Clinical Study Protocol	
Study Interventions	[^{111}In]-FPI-2107, FPI-2053, and [^{225}Ac]-FPI-2068
Study Code	FPI-2068-101
Version	3.0
Date	05 June 2023

A Phase 1, First-in-human, Multicentre, Open-label, Dose-escalation Study of [^{225}Ac]-FPI-2068 in Adult Patients with Advanced Solid Tumours

Sponsor Name: Fusion Pharmaceuticals Inc.

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Regulatory Agency Identifier Numbers: IND number for [^{111}In]-FPI-2107: 161010

IND number for [^{225}Ac]-FPI-2068: 161011

Protocol Number: FPI-2068-101

Amendment Number: Not Applicable

Study Interventions: [^{111}In]-FPI-2107, FPI-2053, and [^{225}Ac]-FPI-2068

Study Phase: Early Phase 1: First-in-human study

Short Title: A Phase 1, Dose-escalation Study of [^{225}Ac]-FPI-2068 in Adult Patients with Advanced Solid Tumours

Study Physician Name and Contact Information will be provided separately.

SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
CSP Version 3.0	05 June 2023
CSP Version 2.0	18 April 2023
Original CSP Version 1.0	27 October 2022

CSP Version 3.0 (05 June 2023)

Overall Rationale for the Modification:

This CSP update has been issued to correct internal inconsistencies and includes: removal of 2 visits during treatment period; clarification of PK and biomarker sampling; change to volume of blood to be collected; minor corrections to schedule of assessments.

Other minor typographical errors have also been corrected.

Summary of Changes

List of Substantial Modifications		
Section Number and Name	**Description of Change**	**Brief Rationale**
Section 8 Study Assessments and Procedures	Volume of blood to be collected up to the end of Cycle 1 increased	To include some biomarker samples omitted in error from previous version
Section 8.1 Schedule of Activities	Removed PK samples and ECG assessments on Day 2 and Day 3 of treatment period from Tables 26, 27	To align PK samples and ECG assessments with scheduled visits to reduce participant burden
Section 8.1 Schedule of Activities, Section 8.1.9 Schedule of Activities for Part A PK, ECG and Biomarker Timepoints and Section 8.8.1.1 Collection of blood for RNA	Addition of blood samples for TCR analysis to Tables 17, 19, 20, 21, 22, 23, 24 and 25	Omitted in error from previous version.
	Addition of PK sample collection and ECG assessment at planar scintigraphy and SPECT/CT timepoints in Table 26	
	Added collection of blood to be processed to PBMCs for TCR sequencing	

CT, computed tomography; ECG, electrocardiogram; PBMC, peripheral blood mononuclear cell; PK, pharmacokinetics; SPECT, single-photon emission computed tomography; TCR, T-cell receptor.

List of Non-substantial Modifications		
Section Number and Name	**Description of Change**	**Brief Rationale**
Section 8.1.1 Schedule of Activities for Part A Screening	Minor updates to remove unnecessary entries	For consistency.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 1, First-in-human, Multicentre, Open-label, Dose-escalation Study of [^{225}Ac]-FPI-2068 in Adult Patients with Advanced Solid Tumours

Short Title: A Phase 1, Dose-escalation Study of [^{225}Ac]-FPI-2068 in Adult Patients with Advanced Solid Tumours

Rationale:

Three drug products, all based on the same bispecific antibody, will be used in the proposed Phase 1 study:

- [^{111}In]-FPI-2107 (radioimmuno-SPECT agent),
- FPI-2053 (unconjugated/unlabelled bispecific antibody [cold]), and
- [^{225}Ac]-FPI-2068 (radioimmuno-therapeutic agent [hot]).

The conjugates are produced by chelating actinium-225 or indium-111 to the monoclonal antibody FPI-2053 with a bifunctional chelating agent (FPI-1784).

[^{225}Ac]-FPI-2068 is a radiopharmaceutical therapy containing an alpha particle emitter, actinium-225, an epidermal growth factor receptor (EGFR) and mesenchymal-epithelial transition factor (c-MET) directed bispecific monovalent antibody (bsAb; FPI-2053) and a bifunctional chelate. This bsAb has been modulated to have reduced binding affinity to EGFR, thereby potentially reducing normal tissue toxicity. Nonclinical data from both in vitro and in vivo models indicate that [^{225}Ac]-FPI-2068 has the potential to reduce the size of tumours that are known to have a coexpression of EGFR and c-MET, such as head and neck squamous cell carcinoma (HNSCC), non-small cell lung cancer (NSCLC), metastatic colorectal carcinoma (mCRC), and pancreatic ductal adenocarcinoma (PDAC). Clinical development will include enrolment of participants with HNSCC, NSCLC, mCRC, and PDAC, who have exhausted currently available standard of care options, representing a study population with a high, unmet medical need.

Since [^{225}Ac]-FPI-2068 does not emit radiation that is readily amenable for clinical image acquisition, [^{111}In]-FPI-2107 will be used as a radioimmuno-SPECT imaging agent for calculating dosimetry and to identify participants for inclusion in the study.

In addition to the safety and efficacy of [^{111}In]-FPI-2107, FPI-2053, and [^{225}Ac]-FPI-2068, this study will also evaluate the effect of predose administration of FPI-2053 on the radiation biodistribution and dosimetry of [^{111}In]-FPI-2107 and [^{225}Ac]-FPI-2068 in order to optimise the [^{225}Ac]-FPI-2068 dosing regimen. Predosing with FPI-2053 has the potential to modulate the biodistribution of the radiolabelled drug products and increase tumour uptake relative to

healthy tissues.

Objectives and Endpoints:

Table 1 Objectives and Endpoints

Type	Objectives	Endpoints
Primary		
Safety / Dosimetry	• Evaluate the safety, tolerability, and dosimetry of [^{111}In]-FPI-2107, FPI-2053, and [^{225}Ac]-FPI-2068 • Determine the RP2D of [^{225}Ac]-FPI-2068, given with or without FPI-2053	• Frequency, duration, and severity of AEs, DLTs, and changes in clinical, laboratory, and ECG parameters compared to baseline • Estimates of residence time and absorbed radiation doses to the whole body, organs, and selected regions of interest for [^{111}In]-FPI-2107 and [^{225}Ac]-FPI-2068
Dosimetry	• Determine the effect of predose administration of FPI-2053 on the radiation dosimetry of [^{111}In]-FPI-2107 (whole body, organs, and selected regions of interest) • Estimate the effect of predose administration of FPI-2053 on the radiation dosimetry of [^{225}Ac]-FPI-2068 (whole body, organs, and selected regions of interest)	• Changes in uptake of [^{111}In]-FPI-2107 and projected RAD of [^{225}Ac]-FPI-2068 by imaging following predose administration of FPI-2053 compared to uptake of [^{111}In]-FPI-2107 imaging alone
Secondary		
Efficacy	• Assess preliminary anti-tumour activity of [^{225}Ac]-FPI-2068	• ORR per RECIST 1.1 • TTR, DoR, PFS, DCR, and OS. • Percentage change in total ctDNA (VAF) compared to baseline
Pharmacodynamics	• Obtain preliminary data on the tumour uptake of [^{111}In]-FPI-2107	• Tumour uptake of [^{111}In]-FPI-2107 in selected regions of interest on SPECT/CT and/or planar images
PK	• Determine the PK of [^{111}In]-FPI-2107, FPI-2053, and [^{225}Ac]-FPI-2068, and the effect of predose administration of FPI-2053 on the PK of [^{111}In]-FPI-2107 and [^{225}Ac]-FPI-2068	• Plasma concentrations and PK parameters of [^{111}In]-FPI-2107 and [^{225}Ac]-FPI-2068, including but not limited to: clearance, AUC_{last}, C_{max}, and half-life. • Changes in plasma concentrations and PK parameters (as indicated above) of [^{111}In]-FPI-2107 following FPI-2053 preadministration compared to [^{111}In]-FPI-2107 alone
Immunogenicity	• To assess the immunogenicity of [^{111}In]-FPI-2107, [^{225}Ac]-FPI-2068, and FPI-2053	• Presence of ADA for [^{111}In]-FPI-2107, [^{225}Ac]-FPI-2068, and FPI-2053

