
Statistical Analysis Plan: GaFAPI-2022P2

Study Title: A Phase 2, Multicenter, Single Arm, Open Label Non-Randomized Study of [⁶⁸Ga]FAPI-46 PET in Patients with Resectable or Borderline Resectable Pancreatic Ductal Carcinoma

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2 SIGNATURE PAGE

Study Title: A Phase 2, Multicenter, Single Arm, Open Label Non-Randomized Study of [⁶⁸Ga]FAPI-46 PET in Patients with Resectable or Borderline Resectable Pancreatic Ductal Carcinoma

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3 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	adverse event
ATC	Anatomic Therapeutic Chemical
BMI	body mass index
CA125	cancer antigen 125
CA19-9	cancer antigen 19-9
CEA	carcinoembryonic antigen
CFB	change from baseline
CI	confidence interval
CR	complete response
eCRF	electronic case report form
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DBP	diastolic blood pressure
DSMC	Data and Safety Monitoring Committee
ECOG	Eastern Cooperative Group
EDC	electronic data capturing
EFFS	Efficacy Analysis Set
FAP	fibroblast activation protein
FAPI	fibroblast-activation-protein inhibitors
FDA	Food and Drug Administration
FDG	fluorodeoxyglucose
GCP	good clinical practice
ICH	International Council for Harmonisation
IHC	immunohistochemistry
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NAT	neoadjuvant therapy (chemotherapy, radiation therapy, or both)
NPV	negative predictive value
PD	protocol deviation(s)

PDAC	pancreatic ductal adenocarcinoma
PET	positron emission tomography
PG	performance goal
PPV	positive predictive value
PPS	Per protocol analysis set
PR	partial response
PT	preferred term
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Safety analysis set
SBP	systolic blood pressure
SD	standard deviation
SOC	system organ class
SUV	standardized uptake value
SUV _{max}	maximum standardized uptake value
SUV _{mean}	mean standardized 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 GaFAPI-2022P2, Version 5.0 dated 31 Mar 2023.

5 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives and Endpoints

Table 1. Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the performance of [⁶⁸ Ga]FAPI-46 PET ^a imaging to detect FAP-expressing cells, using histopathology as truth standard.	Sensitivity to detect PDAC will be determined on a per-patient basis. Primary lesion confirmed as positive by histopathology and assessed as positive by the blinded reader will be considered as True Positive (TP). Primary lesion confirmed as positive by histopathology and but not identified by the blinded reader will be considered as False Negative (FN). Sensitivity will be calculated as: TP / (TP + FN).
Secondary	
To correlate the histopathology with FAP staining on FAP IHC assay.	<p>Staining intensity assessed by IHC, using H-score, correlated to the uptake of [⁶⁸Ga]FAPI-46, using SUV_{max}</p> <ul style="list-style-type: none"> Lesions positive for FAP as detected by IHC with available SUV_{max} <p>Note: SUV_{mean} will also be compared to IHC H-score for exploratory purposes.</p>
To further characterize the safety profile of [⁶⁸ Ga]FAPI-46 in patients with PDAC.	Incidence and severity of TEAEs or TSEAEs according to MedDRA/CTCAE V.5.0
Exploratory	
To compare the detection of local and metastatic disease using [⁶⁸ Ga]FAPI-46 PET to a composite of clinical, radiological (ie, CT, MRI) in patients with resectable or borderline resectable PDAC.	<p>Number of lesions identified through Standard of Care (anatomical (ie, CT, MRI) and/or [¹⁸F]-FDG PET) and [⁶⁸Ga]FAPI-46 PET images</p> <p>Radiotracer accumulation observed in identified lesions using SUV</p>
To compare pre and post treatment [⁶⁸ Ga]FAPI-46 PET evaluations obtained in Cohort 2 to identify perturbations, if any, from neoadjuvant therapy treatment.	Percentage change in [⁶⁸ Ga]FAPI-46 PET imaging using SUV levels in the primary lesion between pre- and post-neoadjuvant therapy

Abbreviations: CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; FAP = fibroblast activation protein; FAPI = fibroblast-activation-protein inhibitors; FDG = fluorodeoxyglucose; IHC = immunohistochemistry; MedDRA = Medical Dictionary for Regulatory Activities; MRI = magnetic resonance imaging; PDAC = pancreatic ductal adenocarcinoma; PET = positron emission tomography; SUV = standardized

uptake value; SUV_{max} = maximum standardized uptake value; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event

5.2 Estimands

The estimand approach for the primary and secondary endpoints is presented in [Table 2](#).

Table 2. Endpoints and Estimands

Endpoint	Estimand
Primary	
Per patient Sensitivity to detect PDAC using histopathology as truth standard.	<p>a) Population: EFFS1</p> <p>b) Endpoint: Positive/Negative status according to ⁶⁸Ga]FAPI-46 PET and Positive/Negative status according to histopathology (See Table 10) for the primary lesion</p> <p>c) Intercurrent event(s): There are no intercurrent events prespecified.</p> <p>d) Population level summary measure^a:</p> <ul style="list-style-type: none"> Sensitivity: point estimate, SE, 90% asymptotic normal CI and p-value
Secondary	
H-score correlated to the uptake of ⁶⁸ Ga]FAPI-46, using SUV _{max} .	<p>a) Population: EFFS2</p> <p>b) Endpoint: SUV_{max} and H-score^b</p> <p>c) Intercurrent event(s): There are no intercurrent events prespecified.</p> <p>d) Population level summary measure: Spearman correlation coefficient and 95% CI</p>
Incidence and severity of TEAEs or TESAEs	<p>Note: In addition, sensitivity and specificity of ⁶⁸Ga]FAPI-46 PET to detect FAP-expressing cells using H-score as standard of truth will be presented.</p> <p>a) Population: SAS</p> <p>b) Endpoint: Incidence of AEs</p> <p>c) Intercurrent event(s): There are no intercurrent events prespecified.</p> <p>d) Population level summary measure: Frequency and percentages of patients with each type of TEAE in each cohort.</p> <ul style="list-style-type: none"> TEAEs Serious TEAEs TEAEs by maximum severity Study drug-related TEAEs Fatal TEAEs

Abbreviations: AE = adverse event; CI = confidence interval; CT = computed tomography; Efficacy analysis set; FAP = fibroblast activation protein; FAPI = fibroblast-activation-protein inhibitors; FDG = fluorodeoxyglucose; IHC = immunohistochemistry; NPV = negative predictive value; PDAC = pancreatic ductal adenocarcinoma; PET = positron emission tomography; PPV = positive predictive value; SAS = Safety analysis set; SE = standard error; SUV = standardized uptake value; SUV_{max} = maximum standardized uptake value; TEAE = treatment emergent adverse event; TESAE = treatment emergent serious adverse event

- a The primary focus will be on the 90% confidence interval CI to align with the 5% one-sided test; however, the 95% asymptotic normal confidence interval will also be presented for descriptive purposes.
- b SUV_{mean} will also be compared to IHC H-score for exploratory purposes.

