level. When summarizing TEAEs by maximum severity, at each level of summarization, subjects who report 1 or more TEAEs within that level are only counted once at that level using the event of greatest severity (in severity tables). Subjects who have reported TEAEs that are missing severity or relationship to study drug will not be summarized in the tables by severity or relatedness; however, they will be included in the listings of AEs and tables not summarized by severity or relatedness. All tables will show the number and percent of subjects with at least 1 TEAE (or SAE, per the criteria in the table).

The following listings will be provided:

- Listing of all TEAEs
- Listing of subjects with serious TEAEs
- Listing of subjects with TEAEs leading to study discontinuation

- Listing of subjects with TEAEs leading to death

Refer to Section 7.2 in Protocol Version 5.0, 13 Sep 2024, for AE definitions applicable to this study. This includes definitions for the following: AEs, life-threatening AEs or life-threatening suspected adverse reactions, serious AEs or serious suspected adverse reactions, suspected adverse reactions, unsuspected AEs or unexpected suspected adverse reactions, routine AEs, AEs leading to study discontinuation, and AEs attributable to investigation medical product and study procedures.

The data for these presentations will be obtained from the Adverse Events Details eCRF.

10.8.2 Clinical Laboratory

Descriptive statistics for continuous variables will be presented in separate outputs for serum chemistry and hematology at scheduled time points (including observed values and CFB).

Shift tables will be provided for each parameter illustrating how laboratory values fluctuate from baseline and by visit. These values will be classified according to an assigned reference range, where the result will be considered low, normal, or high. For the by-visit shift summary, the denominator is the number of subjects with non-missing values at baseline and the given visit for the given parameter.

Detailed subject listings of all laboratory data collected during the study will be provided. Laboratory values outside of normal range will be identified in these subject listings. A listing of subjects with at least one abnormal laboratory value will be provided separately. These will be provided for all chemistry, hematology, tumor biomarker, and urinalysis (pregnancy test) labs.

The following is a summary of laboratory result items planned for table presentation for each applicable visit:

- Serum Chemistry
    - CFB with descriptive statistics
    - Shift from Baseline with summary statistics
- Hematology
    - CFB with descriptive statistics
    - Shift from Baseline with summary statistics

A list of local laboratory assays planned to be performed can be found in Table 7. The data for these myriad presentations will be obtained from the following eCRFs:

- Chemistry
- Hematology
- Tumor Biomarkers
- Pregnancy Test

10.8.3 Vital Signs

Continuous vital sign parameters including body temperature (°C), respiratory rate (breaths/min, SBP (mmHg), DBP (mmHg), and heart rate (bpm) will be summarized at each scheduled assessment time point. Due to the nomenclature of the raw data in the CRFs, heart rate will be referred to as "pulse rate" in tables and listings.

CFB for the continuous parameters will be summarized alongside their descriptive statistics (n, mean, SD, Q1, Q3, median, minimum, maximum).

A detailed subject listing of all vital sign data collected during the study will be provided.

The data for these presentations will be obtained from the Vital Signs eCRF.

10.8.4 Physical Examinations

A listing of physical examination findings and continuous data including height (cm), weight (kg), and BMI (kg/m^2) will be presented.

BMI will be calculated as BMI (kg/m^2) = weight (kg)/[height (m)]^2, at each time point. The height measurement collected at screening will be used in the calculation.

The data for these presentations will be obtained from the Physical Examination eCRF.

11 REFERENCES

Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982; 5:649-655.

Progenics Pharmaceuticals. (2021). Study of 18F-DCFPyL PET/CT Imaging in Patents with Suspected Recurrence of Prostate Cancer (CONDOR). https://clinicaltrials.gov/study/NCT03739684#moreinfo. Updated: 14Jun2021. Accessed: 14Nov2024.

12 APPENDICES

APPENDIX 1. SCHEDULE OF ACTIVITIES - INVESTIGATIONAL COHORT

Note: Days are counted as calendar days unless otherwise specified. The day before Study Day 1 is Day -1.

Study Procedure	Screening ≤ 90 days of Day 1	Visit 1 Study Day 1	Visit 2[j] + 24 to 72 hours postinjection	Surgery ≤ 21 days of PET scan	Surveillance Period (14 days)[h]
Informed consent	X				
Complete medical history, including surgical history	X				
Standard of care imaging: CT, MR and/or [18F]-FDG PET	X				
Concomitant medications	X	X	X		
Physical examination[a]	X		X[f]		
ECOG performance status	X	X			
Vital signs[b]	X	X	X[f]		
Serum chemistries[c]	X	X[k]	X		
CBC with differential		X[k]	X		
Tumor biomarkers (eg, CA-19-9, CEA)[d]	X	As per standard of care			
Assessment of tumor burden[d]	X				
Urine pregnancy test[e]	X	X[k]			
Baseline signs and symptoms		X			
Study drug [18F]FAPI-74 administration and PET scan		X			
Capturing administered treatments				X	X
AE assessment[i]		X	X		
Tissue obtained through core biopsy and/or surgical resection	X[g]	As per standard of care			

a AE = adverse event; ALT = alanine aminotransferase; ALP = alkaline phosphatase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CBC = complete blood count; CEA = carcinoembryonic antigen; CT = computed tomography; ECOG = Eastern Cooperative Group; FAPI = fibroblast-activation-protein inhibitor; FDG = fluorodeoxyglucose; MRI = magnetic resonance imaging; PET = positron emission tomography

b Includes height and weight. Height collected only during the screening window.