Exploratory		
Safety/ Dosimetry	• Assess the relationship between organ dosimetry based on imaging with [^{111}In]-FPI-2107 and any observed toxicity following administration of [^{225}Ac]-FPI-2068	• Correlation between organ dosimetry based on imaging with [^{111}In]-FPI-2107 and observed toxicities following administration of [^{225}Ac]-FPI-2068
Pharmacodynamics	• Assess the impact of [^{225}Ac]-FPI-2068 regimen on exploratory, blood-based biomarkers	• Changes in circulating biomarkers such as TCR repertoire following administration of [^{225}Ac]-FPI-2068 regimen
Pharmacodynamics	• Assess the relationship between baseline tumour or circulating biomarkers and response to [^{225}Ac]-FPI-2068	• Correlation between baseline tumour or circulating marker and change in tumour size
Dosimetry	• Assess the association between target expression in the baseline tumour by IHC and tumour uptake of [^{111}In]-FPI-2107	• Correlation between the IHC expression of EGFR and c-MET in baseline tumour and projected RAD
Dosimetry	• Assess the association between RAD and tumour response	• Correlation between RAD and changes in tumour size

ADA, anti-drug antibody; AE, adverse event; AUC_{last}, area under the concentration time curve from 0 to the last quantifiable concentration; C_{max}, maximum concentration after dosing; c-MET, mesenchymal-epithelial transition factor; CT, computed tomography; ctDNA, circulating tumour DNA; DCR, disease control rate; DLT, dose limiting toxicity; DoR, duration of response; ECG, electrocardiogram; EGFR, epidermal growth factor receptor; IHC, immunohistochemistry; ORR, objective response rate; OS, overall survival; PFS, progression free survival; PK, pharmacokinetics; RAD, radiation absorbed dose; RECIST, Response Evaluation Criteria in Solid Tumours; RP2D, recommended Phase 2 dose; SPECT, single-photon emission computed tomography; TCR, T-cell receptor; TTR, time to response; VAF, variant allelic frequency.

Overall Design:

This is a first-in-human, Phase 1, non-randomised, multicentre, open-label clinical study designed to investigate the safety, tolerability, dosimetry, biodistribution, and pharmacokinetics (PK) of [^{225}Ac]-FPI-2068, [^{111}In]-FPI-2107, and the effect of predose administration of FPI-2053 on the PK and biodistribution of [^{225}Ac]-FPI-2068 and [^{111}In]-FPI-2107. In addition, the pharmacodynamics, preliminary anti-tumour activity, and recommended Phase 2 dose (RP2D) of a [^{225}Ac]-FPI-2068 regimen in participants with advanced, metastatic and/or recurrent solid tumours (HNSCC, NSCLC, mCRC, PDAC) that demonstrate uptake of the imaging agent as determined by SPECT/computed tomography (CT) will be evaluated.

The study will be conducted in 2 parts:

- Part A: FPI-2053 dose exploration to determine the optimal predose administration of FPI-2053 with a fixed dose (15 kBq/kg) of [^{225}Ac]-FPI-2068.
- Part B: [^{225}Ac]-FPI-2068 dose escalation with the optimal dose of FPI-2053 as determined in Part A.

Note: participants will be eligible to receive investigational treatment ([^{225}Ac]-FPI-2068 with

or without FPI-2053 per assigned cohort) if they meet all general screening and imaging criteria.

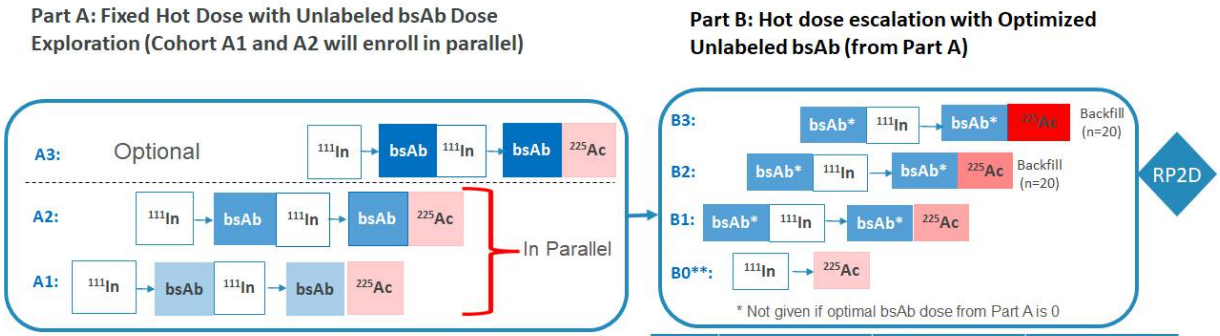
Part A, Cohort A1 and Cohort A2 will be initiated simultaneously and conducted in parallel. Individual participants will be allocated in an alternating manner to Part A, Cohort A1 or Cohort A2 after the General Screening Period but before the Imaging Screening Period, unless one of the cohorts is filled, in which case the recruitment will proceed sequentially until 3 participants have been treated with [225Ac]-FPI-2068 in each cohort. The first participant in Cohort A2 will be treated with [225Ac]-FPI-2068 only after the first participant in Cohort A1 has undergone a minimum of one week of safety observation. Following review of safety, PK, biodistribution, and dosimetry data from Cohorts A1 and A2 by the Sponsor and the Safety Review Committee (SRC), Cohort A3 may be initiated if deemed necessary. The SRC will also determine when to initiate Part B.

Part B will commence once the optimal dose of FPI-2053 is determined in Part A.

The study will employ a modified toxicity probability interval (mTPI-2) design to estimate MTD in Part B. The RP2D will be determined from Part B based on all available safety, efficacy, PK, and dosimetry information.

Disclosure Statement: This is a dose escalation study with 2 Parts that is open-label.

Figure 1 Study Schema



Cohort	Planned FPI-2053 Dose	[111In]-FPI-2107 Dose	[225Ac]-FPI-2068 Dose
A1	0.3 mg//kg	185 MBq	15 kBq/kg
A2	1 mg/kg		
A3	3 mg/kg		

Cohort	FPI-2053 Dose	[111In]-FPI-2107 Dose	Planned [225Ac]-FPI-2068 Dose
B0**	Optimal Dose Defined in Part A	185 MBq	15 kBq/kg
B1			25 kBq/kg
B2			40 kBq/kg
B3			70 kBq/kg

** B0 will open only if unlabeled bsAb not required based on Part A

111In, [111In]-FPI-2107; 225AC, [225Ac]-FPI-2068; bsAb, bispecific antibody (FPI-2053); RP2D, recommended Phase 2 dose.
Participants will be imaged with [111In]-FPI-2107 (with and/or without predose administration of FPI-2053) to determine participant eligibility and to estimate the maximum allowable cycles of [225Ac]-FPI-2068. The cumulative radiation dose of [225Ac]-FPI-2068 will be estimated for organs by cohort and individual participant. Colour intensity of blocks indicates dose levels (higher dose levels are darker).