6 STUDY DESIGN CONSIDERATIONS

6.1 Study Design

This is a prospective, multi-center, single arm, open label, non-randomized study to evaluate the ability of [⁶⁸Ga]FAPI-46 to detect FAP expressing cells in patients with resectable or borderline resectable PDAC. The [⁶⁸Ga]FAPI-46 PET scans were acquired after initial staging using institutional standard methods. If the participant was prescribed NAT, a second [⁶⁸Ga]FAPI-46 PET scan was performed within 21 days prior to planned surgical resection. This was followed by histopathology and IHC analyses and comparison to resected PDAC tumor specimens. The surgeon was not blinded to the [⁶⁸Ga]FAPI-46 scans prior to surgery.

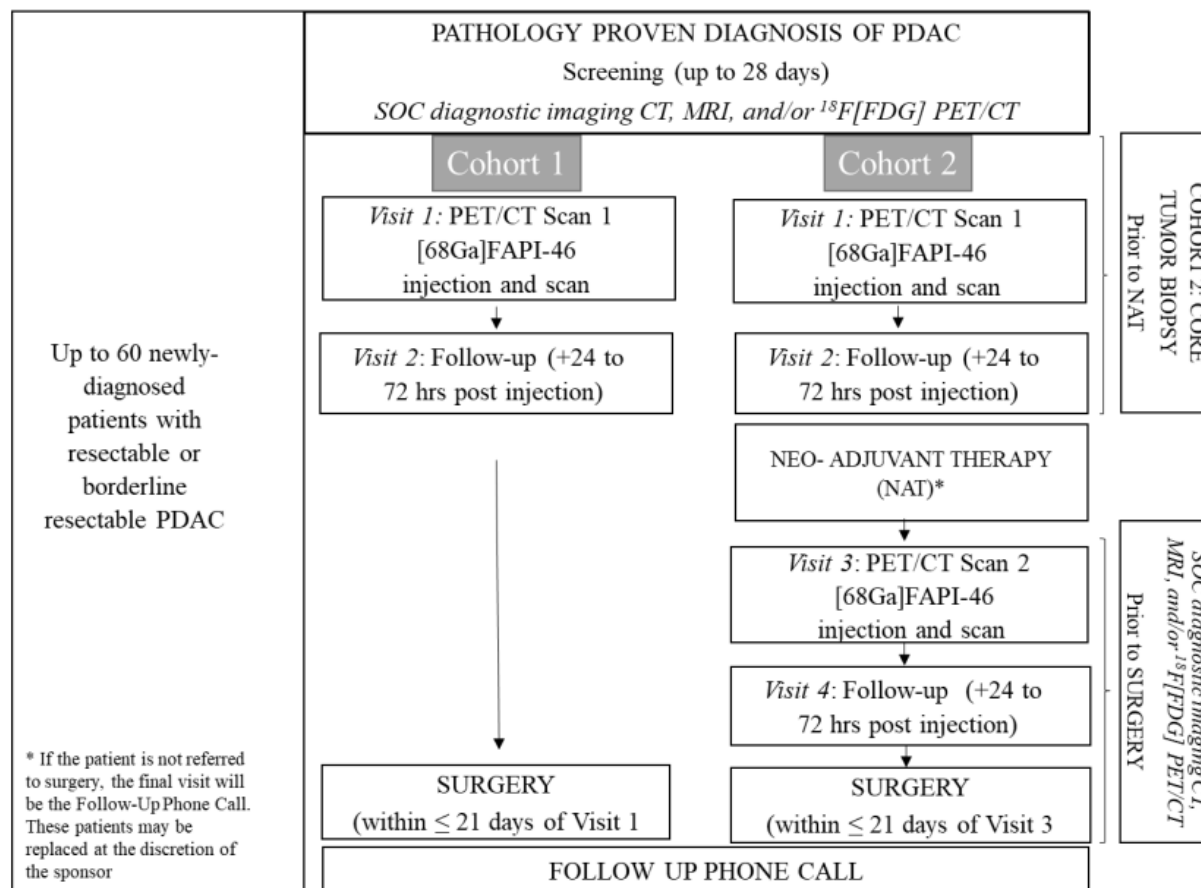
Experimental Design: Phase 2, prospective, multi-center, single arm, non-randomized, open label study

Allocation of treatment: open-label, non-randomized, single intervention

Number of patients planned: Up to 60 patients enrolled.

Summary of Study Visits and Data Collection: Refer to Schedule of Events ([Table 5](#)) for full requirements for each visit. The Schema ([Figure 1](#)) provides a graphical representation of the study visits.

Figure 1. Schema



Abbreviations: CT = computed tomography; FAPI = fibroblast-activation-protein inhibitors; FDG = fluorodeoxyglucose; hrs = hours; PDAC = pancreatic ductal adenocarcinoma; PET = positron emission tomography

All participants

Screening: Screening assessments could be conducted at multiple visits provided they are within 28 days prior to study day 1, including anatomic imaging. Tests performed for standard of care were permitted to be used for screening purposes provided they were within window.

Visit 1: Defines Study Day 1. [⁶⁸Ga]FAPI-46 PET scan obtained.

Visit 2: 24 to 72 hours after [⁶⁸Ga]FAPI-46 injection. Safety assessment with safety labs and, if needed, a symptom directed physical examination. This was the last active study-related event with the participant.

Cohort 1 only:

Participants in Cohort 1 were those not prescribed NAT who directly underwent surgical resection within 21 days post-[⁶⁸Ga]FAPI-46 PET scan. Data were mined from the medical records regarding the surgical procedure and pathologic outcomes. The final study-directed visit is Visit 2.