c Temperature, blood pressure, respiratory rate, and pulse rate. Obtain twice on day of imaging: once prior to injection and once postinjection prior to

discharge

d Glucose, Na, K, Cl, Carbonate (CO_2), Ca, BUN, creatinine, AST, ALT, ALP, total protein, albumin, and total bilirubin

e Frequency and type of test as per institutional standard of care; tumor burden assessment is obtained from surgical, pathology and/or imaging reports

f As per institution's practice. If urine pregnancy test is inconclusive, a serum pregnancy test must be performed with results reviewed prior to study drug administration

g Only if necessary for AE assessment; symptom directed exam is acceptable

h Tissue obtained through core biopsy and/or surgical resection. No treatment is to take place between time of FAPI scan and tissue being obtained. In the event of surgery, the subject is expected to receive surgery within ≤ 21 days of FAPI PET scan. IHC and histopathology will be at a central lab

i Passive follow-up only through chart review to collect information about postsurgical imaging, planned treatment, and outcomes. Fourteen days postsurgery for subjects who undergo surgery. Fourteen days post Visit 2 for subject who do not undergo surgery

j AE assessments will be performed 24 hours post [^{18}F]FAPI-74 injection.

k Follow-up visits may be performed through televisits. Subjects may utilize institution approved local labs/mobile clinics for blood draws as part of follow-up assessment. Subjects may enter surgery < 24 hours postinjection if the time of Visit 2 follow-up assessment is 10 half-lives or more post [^{18}F]FAPI-74 injection.

l Labs obtained during screening period, within 72 hours of Day 1, can be used as preFAPI-74 injection Day1 lab data

APPENDIX 2. SCHEDULE OF ACTIVITIES - HEALTHY VOLUNTEER COHORT

Note: Days are counted as calendar days unless otherwise specified. The day before Study Day 1 is Day -1.

Study Procedure	Screening ≤ 30 days of Day 1	Visit 1 Study Day 1
Informed consent	X	
Complete medical history, including surgical history	X	
Concomitant medications	X	X
Physical examination[a]	X	
Vital signs[b]	X	X
Serum chemistries[c]	X	X[f]
CBC with differential		X[f]
Urine pregnancy test[e]	X	X[f]
Baseline signs and symptoms		X
Study drug [18F]FAPI-74 administration and PET scan		X
PK and ECG assessment	X[g] As per Section 6.1	

a ALT = alanine aminotransferase; ALP = alkaline phosphatase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CBC = complete blood count; ECG = electrocardiogram; FAPI = fibroblast-activation-protein inhibitor; PET = positron emission tomography

b Includes height and weight. Height collected only during the screening window

c Temperature, blood pressure, respiratory rate, and pulse rate. Obtain twice on day of imaging: once prior to injection and once postinjection prior to discharge

d Glucose, Na, K, Cl, Carbonate (CO_2), Ca, BUN, creatinine, AST, ALT, ALP, total protein, albumin, and total bilirubin

e As per institution's practice. If urine pregnancy test is inconclusive, a serum pregnancy test must be performed with results reviewed prior to study drug administration

f Labs obtained during screening period, within 72 hours of Day 1, can be used as preFAPI-74 injection Day1 lab data

g Six healthy volunteers will go through a PK and ECG assessment according to outlined process in Section 6.1. These subjects will undergo a subset of screening as outlined above. These subjects will end their participation at the end of the PK and ECG assessment

APPENDIX 3. SCHEDULE OF ASSESSMENTS AND PROCEDURES FOR PHARMACOKINETIC ANALYSIS

Procedure	Predose	0 hr	5 ± 2 m	15 ± 2 m	30 ± 5 m	1 ± 0.25 hr	2 ± 0.25 hr	3 ± 0.25 hr	4 ± 0.25 hr	6 ± 0.25 hr	8 ± 0.25 hr
[18F]FAPI-74 Dose Administration		X									
[18F]FAPI-74 PET/CT			X			X			X		
Blood and Plasma Collection	X		X	X	X	X	X		X	X	X
Urine Collection			X				X		X		
ECG	X		X								

CT = computed tomography; ECG = electrocardiogram; FAPI = fibroblast-activation-protein; PET = positron emission tomography