Number of Participants:

Approximately 150 participants will be screened to achieve approximately 125 safety-evaluable participants and approximately 110 efficacy-evaluable participants across all parts of the study. This assumes an approximate 20% and 10% general and imaging screen fail rate, respectively.

The total number of participants depends upon the number of dose escalations/de-escalations necessary. Approximately three participants in up to 3 dose cohorts are required in Part A (see Section 9.2). At least three, and up to nine, evaluable participants are required for each dose cohort in Part B. The SRC will make recommendations on imaging requirements, such as timing of image acquisition or decisions to drop imaging assessments. They may also recommend to enrol additional participants at a given dose level if it is deemed necessary to evaluate safety, and they may make decisions to explore alternative (e.g., intermediate) dose levels. Once all three participants in a given dose cohort have been monitored for safety for 56 days, the SRC will convene and will provide guidance for management of the next dose cohort. Dose exploration will not proceed at or beyond a dose level where the dose-limiting toxicity (DLT) rate exceeds 30%.

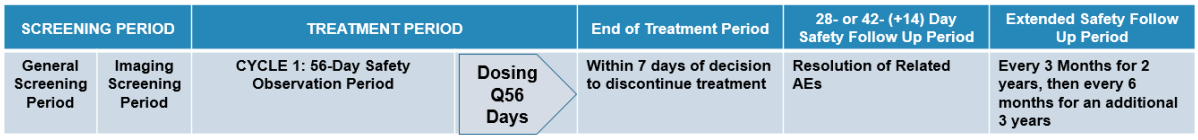
A DLT-evaluable participant is defined as a participant who receives [^{225}Ac]-FPI-2068 and completes the DLT observation period without a DLT or a participant who experiences a DLT. Participants who are unable to complete the 56-day DLT observation period, for reasons other than a DLT (e.g., rapid disease progression or death), will be replaced; therefore, additional participants may be enrolled.

Note: "Enrolled" means a participant's agreement to participate in a clinical study following completion of the informed consent process. Potential participants who consent to participate in the clinical study but are not subsequently entered in the study, are considered “screen failures”, unless otherwise specified by the CSP.

Study Periods:

The study is divided into 5 periods: (1) General Screening Period, (2) Imaging Screening Period, (3) Treatment Period, (4) End of Treatment and 28- or 42- (+ 14 days) Day Safety Follow-Up Period, and (5) Extended Safety Follow-Up Period:

Figure 2 Study Periods



Q56, every 56 days.
The length of each cycle within the treatment period will encompass a minimum of 56 days.

1. *General Screening Period:* All screening procedures **except baseline imaging** are to be performed during the General Screening Period. Participants must satisfy all general screening requirements (inclusion/exclusion) before undergoing baseline imaging.
2. *Imaging Screening Period:* The areas to be imaged with SPECT/CT are to be selected by the Investigator and/or appropriate delegate at the clinical sites and must include bone marrow, kidneys, lungs, and liver. [^{111}In]-FPI-2107 will be administered at a fixed dose of 185 MBq and the participant will undergo SPECT/CT imaging after administration followed by planar imaging. It is currently planned to obtain two SPECT/CT images and four planar images over approximately 5 days following administration of [^{111}In]-FPI-2107 (with or without preadministration of FPI-2053). Following completion of the general screening procedures, and confirmation of preliminary eligibility, the baseline imaging screen will be performed as follows:
    a) **Part A:** Imaging agent [^{111}In]-FPI-2107 will be administered followed by SPECT/CT and planar imaging to be performed over 4 days. After a washout period of 6 to 8 days, participants will be administered FPI-2053, followed by [^{111}In]-FPI-2107 and will once again undergo SPECT/CT and planar imaging. The interval between the administration of FPI-2053 and [^{111}In]-FPI-2107 will be 30 minutes to 2 hours.
    b) **Part B:** Participants will be administered FPI-2053 (at the optimal dose as defined in Part A, if applicable) followed by [^{111}In]-FPI-2107. The interval between the administration of FPI-2053 and [^{111}In]-FPI-2107 will be 30 minutes to 2 hours. The participant will then undergo SPECT/CT and planar imaging.
3. *Treatment Period:* All participants must undergo a washout period of 14 to 17 days following [^{111}In]-FPI-2107 administration in the screening period. After this washout period, if the participant is deemed eligible, based on imaging, and if they continue to satisfy the general screening requirements, they can receive their first treatment dose, as outlined below. The start of the Treatment Period will be marked by the first administration of [^{225}Ac]-FPI-2068, with or without FPI-2053 (Cycle 1, Day 1). The Treatment Period will extend from Cycle 1, Day 1 to the End of Treatment visit.
    a) **Part A:** FPI-2053, followed by a fixed dose of [^{225}Ac]-FPI-2068 on Day 1 of the Treatment Period on a 56 day (+ 28 days) cycle for a maximum of 3 cycles. The interval between the administration of FPI-2053 and [^{225}Ac]-FPI-2068 will be 30 minutes to 2 hours.
    b) **Part B:** FPI-2053 (if applicable), followed by escalating doses of [^{225}Ac]-FPI-2068 on Day 1 of the Treatment Period on a 56-day (+ 28 days) cycle for a maximum of 3 cycles. The interval between the administration of FPI-2053 and [^{225}Ac]-FPI-2068 will be 30 minutes to 2 hours.

All subsequent cycles of [^{225}Ac]-FPI-2068 will be based on individual dosimetry and will not exceed the estimated cumulative radiation dose limit to specified organs (see Section 6.7.3 and Table 15 for retreatment criteria). If a planned dose level exceeds the total allowable cumulative dose, the participant may receive a reduced dose. Refer to Section 4.3.3 for further guidance on cumulative radiation dose limits.

Refer to Sections 8.1.4 through 8.1.7 for the assessment details and timepoints performed and for the biospecimens and information collected during the Treatment Period.

4. *End of Treatment and 28- or 42- day (+ 14 days) Safety Follow-Up Period:* Participants who do not receive any [^{225}Ac]-FPI-2068 (i.e., those who do not enter the Treatment Period) will have a Day 28 (± 3 days) safety visit as their last study visit. Participants who receive treatment with [^{225}Ac]-FPI-2068 will have a safety visit on Day 42 (+ 14 days) before entering the Extended Safety Follow-up Period.
5. *Extended Safety Follow-up Period:* Because cumulative radiation exposure may be associated with an increased risk of delayed onset of radiation-induced toxicity, participants will undergo additional safety assessments at 3-month intervals. The Extended Safety Follow-up Period will begin 3 months following the last dose of [^{225}Ac]-FPI-2068, and will continue every 3 months for 2 years, then every 6 months for an additional 3 years up to 5 years, or until the participant withdraws from the study (see Section 7.2). Refer to Section 8.1.8 for the assessment details and timepoints performed and for the biospecimens and information collected during the Extended Safety Follow-up Period.

Dose Levels:

Table 2 Planned Dose Levels (Part A) – Dose Exploration with FPI-2053 and [^{111}In]-FPI-2107, Followed by FPI-2053 and [^{225}Ac]-FPI-2068

Cohort	FPI-2053 [a]	[^{111}In]-FPI-2107 (imaging)	[^{225}Ac]-FPI-2068
1	0.3 mg/kg	185 MBq	15 kBq/kg
2	1 mg/kg	185 MBq	
3	3 mg/kg	185 MBq	

PK, pharmacokinetic(s); SRC, Safety Review Committee.