Surgery: Surgical resection occurred within 21 days after [⁶⁸Ga]FAPI-46 PET scan. Resected tissue was collected as per laboratory manual. Surgical and pathology reports were collected, codified, and provided for study.

Follow-up: Passive follow-up only through chart review to collect information about post-surgical imaging, planned treatment, and outcomes for 14 days following surgery.

Cohort 2 only:

Participants in Cohort 2 were those who received a tumor biopsy and who were prescribed NAT followed by surgical resection within 21 days after a second [⁶⁸Ga]FAPI-46 PET scan. NAT was beyond the scope of this protocol and was to be administered per standard of care by the institution and treating oncology team. Data were mined from the medical records regarding the NAT administered, surgical procedure and pathologic outcomes. The final study-directed visit was Visit 4.

Visit 3: Second [⁶⁸Ga]FAPI-46 PET scan.

Visit 4: 24 to 72 hours after [⁶⁸Ga]FAPI-46 injection. Safety assessment with safety labs and, if needed, a symptom directed physical examination.

Surgery: Surgical resection occurred within 21 days after [⁶⁸Ga]FAPI-46 PET scan. Resected tissue was collected as per laboratory manual. Surgical and pathology reports were collected.

Follow-up: Passive follow-up only through chart review to collect information about post-surgical imaging, planned treatment, and outcomes for 14 days following surgery.

6.1.1 Safety Review Committee / Data Monitoring Committee

This Phase 2 imaging trial was not considered to have a safety risk or toxicity, thus not meeting any of the FDA criteria highlighted in the DSMC charter. Additionally, the trial had a small accrual goal (n = 60) with a targeted completion of less than 1 year and is in an early stage to determine the efficacy of [⁶⁸Ga]FAPI-46 in identifying pancreatic adenocarcinoma. Thus, a DSMC was not convened as it would not have ameliorated safety risk to participants, it would not have functioned to assess futility, and it would not have overseen unblinded data.

However, the sponsor concurred that independent oversight was critical to protect the rights, safety, and welfare of study participants as well as to ensure scientifically valid data. For this purpose, the sponsor established the necessary independent organizations and individuals.

6.1.2 Justification of Sample Size

The sample size is 60 patients in order to adequately power the primary objective of sensitivity.

For this study, the primary efficacy endpoints is sensitivity, evaluated with a hypothesis test:

H0: Sensitivity \leq PG

H1: Sensitivity $>$ PG

The minimum sample size necessary to achieve power for sensitivity was computed for the hypothesis test above utilizing a one-sample binomial proportion test with a normal approximation, an upper one-sided significance level of 0.05, and the following parametric assumptions:

- PG = 0.75 for sensitivity
- True Sensitivity = 0.90

Given the parametric assumptions above, 60 patients yields 92.7% power to demonstrate that the true sensitivity is greater than 0.75.

6.2 Efficacy Measures

Refer to [Section 10.6](#) for a complete description of the efficacy analyses.

Only the primary tumor and a maximum of three lymph nodes will be considered for analysis and handled based on the available information.

6.2.1 Primary Efficacy Measures

The primary efficacy endpoints will be defined based on a [⁶⁸Ga]FAPI-46 PET image result (positive or negative) and a histopathology result (positive and negative) at patient level. Imaging data reads were conducted by a single reader at a central image reading lab followed by quantitative recording of PET image SUV data. The primary tumor and up to a maximum of three lymph nodes were assessed by the central lab and only those lesions that have both imaging and histopathology results will be used for primary endpoint calculation.

For the primary analysis, sensitivity will be determined based on a single tissue sample from biopsied or resected specimens collected from the primary tumor

Refer to [Table 10](#) to determine positive imaging and histopathology results.

6.2.2 Secondary Efficacy Measures

The secondary efficacy endpoint will compare the results from [⁶⁸Ga]FAPI-46 PET and IHC using:

The secondary efficacy endpoints to be analyzed include:

- Correlation between SUV_{max} and H-score
- Correlation between SUV_{mean} and H-score

Besides, the sensitivity and specificity of [⁶⁸Ga]FAPI-46 PET to detect FAP-expressing cells using H-score as SoT will be tabulated. Refer to [Table 10](#) to determine positive imaging and IHC results.

6.2.3 Exploratory Efficacy Measures

The exploratory endpoints to be analyzed include:

- Number of lesions identified (0, 1, 2, 3 or more) through Standard of Care (anatomical (ie, CT, MR) and/or [¹⁸F]-FDG PET) and [⁶⁸Ga]FAPI-46 images
- Radiotracer accumulation observed in identified lesions SUV_{max}, SUV_{mean}, and tumor-to-background ratio (TBR) . If different background regions (such as muscle, blood, etc...) are used, TBR will be calculated and presented for all of them.
- Percentage change in [⁶⁸Ga]FAPI-46 PET SUV_{max} in the primary lesion between pre- and post-neoadjuvant therapy

6.3 Safety Measures

All patients who receive any amount of [⁶⁸Ga]FAPI-46 will be included in the final summaries and listings of safety data.

The safety endpoints to be analyzed include:

- Any reported TEAE
- Any Serious TEAE
- TEAEs by maximum severity grade
- Any Study drug related TEAE
- Any Fatal TEAE
- Clinical laboratory results, including hematology and serum chemistry
- Vital signs, including body temperature, respiratory rate, SBP, DBP, and heart rate
- Physical examination results

6.4 Pharmacokinetic Measures/Parameters

Not applicable.

6.5 Pharmacodynamic Measures/Parameters

Samples of serum for CA19-9 (or CA125, CEA if non-secretors for pancreas cancer), CEA and CA125 as applicable, any tumor marker appropriate to the given cancer or that is known to be elevated in each patient, were collected and processed as per the instructions provided in the respective laboratory manuals. Serum tumor biomarkers levels were also determined as per the instructions provided in the respective lab manuals.

7 STUDY POPULATIONS

7.1 Analysis Populations

7.1.1 Safety Analysis Set (SAS)

All patients who received any amount of [⁶⁸Ga]FAPI-46. The SAS will be used for all safety evaluations.

7.1.2 Efficacy Analysis Sets

Patients with uninterpretable [⁶⁸Ga]FAPI-46 PET data will be excluded from the efficacy analyses. Number (%) of patients with uninterpretable [⁶⁸Ga]FAPI-46 PET images will be summarized. Uninterpretable image data is defined as a response of “No” to the eCRF question: “Is Image of technical quality for interpretation?”.