APPENDIX 4. IMPUTATION OF PARTIAL DATES

Table 5. Imputation Rules for Partial Dates – Adverse Events

Parameter	Missing	Additional Condition	Imputation
Start Date	D only	M and Y are prior to first study drug dose	First day of indicated month
		M and Y is same as first study drug dose	Date of first study drug dose
		M and Y are after first study drug dose	First day of indicated month
	M and D	Y is prior to first study drug dose	01 Jan of indicated year
		Y is same as first study drug dose	Date of first study drug dose
		Y is after first study drug dose	01 Jan of indicated year
	M, D, and Y	-	assumed to be TEAE
End Date	D only	M and Y are prior to last study drug dose	Last day of indicated month
		M and Y is same as last study drug dose	Date of last observation
		M and Y are after last study drug dose	First day of indicated month
	M and D	Y is prior to last study drug dose	31 Dec of indicated year
		Y is same as last study drug dose	Date of last observation
		Y is after last study drug dose	01 Jan of indicated year
	M, D, and Y	-	TEAE is ongoing
	-	Estimated end date is before a complete or imputed AE start date	Last day of the month of AE start date

AE = adverse event; D = day; M = month; Y = year; TEAE = treatment-emergent adverse event.
Note: The imputation of end date must be later than start date.

Table 6. Imputation Rules for Partial Dates – Prior and Concomitant Medications

Parameter	Missing	Additional Condition	Imputation
Start Date	D only	M and Y same as M and Y of first study drug dosing	Date of first study drug dose
		M and/or Y not the same as M and Y of first study drug dosing	First day of indicated month
	M and D	Y same as Y of first study drug dosing	Date of first study drug dose
		Y not the same as Y of first study drug dosing	01 Jan of indicated year
	M, D, and Y	none – date completely missing	Date of first study drug dose
End Date	D only	M and Y same as M and Y of last study drug dosing	Date of last study drug dose
		M and/or Y not the same as M and Y of last study drug dosing	Last day of indicated month
	M and D	Y same as Y of last study drug dosing	Date of last study drug dose
		Y not the same as Y of last study drug dosing	31 Dec of indicated year
	M, D, and Y	none – date completely missing	Date of last study drug dose

D = day; M = month; Y = year

APPENDIX 5. PLANNED LABORATORY ASSAYS

Table 7. Planned Laboratory Assays

Laboratory Category	Assay Grouping	Assay
Chemistry	Electrolytes	Glucose
		Potassium
		Sodium
		Calcium
		Chloride
		Magnesium
		Bicarbonate
	Renal function	BUN
		Creatinine
	Liver function	ALT
		AST
		Albumin
		ALP
		Total bilirubin
		Total protein
Hematology		Platelet count
		Hemoglobin
	WBC count with differential	Neutrophils – absolute
		Lymphocytes – absolute
		Monocytes – absolute
	Coagulation	INR
Tumor Biomarker		Cancer Antigen 19-9
		Carcinoembryonic Antigen
		C-Reactive Protein
		Possible Other

ALT = alanine aminotransferase; ALP = alkaline phosphatase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; INR = International Normalized Ratio; WBC = white blood cell

APPENDIX 6. NATIONAL CANCER INSTITUTE COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (NCI CTCAE) VERSION 5.0

The NCI CTCAE Version 5.0 can be found by going to the following web site:
http://ctep.cancer.gov/reporting/ctc.html

Inquiries specifically regarding the Common Toxicity Criteria (CTC) should be addressed to:
ncictephelp@ctep.nci.nih.gov

APPENDIX 7. CRITERIA FOR POSITIVITY

Table 8. Criteria for Positivity

Test	Parameter	Category	Criteria
[^{18}F]FAPI-74 PET	SUV_{max}	Positive	≥ 3
		Negative	< 3
Immunochemistry	H-score	Negative	≤ 50
		Weak	1 - 50
		Positive	> 50
		Low	51 - 100
		Moderate	101 - 200
		High	> 200
Histopathology	Biopsy	Positive	Presence of tumor

FAPI = fibroblast-activation-protein inhibitor; PET = positron emission tomography; SUV_{max} = standard uptake value max

APPENDIX 8. EASTERN COOPERATIVE GROUP (ECOG) PERFORMANCE STATUS SCALE

Table 9. ECOG Performance Status

ECOG PERFORMANCE STATUS*	
Grade	**ECOG**
0	Fully active, able to carry on all predisease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light housework, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead
ECOG = Eastern Cooperative Group * From ECOG (Oken et al., 1983)	

APPENDIX 9. SAS CODE TO DETERMINE EFFICACY ESTIMATES AND CIS



Code for the inferences of the primary hypothesis (asymptotic one-sided test) for Sensitivity:

```
title 'Sensitivity’:
PROC FREQ DATA = RESULT;
  WHERE IMAGE = 0;
  TABLES PET/binomial(level = "1" P = 0.75);
  RUN;
```

Code for the inferences for the secondary and exploratory analyses testing for the [redacted]