[a] Individual participants will be allocated in an alternating manner to Cohorts A1 and A2 until 3 participants have been treated in each cohort. The SRC will review safety, PK, biodistribution, and dosimetry data from Cohorts A1 and A2, prior to Cohort A3 being initiated if deemed necessary. The SRC will decide when to initiate Part B based on the totality of the data from Part A.

Table 3 Potential Dose Levels (Part B) - [^{225}Ac]-FPI-2068 Dose Escalation with Optimised FPI-2053 Dose

Cohort	FPI-2053 (mg/kg)	[^{111}In]-FPI-2107 (imaging)	[^{225}Ac]-FPI-2068 [a]
0	0	185 MBq	15 kBq/kg
1	Optimal Dose Defined in A	185 MBq	25 kBq/kg
2	Optimal Dose Defined in A	185 MBq	40 kBq/kg
3	Optimal Dose Defined in A	185 MBq	70 kBq/kg

AE, adverse event; MTD, maximum tolerated dose; PK, pharmacokinetics; SRC, Safety Review Committee.

[a] The SRC may choose to dose escalate at a lower incremental step than outlined in the table based on a full review of available safety data, including type, frequency, and grade of AEs and laboratory assessments, as well as PK and dosimetry, if applicable. If the MTD is not reached after the highest planned dose level, dose escalation may continue to higher doses if deemed safe by the SRC and per dose escalation rules. Each additional dose level will not exceed ~35% increase relative to the previous dose level.

Safety Review Committee:

A SRC will be convened to provide review of the accumulating safety data during the conduct of the study. The SRC will be responsible for making recommendations for dose escalation or dose de-escalation decisions and making recommendations regarding further conduct of the study during all phases of the study including suspension or stopping of the study. Refer to Section 6.7.8 for further details.

Statistical Methods:

General Methods:

This study will employ an mTPI-2 design for the dose escalation of [^{225}Ac]-FPI-2068. The mTPI-2 design employs a simple beta-binomial Bayesian model. The posterior density of the toxicity probability is divided into multiple intervals with equal length. These intervals are categorised as underdosing, proper dosing, and overdosing in terms of toxicity. The underdosing interval corresponds to a dose escalation, overdosing corresponds to a dose de-escalation, and proper dosing corresponds to staying at the current dose. The design for the dose escalation phase of the study uses a target DLT rate of 30% and an equivalence interval (25%, 35%) for dose escalation/de-escalation decisions as well as maximum tolerated dose (MTD) determination. A dose level is considered unsafe, with no additional participants enrolled at that dose level, if it has an estimated 95% or more probability of exceeding the target DLT rate of 30% (i.e., P [DLT > 30% data] ≥ 95%).

All collected data will be reported using summary tables and figures, as appropriate. Data summaries will be presented separately by cohort and/or dose level, as applicable. Tabulations will be produced for appropriate disposition, demographic, baseline, PK, anti-drug antibody (ADA), efficacy, and safety parameters.

Statistical Methods will be detailed in the Statistical Analysis Plan (SAP).

1.2 Schedule of Activities

Study procedures and their timing are presented in Section 8.1, as outlined below, as individual Schedule of Activities (SoA) tables for each study part and study period. At the End of Treatment, all participants must follow the procedures and timings outlined in the SoA table in Section 8.1.8.

- Part A – Dose Exploration with Unlabelled bsAb
    - Screening Period (see Section 8.1.1)
    - Treatment Period
    - Cycle 1 (see Section 8.1.4)
    - Cycle ≥ 2 (see Section 8.1.7)
    - PK, ECG, and biomarker sampling (see Section 8.1.9)
- Part B – Hot Dose Escalation with Unlabelled bsAb
    - Screening Period (see Section 8.1.2)
    - Treatment Period
    - Cycle 1 (see Section 8.1.5)
    - Cycle ≥ 2 (see Section 8.1.7)
    - PK, ECG, and biomarker sampling (see Section 8.1.10)
- Part B – Hot-only Dose Escalation
    - Screening Period (see Section 8.1.3)
    - Treatment Period (see Section 8.1.6)
    - PK, ECG, and biomarker sampling (see Section 8.1.11)

2 INTRODUCTION

[225Ac]-FPI-2068 is a novel radiopharmaceutical therapy that contains an alpha particle emitter, actinium-225, an epidermal growth factor receptor (EGFR) and mesenchymal-epithelial transition factor (c-MET) directed bispecific monovalent antibody (bsAb; FPI-2053), and a bifunctional chelate. [111In]-FPI-2107 is a novel imaging agent in which indium-111 is conjugated to the same EGFR and c-MET directed bispecific antibody. This first-in-human study will assess the safety, tolerability, dosimetry, biodistribution, pharmacokinetics (PK), pharmacodynamics, immunogenicity, and preliminary efficacy of the above theranostic pair in the treatment of advanced head and neck squamous cell carcinoma (HNSCC), non-small cell lung cancer (NSCLC), pancreatic ductal adenocarcinoma (PDAC), and metastatic colorectal cancer (mCRC).

Further information for [111In]-FPI-2107, FPI-2053, and [225Ac]-FPI-2068 is provided in the Investigator's Brochure (IB).

2.1 Background

2.1.1 EGFR and c-MET

The epidermal growth factor family of receptor tyrosine kinases, of which EGFR is the first to be identified, is essential for regulation of cell proliferation, differentiation, migration and survival. EGFR is frequently upregulated in NSCLC, CRC, glioblastoma, HNSCC, PDAC, and breast cancer (Wieduwilt and Moasser, 2008; Wee and Wang, 2017). c-MET is a tyrosine kinase receptor expressed on epithelial and endothelial cells and is activated by its only known ligand, hepatocyte growth factor (HGF) (Giordano et al, 1989; Ma et al, 2003). Met pathway activation is crucial during embryonic development, however, it is rarely active in adults (Birchmeier and Gherardi, 1998; Pothula et al, 2020). Dysregulation of the pathway by c-MET overexpression has been implicated in a number of malignancies including NSCLC, CRC, breast, ovarian, prostate, PDAC, and HNSCC (Fujita and Sugano, 1997; Resnick et al, 2004; Lengyel et al, 2005; Sawada et al, 2007; Spigel et al, 2013; Cancer Genome Atlas Research Network, 2014; Verhoef et al, 2016; Vsiansky et al, 2018; Pothula et al, 2020).

The role of EGFR and c-MET as effective druggable targets is well characterised with a number of therapies now established in clinical practice (Tagrisso USPI, 2018; Tabrecta USPI, 2020). Though the associated mechanism is not fully understood, overlapping biology and cross-talk between c-MET and EGFR pathway signal transduction has been demonstrated in a broad range of tumours, including cancers of the breast, lung, brain, and pancreas (Mueller et al, 2008; Agarwal et al, 2009; McDermott et al, 2010; Breindel et al, 2013; Park et al, 2015a; Kim, 2017; Zhang et al, 2018) and has manifested as an escape route during EGFR inhibitor monotherapy by upregulation and amplification of c-MET and HGF (Sellmann et al, 2016). Therefore, simultaneous targeting of the two pathways by monotherapy or drug combinations is currently being explored as a treatment strategy (Oxnard et al, 2019; Park et

al, 2021; Smit et al, 2022). One such monotherapy, amivantamab, an EGFR and c-MET directed bsAb, has recently gained approval from a number of regulatory authorities for the treatment of adults with locally advanced or metastatic NSCLC with activating EGFR Exon 20 insertion mutations, whose disease has progressed on or after platinum-based chemotherapy (Rybrevant SmPC, 2021; Rybrevant USPI, 2021). Properties of bsAbs, such as improved specificity and internalisation, are also being investigated as drug delivery mechanisms in two novel antibody-drug conjugates (ADCs) that are currently under development; ZW49 and bsHER2xCD63his (Antonarelli et al, 2021).