SUV values from [⁶⁸Ga]FAPI-46 PET imaging were only reported for regions judged positive by the blinded reader. Missing SUV values for the primary tumor within the transfer file, where the response in the EDC is interpretable (i.e., ‘Yes’ to the eCRF question: ‘Is the image of technical quality for interpretation?’), will be treated as a negative region.

Furthermore, patients with missing or invalid histopathology data (standard of truth) will be imputed as positive for the primary region of interest, in line with the study design, which requires all patients to be positive for PDAC to be eligible for inclusion.

7.1.2.1 Efficacy Analysis Set 1 (EFS1)

All patients in Cohort 1 who received [⁶⁸Ga]FAPI-46, with an interpretable (when answer to eCRF question: “Is Image of technical quality for interpretation?” is “Yes”) FAPI-46 PET image result (positive or negative) for at least 1 lesion with a corresponding histopathology result (positive or negative).

All patients in Cohort 2 who received [⁶⁸Ga]FAPI-46, with an interpretable FAPI-46 PET image result for at least 1 lesion with a corresponding histopathology result. For patients with multiple PET scans, only one PET scan will be considered for analysis. The most recent PET scan performed prior to surgery for patients with multiple scans will take precedence for analysis.

7.1.2.2 Efficacy Analysis Set 2 (EFS2)

All patients in Cohort 1 who received [⁶⁸Ga]FAPI-46, with interpretable FAPI-46 PET image results (positive or negative) for at least 1 lesion with corresponding IHC results (positive or negative).

All patients in Cohort 2 who received [⁶⁸Ga]FAPI-46, with interpretable FAPI-46 PET image results for at least 1 lesion with corresponding IHC results. For patients with multiple PET scans,

only one PET scan will be considered for the main analysis. The most recent PET scan performed prior to surgery for patients with multiple scans will take precedence for analysis.

7.1.2.3 Efficacy Analysis Set 3 (EFFS3)

All patients from Cohort 1 and Cohort 2 who received [⁶⁸Ga]FAPI-46, have interpretable FAPI-46 PET and standard of care images (ie, CT or MRI or [¹⁸F]-FDG PET).

7.1.2.4 Efficacy Analysis Set 4 (EFFS4)

All patients in Cohort 2 who received [⁶⁸Ga]FAPI-46, with interpretable FAPI-46 PET image results prior to NAT and post NAT for the same lesion.

7.1.3 Per Protocol Analysis Set (PPS)

All patients in the EFFS1 who completed the study according to the protocol with no critical protocol deviations. The decisions regarding critical protocol deviations, and the definition of the analysis set, will be finalized prior to database lock.

7.2 Subgroups

Not applicable.

8 CHANGES IN CONDUCT OR PLANNED ANALYSES FROM THE PROTOCOL

Per protocol, the primary efficacy endpoint compares the results from [⁶⁸Ga]FAPI-46 PET and histopathology and potential metastases were to be assessed as follows:

“[⁶⁸Ga]FAPI-46 PET/CT will be analyzed for lesions that are visually considered as suggestive of metastases based on the morphology, focality and intensity of [⁶⁸Ga]FAPI-46 uptake. Lesions will be counted, classified with respect to their locations (liver, peritoneum, non-regional lymph nodes, lung, bone, and other), and their [⁶⁸Ga]FAPI-46 avidity will be semi-quantitatively analyzed through SUV_{max}.”

During the blinded read of the [⁶⁸Ga]FAPI-46 PET, the reader assessed the pancreas as well as a maximum of 3 lymph nodes and recorded the SUV for lesions judged positive. The exact location of the lymph nodes assessed, while some are available in the DICOM RT structures, is not recorded in the database. Consequently, the comparison with histopathology results can only be done for the primary pancreatic lesion.

Protocol	SAP	Description
Primary Efficacy Endpoint: Sensitivity, specificity, and accuracy determined on a per-lesion basis for all lesions with tissue available for analysis	Primary Efficacy Endpoint: Sensitivity to detect PDAC determined on a per-patient basis using histopathology as standard of truth	Histopathology result and Blinded read assessment are both available for the primary pancreatic lesion only. Besides, per inclusion criteria, subjects were included with a confirmed PDAC. Consequently, only per-subject sensitivity can be assessed for the primary endpoint.
Exploratory Efficacy endpoints: Number of malignant lesions (local, metastatic) identified through anatomical (i.e, CT, MR) and/or [18F]-FDG PET Number of [⁶⁸ Ga]FAPI-46 identified lesions and the radiotracer accumulation observed in local and metastatic disease using SUV	Number of lesions identified (0, 1, 2, 3 or more) through Standard of Care (anatomical (ie, CT, MRI) and/or [18F]-FDG PET) and [⁶⁸ Ga]FAPI-46 PET images Radiotracer accumulation observed in identified lesions using SUV	With both Standard of Care and [⁶⁸ Ga]FAPI-46 PET images, the reader recorded uptake values observed in the pancreas and a maximum of 3 lymph nodes judged positive. Consequently, the detection of metastatic disease cannot be compared.
Exploratory Efficacy endpoints: Percentage change in [⁶⁸ Ga] FAPI-46 PET imaging using SUV levels and number of identified	Percentage change in [⁶⁸ Ga]FAPI-46 PET imaging using SUV levels in the primary lesion between pre- and post-neoadjuvant therapy	Given the lack of correspondence in the regions of interest between the pre- and post-NAT PET scans, changes in SUV between Visit 1 and Visit 3 can only be observed for the primary lesion

lesions between pre- and post-neoadjuvant therapy		
The primary analysis of sensitivity and specificity will be summarized using frequency counts and percentages as well as 95% asymptotic normal confidence intervals.	The point estimate, SE, as well as the 90% asymptotic normal CI will be presented for sensitivity. The 95% asymptotic normal CI will also be presented; however, the primary focus will be on the 90% CI to align with the 5% one-sided test.	The primary focus will be on the 90% CI to align with the 5% one-sided test; however, the 95% asymptotic normal confidence interval will also be presented.

9 OVERALL STATISTICAL CONSIDERATIONS

9.1 General Conventions

Statistical testing for 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).

Standard deviation (SD), (N + 2).

Median, Q1, Q3, (N + 1).