2.1.2 Radiation Therapy

Radiation therapy as an effective anticancer treatment modality has been recognised for over a century, with the potential to benefit approximately 50% of cancer patients during the course of their disease (WHO/IAEA, 2021). A wide range of tumours including HNSCC, PDAC, and mCRC are currently treated with conventional external beam radiotherapy that uses photon emissions.

Radiopharmaceuticals are pharmaceuticals which contain an unstable radionuclide. Often, the radionuclide is bound, either covalently or non-covalently, to an antibody, peptide, or small molecule designed to selectively target specific proteins expressed on tumour cells. Compounds used for diagnostic interventions usually emit beta particles (positrons or electrons) or gamma rays, while compounds that emit Auger electrons, high energy beta particles or alpha particles (helium nuclei), are generally for therapeutic interventions (Munjal and Gupta, 2021). In comparison to beta particle emissions, alpha particles have a shorter path length and higher linear energy transfer, which may result in reduced normal organ toxicity and a higher potency, respectively (Sgouros et al, 2020).

A number of therapeutic radiopharmaceuticals have received regulatory approval. They include the alpha emitter radium-223 dichloride (Xofigo USPI, 2013) for patients with symptomatic bone metastases from castration-resistant prostate cancer, the beta emitter lutetium-177 dotatate (Lutathera USPI, 2022) for somatostatin receptor positive gastroenteropancreatic neuroendocrine tumours, and more recently, lutetium-177 vipivotide tetraxetan for patients with prostate-specific membrane antigen (PSMA)-positive metastatic castrate-resistant prostate cancer [mCRPC]) who have been treated with androgen receptor pathway inhibition and taxane-based chemotherapy. The approval for lutetium-177 vipivotide tetraxetan was underpinned by compelling data from the Phase III VISION study, which demonstrated a statistically significant median overall survival (OS) benefit for lutetium-177 vipivotide tetraxetan versus standard of care in advanced-stage PSMA-positive mCRPC (Pluvicto USPI, 2022).

Most alpha emitters have low yields of imageable gamma emissions at clinically relevant injected activities making direct quantitative imaging difficult. Subsequently, if an alpha emitter such as actinium-225 is used in treatment, a gamma or positron emitting surrogate diagnostic agent that binds to the same molecular target is required to assess the

biodistribution and dosimetry (Kelly et al, 2020). Zirconium-89, indium-111 and the therapeutic radioisotope lutetium-177 have all been investigated as surrogate imaging isotopes for actinium-225 (Miller et al, 2020).

2.1.3 Investigational Agents

Three drug products will be used in the proposed Phase 1 study:

- [^{111}In]-FPI-2107 (radioimmuno-SPECT agent),
- FPI-2053 (unconjugated/unlabelled bispecific antibody [cold]), and
- [^{225}Ac]-FPI-2068 (radioimmuno-therapeutic agent [hot]).

The conjugates are produced by chelating actinium-225 or indium-111 to the monoclonal antibody FPI-2053 with a bifunctional chelating agent (FPI-1784).

FPI-2053 is a monovalent bispecific humanised IgG1 monoclonal antibody that targets both EGFR and c-MET. It employs the DuetMAb monovalent bispecific format, which allows for individual tuning of each binding arm to enhance target selectivity (Mazor et al, 2015). One Fab arm specifically binds to EGFR and the other Fab arm specifically binds to c-MET. The EGFR binding arm of the bispecific has a relatively lower affinity as compared to the c-MET arm in order to mitigate potential toxicity in tissues, such as the skin, that express substantial EGFR, but little c-MET. The antibody carries the well characterised “triple mutation” L234F/L235E/P331S (Oganesyan et al, 2008) in the Fc region, which was incorporated to reduce binding to Fc gamma receptors and thus reduce effector function.

[^{225}Ac]-FPI-2068 is a radiopharmaceutical therapy in which an alpha emitter, actinium-225, is conjugated to an EGFR and c-MET directed bsAb (FPI-2053). This bsAb has been modulated to have reduced binding affinity to EGFR, thereby potentially reducing normal tissue toxicity. Nonclinical data from both in vitro and in vivo models indicate that [^{225}Ac]-FPI-2068 has the potential to reduce the size of tumours that are known to have coexpression of EGFR and c-MET, such as HNSCC, NSCLC, mCRC, and PDAC, where an unmet need for a safe and effective radiation treatment modality exists. The rationale for the current study assumes that simultaneous targeting of both EGFR and c-MET using a bsAb would drive internalisation of actinium preferentially in tumour cells with a high coexpression of the targets, while minimising radiation injury to normal tissue.

Leveraging the internalisation mechanism of the EGFR-c-MET bispecific antibody, [^{225}Ac]-FPI-2068 aims to deliver the alpha particle-emitting radioisotope actinium-225 not only to the surface but also to interior of targeted tumour cells. As alpha particles traverse the nucleus of a targeted cell, they create a linear track of direct chromosomal damage leaving behind multiple clusters of double strand DNA breaks (DSB) while also producing single strand DNA breaks and other cellular damage due to ionisation and free radical formation as per traditional ionising radiation therapies. DSB formed by alpha particles have been shown to be more extensive, more persistent, and more difficult to repair than other types of DNA

damage (van de Kamp et al, 2021).

Since [225Ac]-FPI-2068 does not emit radiation that is readily amenable for clinically useful image acquisition, [111In]-FPI-2107 will be used as a radioimmuno-SPECT imaging agent for calculating dosimetry and to identify participants for inclusion in the study.

[177Lu]-FPI-2071 is the lutetium-177 analogue of the [225Ac]-FPI-2068 and was used as a laboratory reagent for in vitro experiments and biodistribution studies. Nonclinical pharmacological assessment of [177Lu]-FPI-2071 demonstrated that the radioimmunoconjugate is capable of binding to lung and CRC cell lines expressing EGFR and c-MET receptors and deliver the radionuclide to the surface of and inside the cells. Single doses of [225Ac]-FPI-2068 resulted in prolonged tumour regression in most tumour models (> 28 days). Treatment-induced formation of DSB, induction of DNA Damage Response pathway proteins and apoptosis contribute to the mechanism of action of [225Ac]-FPI-2068.

A repeat dose toxicology study in cynomolgus monkeys of FPI-2054, which consists of FPI-2053 conjugated with the FPI-1784 bifunctional linker without a radiometal chelated, and the unconjugated bispecific antibody FPI-2053, was conducted to characterize the chemical toxicity profile of the targeting molecule used for [225Ac]-FPI-2068 and [111In]-FPI-2107. The pivotal Good Laboratory Practice (GLP) toxicity study was a 5-week repeat dose (Q1W x 5) IV study with a 4-week recovery period in the cynomolgus monkey at dose levels of FPI-2053/FPI-2054 of 10/0.5 mg/kg, 50/2.5 mg/kg, and 100/5 mg/kg and 0/5 mg/kg. All major organs and functions (respiratory, cardiovascular, renal, liver, and nervous system) were assessed and no FPI-2054 or FPI-2053-related clinical signs or effects were noted on survival, local (skin) tolerance, electrocardiogram, blood pressure, respiration rate, ophthalmoscopy, neurological endpoints, clinical pathology or anatomical pathology (macroscopic or microscopic) at any dose level tested. The no-observed-adverse-effect level (NOAEL) was 100 mg/kg FPI-2053 and 5 mg/kg FPI-2054 Q1W for 5 doses.

A detailed description of the chemistry, pharmacology, efficacy, and safety of [225Ac]-FPI-2068, [177Lu]-FPI-2071, and FPI-2053, is provided in the IB.

2.1.4 Previous Clinical Experience

There are a number of actinium-225 conjugates in development. Two of these representative actinium-225 conjugates ([225Ac]-lintuzumab and [225Ac]-PSMA-617) have reported clinical data in cancer participants (Jurcic et al, 2011; Jurcic et al, 2016; Finn et al, 2017; Kratochwil et al, 2017). Although these conjugates use different targeting molecules for delivery of actinium-225, the safety experience with these agents is relevant for the potential risks that may be associated with the use of [225Ac]-FPI-2068 injection.

Table 4 Dose of Actinium-225 Conjugates With Reported Outcomes

Investigational product	Current status of development	Starting human dose (kBq/kg)	Maximum tolerated dose (kBq/kg)
[^{225}Ac]-lintuzumab [a]	Phase II clinical study	18.5 (0.5 µCi/kg)	111 (3 µCi/kg) [b]
[^{225}Ac]-PSMA-617 [c]	Phase 1 / Compassionate use	NA	100 every 8 weeks [d]
[^{225}Ac]-J591 [e]	Phase I dose escalation study	13.3	93.3 [f]

NA, not applicable.
[a] Jurcic et al, 2011.
[b] Single dose.
[c] Kratochwil et al, 2017.
[d] Recommended dose in advanced prostate cancer participants based on compassionate use observations.
[e] Tagawa et al, 2021.
[f] Highest dose level.

2.1.4.1 [^{225}Ac]-Lintuzumab

In the first-in-human, single dose, 3 + 3 dose escalation design study, 18 participants received a single infusion of the CD33 targeted alpha therapeutic, [^{225}Ac]-lintuzumab, at doses of 18.5, 37, 74, 111, or 148 kBq/kg with total administered radioactivity ranging from 888 to 14,874 kBq (Rosenblat et al, 2022). To limit binding of the radiolabelled antibody in the liver, 250 µg of unlabelled lintuzumab was given by IV infusion before administration of [^{225}Ac]-lintuzumab. The maximum tolerated dose (MTD) of [^{225}Ac]-lintuzumab was determined to be 111 kBq/kg; dose limiting toxicities (DLTs) included myelosuppression in 1 participant receiving 148 kBq/kg and death from sepsis in 2 participants treated with 111 and 148 kBq/kg. Overall, the most common toxicity was myelosuppression. The duration of myelosuppression was shown to correlate with administered activity but not CD33 expression or number of prior treatments. Significant extramedullary toxicities included transient Grade 3 liver function abnormalities but no evidence of renal toxicity.

2.1.4.2 [^{225}Ac]-PSMA-617

[^{225}Ac]-PSMA-617 is a small molecule radioligand therapy, targeting PSMA, one of the proteins overexpressed on the surface of prostate carcinoma cells. A retrospective, clinical summary was reported for 14 participants with mCRPC, who had exhausted approved treatments, and who had a PSMA-positive tumour phenotype as demonstrated by a preceding imaging study (Kratochwil et al, 2017). Treatment with [^{225}Ac]-PSMA-617 was empirically conducted with a single infusion of 50 kBq/kg (n = 4), 100 kBq/kg (n = 4), 150 kBq/kg (n = 2), or 200 kBq/kg (n = 4). Eight of the 14 participants received further cycles in either 2- or 4-month intervals with identical or de-escalated activities. Xerostomia/xerophthalmia due to high salivary and lacrimal gland uptake were the DLTs. PSMA expression is known to be

high in the salivary gland. There were no measurable changes in liver and kidney laboratory tests, nor any treatment-related haematological Grade 3 or 4 adverse events (AEs) in participants who were chemotherapy-naïve. Only one participant in the highest dose cohort (200 kBq/kg) experienced combined Grade 2 thrombocytopenia/leucopenia. Based on preliminary data, it was concluded that treatment activity of 100 kBq/kg administered every 2 months is tolerable and presents promising potential for anti-tumour activity.

In a pilot study of [^{225}Ac]-PSMA-617 in 17 participants with chemotherapy-naïve advanced prostate cancer, [^{225}Ac]-PSMA-617 was administered in 2-month intervals (Sathekge 2018). Grade 1 and 2 xerostomia were reported in all participants; however, none resulted in treatment discontinuation. One participant with extensive bone marrow metastases and baseline anaemia developed Grade 3 anaemia while another participant with solitary kidney and pretreatment Grade 3 renal failure developed treatment-emergent Grade 4 renal toxicity.

In another clinical study, 10 participants with mCRPC, refractory not only to first- and second-generation anti-androgen therapies, but also to taxane-based chemotherapies and [^{177}Lu]-PSMA-617 therapy were treated with [^{225}Ac]-PSMA-617 (Bal et al, 2019). Participants received 100 kBq/kg body weight, at eight-week intervals, for up to three cycles. All 10 participants had extensive PSMA-avid skeletal metastases on baseline 68Ga-PSMA positron emission tomography (PET)/computed tomography (CT). The participants received a median of two cycles. No participant experienced Grade 3 or 4 haematologic or kidney toxicity. Grade 1 or 2 xerostomia was observed in 80% and Grade 2 anorexia in 30% of participants.

In a meta-analysis comprising 256 participants, xerostomia was the most commonly-reported treatment-related AE (TEAE), observed in 72.7% (95% CI: 50.5–90.1%) of the patients (Satapathy et al, 2021). Grade ≥ 3 xerostomia, anaemia, leucopenia, thrombocytopenia, and nephrotoxicity was reported in 1.2%, 12.3%, 8.3%, 6.3%, and 3.8% of the participants, respectively. Treatment discontinuation due to AEs was noted in 20/208 participants. The Investigators concluded that ^{225}Ac-PSMA-radioligand therapy is a safe treatment option for patients with mCRPC.

2.1.4.3 [^{225}Ac]-J591

[^{225}Ac]-J591 is a monoclonal anti-PSMA antibody-based radioimmunoconjugate. Antitumour activity using the mAb, J591, as a radioimmunoconjugate was first demonstrated in a Phase I study of ^{90}Y-J591 in which partial responses and a (prostate-specific antigen) PSA decline of > 50% occurred in two participants (Milowski et al, 2004). Subsequently, ^{177}Lu-J591 has been evaluated in a number of Phase I/II clinical studies with demonstrated antitumour activity (Bander et al, 2005; Tagawa et al, 2013).