Minimum, (N + 0).

Maximum, (N + 0).

9.2 Multiple Comparisons and Adjustment for Multiplicity

No alpha adjustment is required for statistical testing in this Phase 2 study. The type I error rate will be preserved by requiring the rejection of the sensitivity null hypothesis to conclude that [⁶⁸Ga]FAPI-46 is effective for the detecting PDAC.

9.3 Baseline Definition

Baseline for a given parameter is defined as the last non-missing evaluation before the first dose of [⁶⁸Ga]FAPI-46 for Cohort 1 and 2.

In addition, given NAT in Cohort 2 and [⁶⁸Ga]FAPI-46 are excreted from the body after 10 half-lives (\pm 10 hours), assessments after NAT and the last non-missing evaluation before the second dose of [⁶⁸Ga]FAPI-46 will be considered as post-NAT Baseline. Also, a pre- and post- NAT evaluation will be considered to evaluate the change in assessments before and after NAT and will be described in each relative section. Any assessment between the first dose of [⁶⁸Ga]FAPI-46 and NAT will be considered as post study treatment. Summaries will clearly indicate the difference between change from baseline (CFB) (if applicable) and change from pre-NAT.

9.4 Imputation and Handling of Partial Dates

Patients with missing or invalid histopathology data (the standard of truth) will be considered positive for the primary region of interest, in line with the study design, which requires all

patients to be positive for PDAC in order to be eligible for inclusion. Missing SUV values for the primary tumor, where the response in the EDC is interpretable (i.e., ‘Yes’ to the eCRF question: ‘Is the image of technical quality for interpretation?’), will be treated as a region considered negative by the blinded reader. Otherwise, no imputation for missing data will be performed unless explicitly specified. Rules for partial and missing dates for AEs and medications are given in the [Appendices](#).

9.5 Interim Analysis

No formal interim analysis is planned for this study.

9.6 Pooling Strategy for Study Sites

Patient 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, thereby, visit windows will not be applied.

Unscheduled visits will not be included in by-visit summaries or analyses but may contribute to the baseline, last pre-NAT (Cohort 2 only), worst post baseline, and worst post-NAT (Cohort 2 only) 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

Cohort	Visit Description/Window	Visit Format within TLFs
Cohort 1	≤ 28 days of day 1	Screening*
	Study day 1	Visit 1*
	+ 24 to 72 hours post-injection	Visit 2
	≤ 21 days of PET scan	Surgery
	14 days following surgery	Surveillance
	Any unscheduled visit	Unscheduled
	End of study assessments	End of Study
Cohort 2	≤ 28 days of day 1	Screening*
	Study day 1	Visit 1*
	+ 24 to 72 hours post-injection (1 st)	Visit 2
	Post Neo-adjuvant Treatment Monitoring	NAT
	≤ 21 days of surgery	Visit 3*
	+ 24 to 72 hours post-injection (2 nd)	Visit 4
	≤ 21 days of PET scan	Surgery
	14 days following surgery	Surveillance
	Any unscheduled visit	Unscheduled
	End of study assessments	End of Study

Abbreviations: NAT = neoadjuvant therapy; PET = positron emission tomography; TLFs = table, listing, and figure's

*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

10.1 Patient Disposition

All screened patients who provided informed consent will be accounted for in the study. The number of patients in the following disposition categories will be summarized in a summary table by cohort and overall:

- The number of patients screened, enrolled, and completed the study
- The number of patients in each analysis population
- Patients who discontinued prematurely, reasons for study discontinuation (possible options are progressive disease, AEs, death, protocol deviation, physician decision, sponsor request, withdrawal by patient, lost to follow-up, study terminated by sponsor, patient non-compliance, or other).

The following listings will be presented:

- Screen Failures: A list of all screen failures, including the date of informed consent, reason for failure, and the associated inclusion/exclusion violation number.
- Inclusion/Exclusion Violations: A list of all inclusion/exclusion violations.
- Disposition: A list indicating the first and second dose dates, Cohort 2 patients who underwent NAT, date of study completion or discontinuation, and reason for discontinuation for all enrolled patients.
- Exclusion from Analysis: A list of reasons for exclusion from the analysis populations for all enrolled patients.

10.2 Protocol Deviations

Summary statistics of the frequency and percentage of patients in the SAS with critical PDs for each deviation category will be provided by cohort and overall. A patient with multiple occurrences of a critical PD in the same deviation category will only be counted once in that category. A listing of PDs by cohort will be provided for all patients in the SAS, along with the classification of deviation.

10.3 Demographics and Baseline Characteristics

The list below presents the list of demographic and baseline characteristic variables that will be summarized by cohort and overall, for patients in the SAS; and repeated for the EDFS1, if unique to support the primary endpoint.

- Age (years). Age will be used as calculated in the database.
- Sex (Female, Male, Unknown, Not Reported)

- Childbearing potential (Yes, No)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Unknown, Not reported)
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Not Reported, Unknown, Multiracial, Not reported, Other)
- Height (cm) at screening
- Weight (kg) at screening
- BMI (kg/m²) at screening. BMI will be derived by using the following formula:
$$BMI = Weight (kg) / [Height (m)]^2$$
- ECOG performance status at baseline (0, 1, 2, 3, 4, 5)

For continuous parameters, mean, standard deviation, Q1, median, Q3, minimum, and maximum will be displayed. Categorical data will be presented using numbers and percentages. The denominators for percentages will be the number of patients in each cohort and overall, with non-missing data for the variable of interest. A listing for patient's demographics and baseline characteristics based on the SAS will also be produced.

10.3.1 Medical and Surgical History

Medical history, including surgical history, will be coded using MedDRA Version 25.0. A summary table by SOC and PT, along with a corresponding by patient listing of medical history (including SOC and PT), will be presented 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. All medications started and ended prior to the first administration of study drug will be considered prior medications. All medications started prior to the first study drug administration and ongoing at the time of administration, or taken from the time of first study drug administration to the end of follow-up will be considered concomitant medications.

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 for the SAS by WHO ATC level 3, preferred term, and cohort.

Concomitant non-pharmacologic treatments/procedures will be coded using MedDRA Version 25.0 and will be listed per patient for the SAS. The listing includes 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 [⁶⁸Ga]FAPI-46 Administration and PET Scan

The proportion and percentage of patients receiving each dose, along with descriptive statistics summarizing the dose amount and corresponding image quality of the PET scan, will be summarized by cohort for the SAS.