Tagawa et al, 2021 recently reported the outcomes of a dose escalation first-in-human study of [^{225}Ac]-J591 in men with progressive mCRPC following at least one androgen receptor pathway inhibitor (ARPI) and chemotherapy (including Ra-223 or prior ^{177}Lu-PSMA). Dose-escalation was with a single infusion of [^{225}Ac]-J591 starting at 13.3 kBq/kg with escalation

up to 93.3 kBq/kg. DLTs were defined as attributable Grade 4 haematological or Grade 3/4 non-haematological toxicities. Thirty-two men were treated with a single dose of [^{225}Ac]-J591 at seven dose levels and the highest dose level (93.3 kBq/kg) was expanded (n = 16). Of the total number of participants, 75% had been treated with > 2 prior ARPIs, 62.5% with prior chemotherapy, 28% with prior Ra-223 and 43.7% with prior ^{177}Lu-PSMA. While PSMA uptake was not a prerequisite for treatment, of the 28 participants with pretreatment PSMA PET, none had tumour maximum standardised uptake value (SUV_{max}) < liver, 5 (17.8%) had tumour SUV_{max} 1-2.5 x liver, 2 (7.2%) had tumour SUV_{max} 2.5-5 x liver and 21 (75%) had tumour SUV_{max} >5 x liver SUV_{mean}. One out of six participants in the 80 kBq/kg cohort had DLTs (Grade 4 anaemia and thrombocytopenia) with 0 out of six participants at the highest dose level (93.3 kBq/kg) experiencing any DLTs. In addition to DLTs, four (12.5%) cases of Grade 3 thrombocytopenia and two (6.2%) with Grade 3 neutropenia were observed. Non-haematological AEs were restricted to Grade 1/2 and included: 10 (31.2%) fatigue, 5 (15.6%) pain flare, 14 (43.7%) nausea, 8 (25%) with Grade 1 xerostomia (of which 5 received prior ^{177}Lu-PSMA) and 12 (37.5%) aspartate aminotransferase (AST) elevation. Despite prior treatment including ^{177}Lu-PSMA, 22 (68.7%) experienced any PSA decline and 12 (37.5%) experienced >50% PSA decline. Of the 21 participants with paired baseline and 12-week CTC counts, 12 declined (five converting from unfavourable to favourable and five converting detectable to 0), five remained 0, four increased. Following a single dose of ^{225}Ac-J591, a median progression free survival (PFS) of 7.2 months [95% CI 4.6-NR] and a median OS of 10.9 months [7.6-21.1] were achieved. Based on these results, the Investigators concluded that ^{225}Ac-J591 is tolerable with early evidence of clinical activity. A study investigating multiple and fractionated dosing of ^{225}Ac-J591 is currently in progress.

2.1.4.4 Indium-111 Conjugates

Indium-111 conjugates have been generally well tolerated with adverse reactions primarily related to the peptide or protein ligand. The following adverse effects were observed in clinical studies with OctreoScan (indium-111-Octotreotide; indium-111-pentetreotide) at a frequency of less than 1% of 538 participants: dizziness, fever, flush, headache, hypotension, changes in liver enzymes, joint pain, nausea, sweating, and weakness. These adverse effects were transient. In clinical studies, there was one reported case of bradycardia and one case of decreased haematocrit and haemoglobin (OctreoScan Package Insert, 2021). ProstaScint (indium-111-capromab pendetide) was generally well tolerated in the clinical studies. Adverse reactions were observed in 4% of participants; most commonly, increases in bilirubin, hypotension, and hypertension, which occurred in 1% of participants. Elevated liver enzymes and injection site reactions occurred in slightly less than 1% of participants. Other adverse reactions, listed in order of decreasing frequency, were pruritus, fever, rash, headache, myalgia, asthenia, burning sensation in thigh, shortness of breath, and alteration of taste (ProstaScint Kit, Package Insert, 2012). Most adverse reactions were mild and readily reversible.

The proposed dose for [^{111}In]-FPI-2107 for use as a SPECT/CT imaging agent is 185 MBq

(5 mCi), containing up to 5 mg of targeting protein. For justification of the proposed dose for FPI-2107, see Section 4.3.1. The administered radioactivity dose (185 MBq [5 mCi]) of indium-111 is consistent with the approved doses of indium-111 containing diagnostic agents such as OctreoScan and ProstaScint.

2.1.5 Therapeutic Indications

EGFR and c-MET coexpression has been reported in multiple cancer types, including NSCLC, HNSCC, colorectal, gastric, and pancreatic cancers among others (Dulak et al 2011; Sierra and Tsao 2011; Zhang et al, 2018).

2.1.5.1 Head and Neck Squamous Cell Carcinoma (HNSCC)

HNSCC is the 6th most common cancer globally with 890,000 new diagnoses and 450,000 deaths in 2018. The incidence of HNSCC continues to rise and is anticipated to increase by 30% by 2030 (Johnson et al, 2020). Alcohol and tobacco use are most associated with emergence of head and neck cancers, including metastases to the lungs and gastrointestinal system (Gillison et al, 2000; D'Souza et al, 2007; Schlecht et al, 2007; Sturgis and Cinciripini, 2007; Adelstein et al, 2008; Snow and Laudadio, 2010; Agalliu et al, 2016). Human papilloma virus (HPV) infection is a primary cause of tonsil and tongue base cancers and is increasing in the US, particularly in younger patients. Overall, HNSCC HPV-negative cancers (alcohol- and tobacco-use related) are decreasing in the US. Locally advanced HPV-positive cancers have better responses to treatment and survival rates compared to patients with HPV-negative cancers (Ang et al, 2010; Rischin et al, 2010; Posner et al, 2011; Fakhry et al, 2014; Fakhry et al, 2017; Ren et al, 2019; Fullerton et al, 2020).

The location of the cancer, stage, and pathology of HNSCC determine the specific treatment regimens, which typically includes surgery, radiation, or systemic chemotherapy. Early-stage disease is usually treated with surgery or radiation therapy, a decision made based on treatment options and expected morbidity. Combination therapy is usually recommended for patients with locally recurrent or metastatic lesions (NCCN Guidelines for Head and Neck Cancers V.1.2021).

EGFR overexpression is common in HNSCC and is associated with poor survival outcomes (Grandis et al, 1998; Zhu et al, 2013). Bonner et al randomly assigned 424 participants with locally advanced Stage III–IV squamous cell carcinomas of the hypopharynx, oropharynx, and larynx to receive definitive radiotherapy with or without cetuximab, an EGFR-targeting monoclonal antibody (Bonner et al, 2006). Locoregional control and median OS (49.0 vs. 29.3 months; P = 0.03) were significantly improved in participants treated with radiotherapy and cetuximab compared to radiotherapy alone. Five-year OS was 45.6% in participants treated with radiotherapy and cetuximab, and 36.4% in participants who received radiotherapy alone (HR, 0.73; 95% CI, 0.56–0.95; p = 0.018) (Bonner et al, 2010).

2.1.5.2 Non-small Cell Lung Cancer (NSCLC)

Lung cancer is a leading cause of mortality worldwide and in the US (Bray et al, 2018; Siegel

et al, 2022), and the majority (80% to 90%) of lung cancers are NSCLC (Planchard et al, 2018). In the US, approximately 57% of patients with NSCLC have metastatic disease at diagnosis, and 20% present with brain metastases at diagnosis (Siegel et al, 2019; Barnholtz-Sloan et al, 2004).

Because patients with advanced or metastatic NSCLC can undergo rapid clinical deterioration during disease progression, less than half of these patients ever receive second-line therapy (Davies et al, 2017; Lazzari et al, 2017).

In EGFRm NSCLC, amplification of the MET gene and/or overexpression of its protein product has been identified as the most common mechanism of clinical resistance to third generation EGFR tyrosine kinase inhibitors, such as osimertinib and abivertinib (Leonetti et al, 2019; Zhang et al, 2019). Therefore, targeting the two pathways by EGFR and c-MET inhibitor drug combinations and inhibition by a single molecule (small molecule or bsAb) are both currently being explored as treatment strategies for overcoming EGFR inhibitor resistance (Lee, 2016; Park et al, 2021; Smit et al, 2022).

In patients with EGFR-wild-type (wt) NSCLC, checkpoint inhibitors, either alone or in combination with chemotherapy, have recently been established as treatment of choice in first-line. Nearly half of EGFR wt NSCLC tumours were shown to express high levels of membranous c-MET, and these patients had poorer survival than c-MET-negative patients (Huang et al 2014). Recently, among participants with non-squamous NSCLC EGFR wt, telisotuzumab vedotin and ADC targeting c-MET achieved 52.2% objective response rate (ORR) in participants with high c-MET and an ORR of 24.1% in c-MET intermediate group in the second or third line setting (Camidge et al 2022). Despite these advances, there is still a high unmet need for this large patient segment of NSCLC.