A listing displaying each dose (single dose in Cohort 1 and 2 doses in Cohort 2) of [⁶⁸Ga]FAPI-46, including the date and time of study drug administration, dose (mCi), date of image, imaging start time, and image quality will be provided using the SAS.

10.6 Efficacy

Efficacy analysis will be presented overall, ie, both cohorts combined. For the primary analysis, a single readable [⁶⁸Ga]FAPI-46 PET image result will be compared with a corresponding histopathology result. For patients in Cohort 2 with multiple PET scans, the most recent PET scan performed prior to surgery will take precedence for analysis.

10.6.1 Testing Statistical Assumptions Including Comparability at Baseline

10.6.1.1 Test of Proportions

The assumption underlying the normal approximation to the binomial distribution, used in the computation of CIs for sensitivity is that the sample size is such that $np > 5$ and $n(1-p) > 5$, where n is the sample size and p is the binomial probability. It is expected that the sample size for each statistic will be sufficient to meet this assumption. In the event that the sample size is not sufficient, Agresti-Coull exact tests will be used. As there is only 1 treatment in this study, there will be no testing of baseline comparability.

10.6.2 Primary Analysis

The primary analysis will evaluate the performance (measured by sensitivity) of [⁶⁸Ga]FAPI-46 PET imaging to detect PDAC, using histopathology as truth standard.

The primary efficacy endpoints will compare positive/negative status from [⁶⁸Ga]FAPI-46 PET and histopathology of the primary lesion and the analysis will be based on the EFS1, as defined in [Section 7.1.2.1](#).

The table below contains terms used to define sensitivity.

Table 4. ⁶⁸Ga]FAPI-46 PET vs Histopathology

		Histopathology		
		Positive	Negative	
⁶⁸ Ga]FAPI-46 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; FAPI = fibroblast-activation-protein inhibitors; PET = positron emission tomography
 N indicates the number of patients with FAPI-46 and corresponding histopathology results.

The sensitivity, which evaluates how good a test is at detecting a positive disease, will be calculated as:

$$\text{Sensitivity} = A / (A + C)$$

The point estimate, SE, as well as the 90% asymptotic normal CI will be presented for sensitivity. The 95% asymptotic normal CI will also be presented; however, the primary focus will be on the 90% CI to align with the 5% one-sided test.

Inference for the primary hypotheses will be conducted utilizing a one-sample binomial proportion test with a normal approximation given the assumptions have been met (see [Section 10.6.1.1](#)), a one-sided upper significance level of 0.05, and assumed null proportions/PGs of 0.75 for sensitivity. Success for the primary efficacy analysis will be defined as demonstrating that the sensitivity is statistically significantly greater than its PG. The one-sided asymptotic p-value will be provided for sensitivity. Refer to [REDACTED]

A listing of ⁶⁸Ga]FAPI-46 PET imaging results, including histopathology disease presence associated with the corresponding region (same lesion) will be presented for the SAS with a record identifier for patients in the EDFS1.

10.6.3 Secondary Analysis

The secondary analysis will determine the correlation between ⁶⁸Ga]FAPI-46 PET imaging and IHC, using SUV_{max} and H-score respectively.

The analysis will be based on the EDFS2, as defined in [Section 7.1.2.2](#). The correlation between SUV_{max} and H-score will be analyzed by Spearman's rho test. The correlation coefficient and 95% CI will be provided. Spearman's rho test assesses how well the relationship between 2 variables (ordinal or continuous) can be described using monotonic functions. As it is not evident that the relationship between SUV_{max} and H-score will be linear, Spearman's rho test has been selected instead of Pearson's correlation. The correlation between SUV_{mean} and H-score will also be analysed in a similar manner to SUV_{max}.

The correlation between SUV_{max} vs H-score will be plotted graphically by using a scatterplot.

Sensitivity and specificity will be calculated and presented in the same manner as described for the primary analysis, using IHC as the truth standard. This analysis is for exploratory purposes only.

The specificity, which estimates how likely patients without the disease can be correctly ruled out, will be calculated as:

$$\text{Specificity} = D / (B + D)$$

10.6.4 Other Secondary Analyses

Refer to [Section 10.7](#) for the safety analysis (third secondary endpoint).

10.6.5 Exploratory Analyses

All exploratory analyses will be conducted on the efficacy population defined for each analysis, and will be summarized by cohort, visit, and, where applicable, by region. The data for these presentations will be obtained from the following eCRFs (and associated imaging results):

- Non – Target/Non-Index Lesions
- Target/Index Lesions

10.6.5.1 PET Intensity

Descriptive analyses will be performed on PET intensity parameters and the following summaries will be produced:

- SUV_{max}, SUV_{mean}, and TBR in identified lesions using PET scan (EFFF1).
- SUV_{max}, SUV_{mean}, and TBR in identified lesions using PET scan and correlated with conventional [¹⁸F]-FDG PET scan for the same lesion if data is available. The correlation between [⁶⁸Ga]FAPI-46 PET and [¹⁸F]-FDG PET scan will be analyzed by Pearson's correlation test. The correlation coefficient and 95% CI will be provided (EFFF3).
- SUV_{max}, SUV_{mean}, and TBR differences between pre-NAT and post-NAT in the primary lesion for Cohort 2 using PET scan (EFFF4).

10.6.5.2 Tumor Lesions Detected by [⁶⁸Ga]FAPI-46 PET in Comparison with CT/MRI and/or [¹⁸F]-FDG PET

In addition to the primary lesion, a maximum of 3 LN was assessed by the reader. The number of identified LN detected by [⁶⁸Ga]FAPI-46 PET scan versus the standard of care assessments CT/MRI and/or [¹⁸F]-FDG PET, will be presented for the EFFF3 by cohort and visit, including pre-NAT and post-NAT differences for Cohort 2.

10.6.6 Other Exploratory Analysis

No other exploratory analyses are planned for this study.

10.6.7 Interim Analysis

No formal interim analysis is planned for this study.

10.7 Safety and Tolerability

All safety analyses will be based on the SAS.

Safety variables will be summarized by cohort (including overall) and visit where applicable.

10.7.1 Adverse Events

The verbatim terms used in the eCRF to identify AEs will be coded using MedDRA Version 25.0. AE severity will be evaluated utilizing the CTCAE Version 5.0 ([Appendices](#)) toxicity grade as Grade 1, Grade 2, Grade 3, Grade 4, or Grade 5.

For the purposes of this study, the AE collection window is from the time of injection with [⁶⁸Ga]FAPI-46 through 24 hours postinjection. If the 24-hour window ends on a holiday or nonclinic day (or the patient cannot return to clinic due to unforeseen circumstances, such as weather), the window may be extended until 72 hours postinjection. TEAE summaries will present all AE recorded in the eCRF.

AE collection windows are tied to the number of [⁶⁸Ga]FAPI-46 injections. Cohort 1 will have 1 AE collection window whereas Cohort 2 will have 2 discrete AE collection windows. All collected AEs will be considered TEAE.

A TEAE overview table containing the frequency and percentage of patients as well as number of reported events in each of the following categories (summarized by cohort) will be presented:

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

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

- TEAEs
- Serious TEAEs

- TEAEs by maximum toxicity grade (CTCAE Version 5.0)
- Study drug-related TEAEs
- Fatal TEAEs

Summaries of TEAEs by SOC and PT will be sorted alphabetically by SOC and by decreasing frequency of PT overall. If a patient has more than 1 TEAE at a given level (eg, SOC and/or PT), the patient will only be counted once within that level. When summarizing TEAEs by maximum CTCAE toxicity grade, at each level of summarization, patients who report 1 or more TEAEs within that level are only counted once at that level using the event of greatest CTCAE toxicity grade (in toxicity tables). Patients who have reported TEAEs that are missing CTCAE toxicity grade or relationship to study drug will not be summarized in the tables by toxicity grade or relatedness, however they will be included in the listings of AEs and tables not summarized by toxicity grade or relatedness. All tables will show the number and percent of patients 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 patients with serious TEAEs
- Listing of patients with TEAEs leading to Death

Refer to Section 7.2 in the protocol Version 5.0, 31 Mar 2023, for AE definitions applicable to this study. This includes definitions for: life-threatening AEs or life-threatening suspected adverse reaction, suspected adverse reaction, routine AEs, serious AEs or serious suspected adverse reaction, unexpected AEs or unexpected suspected adverse reaction, severity grading, AEs leading to study discontinuation, attribution to investigation medical product and study procedures.

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

10.7.2 Clinical Laboratory

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

Shift tables will be provided summarizing the shift in laboratory values from baseline over time with respect to abnormality criteria based on the normal range for each parameter (low, normal, high). For the by-visit shift summary, the denominator is the number of patients with nonmissing values at baseline and the given visit for the given parameter, and cohort.

Detailed patient listings of all laboratory data collected during the study will be provided. Laboratory values outside normal limits will be identified in the patient data listings. A listing of patients with at least one abnormal laboratory value will be provided separately.

The following is a summary of laboratory result items planned for table presentation, by cohort and overall, 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 8](#).

The data for these presentations will be obtained from the following eCRFs (and associated laboratory analysis results):

- Chemistry
- Hematology
- Pregnancy Test

10.7.3 Vital Signs

Continuous vital sign parameters including SBP and DBP (mmHg), heart rate (bpm), respiratory rate (breaths/min), and body temperature (°C) will be summarized at each scheduled assessment time point, by cohort.

Absolute CFB for the continuous parameters will also be summarized by cohort. Descriptive statistics (N, mean, SD, median, minimum, maximum) will be presented.

A detailed patient 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 eCRFs.

10.7.4 Physical Examinations

Separate listings of all physical examination findings and clinically significant findings will be presented by cohort.

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

10.8 Pharmacodynamic Analysis

Detailed patient listings of all tumor biomarker data collected during the study will be provided. Tumor biomarker values outside normal limits will be identified in the patient data listings. A listing of patients with at least one abnormal tumor biomarker value will be provided separately.

A list of tumor biomarker assays planned to be performed can be found in [Table 8](#).

The data for these presentations will be obtained from the Tumor Biomarker eCRF.

10.9 Other Relevant Data Analyses/Summaries

These summaries will be included in Section 14.2 of the efficacy analysis TLFs to support the study objectives.

10.9.1 Histopathology Disease Presence

Histopathology summaries will be based on the EDFS1.

Disease presence will be summarized using frequency counts and percentages for each region of interest. Data from histopathology reports will be listed for the SAS.

10.9.2 Immunohistochemistry

IHC summaries will be based on the EDFS2.

Continuous IHC parameters including stroma (%), tumor (%), abundance (0 - 3), and H-score (0 - 300) will be summarized descriptively by cohort. H-score categories (see [Table 10](#)) will be presented by means of frequency counts and percentages for each category.

A listing of IHC results will be presented for the SAS with a record identifier for patients in the EDFS2.

10.9.3 Standard of Care CT/MRI

Standard of care CT/MRI results will be listed for the SAS, including a record identifier for patients in the EDFS3.

11 REFERENCES

EMA. Structure and Content of Clinical Study Reports. ICH E3. Jul1996.

EMA. Statistical Principles for Clinical Trials. ICH E9. Sep1998.

Oken MM, C.R. Toxicity and Response Criteria of The Eastern Cooperative Oncology Group.
Am J Clin Oncol. 1982; (5), 649-655.

12 APPENDICES

Appendix 1. Schedule of Assessments and Procedures

Table 5. Schedule of Assessments

Cohort 1: Participants who are considered surgical candidates by their doctor

Study Procedure	Screening	Visit 1	Visit 2 ^j	Surgery	Surveillance Period (14 days) ^h
	≤ 28 days of D1	Study day 1	+ 24 to 72 hours post-injection	≤ 21 days of PET scan	
Informed consent	X				
Complete medical history, including surgical history	X				
Core biopsy diagnosis of PDAC	X				
Standard of care imaging: CT, MR and/or [¹⁸ F]-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		
Serum chemistries ^c	X	X ^k	X		
CBC with differential		X ^k	X		
Tumor biomarkers (e.g., CA-19-9, CEA) ^d	X	As per standard of care			
Urine pregnancy test ^e	X	X ^k			
Baseline signs and symptoms		X			
Study drug [⁶⁸ Ga]FAPI-46 administration and PET scan		X			
Assessment of tumor burden ^d			X		
Capturing administered treatments				X	X
AE assessment ⁱ		X	X		
Surgical resection and tissue collection				X ^g	

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

^b Temperature, blood pressure, respiratory rate and pulse rate. Obtain twice on day of imaging: once prior to injection and once post-injection prior to discharge.

^c Glucose, Na, K, Cl, Carbonate (CO₂), Mg, Ca, BUN, creatinine, AST, ALT, ALP, total protein, albumin, and total bilirubin.

^d Frequency as per institutional standard of care; tumor burden assessment is obtained from surgical, pathology and/or imaging reports.

- 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: Only if necessary for adverse event assessment; symptom directed exam is acceptable.
- f Only if necessary for adverse event assessment; symptom directed exam is acceptable.
- g IHC will be performed for FAP expression at a central lab on biopsy tissue; Histopathology for the detection of pancreatic cancer is performed locally.
- h Passive follow-up only through chart review to collect information about post-surgical imaging, planned treatment, and outcomes for 14 days following surgery.
- i AE assessments will be performed 24 hours post [⁶⁸Ga]FAPI-46 injection.
- j Follow up visits may be performed through televisits. Patients may utilize institution approved local labs/mobile clinics for blood draws as part of follow up assessment. Patients may enter surgery <24 hours post-injection if the time of Visit 2 follow-up assessment is 10 half-lives or more post [⁶⁸Ga]FAPI-46 injection.
- k Labs obtained during screening period, within 72 hours of Day 1, can be used as pre-FAPI-46 injection Day1 lab data.

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

Source: Protocol GaFAP-2022P2 Version 5.0, 31st March 2023

Cohort 2: Participants who undergo NAT before being considered as surgical candidates by their doctor

Study Procedure	Screening	Visit 1	Visit 2 ^j	Neo- adjuvant Treatment Period	Visit 3	Visit 4 ^j	Surgery	Surveillance Period (14 days) ^h
	≤ 28 days of D1	Study day 1	+ 24 to 72 hours post- injection		≤ 21 days of surgery	+ 24 – 72h post- injection		
Informed consent	X							
Complete medical history, including surgical history	X							
Core biopsy obtained prior to NAT	X							
Standard of care imaging: CT, MR and/or [¹⁸ F]-FDG PET	X				X ^k			
Record Concomitant medications	X	X	X	X	X	X		
Physical examination ^a	X		X ^f		X ^f	X ^f		
ECOG performance status	X	X						
Vital signs ^b	X	X			X	X		
Serum chemistries ^c	X	X ^l	X		X	X		
CBC with differential		X ^l	X		X	X		
Tumor biomarkers (e.g., CA-19-9, CEA) ^d	X	As per standard of care						
Urine pregnancy test ^c	X	X ^l			X			
Baseline signs and symptoms		X			X			
Study drug [⁶⁸ Ga]FAPI-46 administration and PET scan		X			X			
Assessment of tumor burden ^d	X							
Capturing administered treatments				X			X	X
AE assessment ⁱ		X	X		X	X ^h		
Surgical resection and tissue collection							X ^g	

a Includes height and weight. Height measured only at screening.

b Includes temperature, blood pressure, respiratory rate and pulse rate.

c Assessments to include glucose, Na, K, Cl, Mg, Ca, BUN, creatinine, AST, ALT, ALP, total protein, albumin and total bilirubin.

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

- 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: Only if necessary for adverse event assessment; symptom directed exam is acceptable
- g IHC will be performed for FAP expression at a central lab on biopsy tissue; Histopathology for the detection of pancreatic cancer is performed locally
- h Passive follow-up only through chart review to collect information about post-surgical imaging, planned treatment, and outcomes for 14 days following surgery.
- i AE assessments will be performed 24 hours post [⁶⁸Ga]FAPI-46 injection
- j Follow up visits may be performed through televisits. Patients may utilize institution approved local labs/mobile clinics for blood draws as part of follow up assessment
- k Standard of care imaging post NAT Cycle 1 and prior to surgery. If multiple Standard of care images are taken post-surgery, the one closest to the surgery date will be used for image analysis
- l Labs obtained during screening period, within 72 hours of Day 1, can be used as pre-FAPI-46 injection Day1 lab data.

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

Source: Protocol GaFAP-2022P2 Version 5.0, 31st March 2023

Appendix 2. Imputation of Partial Dates

Table 6. 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

Abbreviations: D = day; M = month; Y = year; TEAE = treatment emergent adverse event

Note: The imputation of end date must be later than start date. In general, the minimum between AE end date and study drug date should be use for start date where applicable.

Table 7. 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
		Y same as Y of first drug dose and Y is equal to screening Y	Screening 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

Abbreviations: D = day; M = month; Y= year

Note: The imputation of end date must be later than start date

Appendix 3. Planned Laboratory Assays

Table 8. 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	WBC count with differential	Platelet count
		Hemoglobin
		Neutrophils – absolute
		Lymphocytes – absolute
		Monocytes – absolute
	Coagulation	INR
Tumor Biomarker		CA 19-9 (or CA125)
		Carcinoembryonic Antigen
		C-Reactive Protein
		Possible Other

Abbreviations: ALT = alanine aminotransferase; ALP = alkaline phosphatase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CA125 = cancer antigen 125; CA19-9 = cancer antigen 19-9; INR = International Normalized Ratio; WBC = white blood cell

Appendix 4. 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 5. ECOG Performance Status Scale

Table 9. ECOG Performance Status

ECOG PERFORMANCE STATUS*	
Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., 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

Abbreviations: ECOG = Eastern Cooperative Group

* From ECOG (Oken MM., 1982), Robert Comis, MD, Group Chair

Appendix 6. Criteria for Positivity

Table 10. Criteria for Positivity

Test	Parameter	Category	Criteria
⁶⁸ Ga]FAPI-46 PET	SUVmax	Positive	All SUV values from ⁶⁸ Ga]FAPI-46 PET imaging reported within the transfer file is considered a positive region
		Negative	Missing SUV values for the region of interest within the transfer file, where the response in the EDC is interpretable (i.e., 'Yes' to the eCRF question: 'Is the image of technical quality for interpretation?'), will be treated as a negative region
Immunohistochemistry	H-score	Negative	≤ 50
		Positive	> 50
		Low	51 - 100
		Moderate	101 - 200
Histopathology	Biopsy	High	> 200
		Positive	Presence of tumor

Abbreviations: PET = positron emission tomography