2.1.5.3 Metastatic Colorectal Cancer (mCRC)

Colorectal cancer is one of the most frequently diagnosed cancers in the world and has the second highest mortality rate. Globally in 2020, there were over 1.9 million estimated new cases of colorectal cancer (CRC) and over 900,000 estimated deaths as a result of CRC (GLOBOCAN 2020). Approximately 50-60% of CRC patients develop metastases, and most cases are unresectable (Van Cutsem et al, 2006; Lee et al, 2007). The liver is the most common site of metastasis with the hepatic involvement being the cause of death in most cases (Fong et al, 1997). The prognosis is poor for patients with non-resectable hepatic disease and/or with metastases to other locations (Kemeny, 2006). There are multiple approved regimens for the treatment of unresectable CRC, spanning several drug classes, including EGFR inhibitors, which may be employed alone or in combination with other treatment modalities, depending on the patient's disease characteristics (Folprecht et al, 2010; Folprecht et al, 2014; Ye et al, 2013; Van Cutsem et al, 2016). Nevertheless, for patients who have exhausted available treatment regimens, new treatment modalities are needed.

The anticipated increase in CRC rates with unknown aetiology, particularly in the younger population, combined with the high number of non-resectable cases with hepatic involvement

represents an unmet medical need.

2.1.5.4 Pancreatic Ductal Adenocarcinoma (PDAC)

Pancreatic cancer is the seventh leading cause of cancer death in both men and women, and accounts for almost as many deaths (466,000) as cases (496,000) as per the GLOBOCAN database (Sung et al, 2021). PDAC accounts for 85-90% of all pancreatic cancers, with only 15-20% of cases amenable to surgery due to late presentation of symptomatic disease (Lambert et al, 2019).

Systemic treatment approaches include: chemotherapy (with mainstay being FOLFIRINOX, gemcitabine, capecitabine), the PARP inhibitor olaparib recommended as maintenance treatment of germline BRCA-mutated metastatic disease and the anti PD-1 receptor antibody pembrolizumab, for MSI-H or dMMR tumours. PDAC is a known radiosensitive malignancy with radiation treatment considered an option, commonly as chemoradiation, in most clinical scenarios that include resectable/borderline resectable, adjuvant, locally advanced, and recurrent disease (Tempero et al, 2021).

Despite the availability of various treatment modalities, survival rates for pancreatic cancer remain low with 5-year survival rate for all stages of disease at 11.4% including a 3.1% rate for metastatic disease in the US (SEER 2021).

EGFR expression is common in pancreatic adenocarcinomas, with 2 independent studies demonstrating that greater than 60% of PDACs express the receptor (Handra-Luca et al 2014, Park et al 2015b). Similarly to EGFR, expression of the MET receptor, and its ligand (HGF) have been reported in the majority of PDAC clinical tissue samples (Cazes et al 2015, Neuzillet et al 2015). Recently, a MET-targeting ADC molecule, that is currently in Phase 1 clinical studies, was shown to overcome gemcitabine resistance in animal models of pancreatic cancer (Cazes et al 2015).

2.2 Study Rationale

Nonclinical data from both in vitro and in vivo models indicates that [^{225}Ac]-FPI-2068 has the potential to reduce the size of tumours that are known to express EGFR and c-MET such as HNSCC, NSCLC, mCRC, and PDAC, where an unmet need for a safe and effective radiation treatment modality exists.

This study aims to deliver therapeutic radioactivity to tumour cells that express EGFR and c-MET. Clinical development will include enrolment of participants with HNSCC, NSCLC, mCRC, and PDAC, who have exhausted currently available standard of care options, representing a study population with a high, unmet medical need.

2.3 Benefit/Risk Assessment

More detailed information about the known and anticipated benefits, and potential risks of [^{225}Ac]-FPI-2068 may be found in the IB.

2.3.1 Risk Assessment

Table 5 Risk Assessment

Potential risk of clinical significance	Mitigation strategy
[^{225}Ac]-FPI-2068 and [^{111}In]-FPI-2107]	
Bone marrow suppression leading to haematological toxicity	Eligibility criteria excludes participants with low haematological parameters and previous extensive radiotherapy to pelvis, dosimetry estimates preclude exceeding CSP defined absorbed dose limit (Table 12), haematology evaluations per SoAs, included in DLT criteria, and TMGs in place.
Hepatic disorders, liver function test abnormalities (e.g., raised ALT/AST)	Inclusion criteria excludes participants with abnormal hepatic parameters, dosimetry estimates preclude exceeding CSP defined absorbed dose limit (Table 12), regular clinical chemistry evaluations and ADA monitoring per SoAs, included in DLT criteria, and TMGs in place.
Lung toxicities (e.g., ILD/pneumonitis, radiation pneumonitis)	Investigator advised to monitor for signs and symptoms of ILD/pneumonitis throughout the course of the study. Inclusion criteria requires further evaluation of participants with a history of lung toxicities and excludes those with ongoing pulmonary dysfunction, dosimetry estimates preclude exceeding CSP-defined absorbed dose limits (Table 12), baseline CT scan and further imaging as clinically indicated, blood sample evaluations, ADA monitoring per SoAs, ILD markers as clinically indicated, and TMGs in place.
Renal disorders including renal failure	Inclusion criteria excludes participants with insufficient renal function, dosimetry estimates preclude exceeding CSP defined absorbed dose limit (Table 12), blood sample evaluations, ADA monitoring per SoAs, and TMGs in place.
Other on-target (EGFR, c-MET driven) non-critical organ toxicities such as in skin, eye	Physical examinations and clinical monitoring
ADA formation.	Blood sampling to check for ADA per SoAs and management of organ-specific toxicities detailed above.
Study procedures	
Infusion-related reactions	Participants will be closely monitored during administration of study intervention and for 30 minutes after administration, and TMGs in place.

ADA, anti-drug antibody; ALT, alanine aminotransferase; AST, aspartate aminotransferase; c-MET, mesenchymal-epithelial transition factor; CT, computed tomography; DLT, dose-limiting toxicity; EGFR, epidermal growth factor receptor; ILD, interstitial lung disease; SoA, schedule of activities; TMG, toxicity management guidelines.

2.3.2 Benefit Assessment

[^{225}Ac]-FPI-2068 has the potential to elicit a clinical response in participants with tumours that coexpress EGFR and c-MET, such as HNSCC, NSCLC, CRC, and PDAC. As a novel treatment option, [^{225}Ac]-FPI-2068 will fulfil an unmet need in patients for whom additional effective standard therapy is not available, contraindicated, not tolerable, or not an option for any other reason.

2.3.3 Overall Benefit: Risk Conclusion

Taking into account the measures taken to minimise risk to participants in this study, the potential risks identified in association with [^{225}Ac]-FPI-2068 are justified by the anticipated benefits that may be afforded to participants with advanced solid tumours with limited treatment options.

3 OBJECTIVES AND ENDPOINTS

Table 6 Objectives and Endpoints

Type	Objectives	Endpoints
	Primary	
Safety / Dosimetry	• Evaluate the safety, tolerability, and dosimetry of [^{111}In]-FPI-2107, FPI-2053, and [^{225}Ac]-FPI-2068 • Determine the RP2D of [^{225}Ac]-FPI-2068, given with or without FPI-2053	• Frequency, duration, and severity of AEs, DLTs, and changes in clinical, laboratory, and ECG parameters compared to baseline • Estimates of residence time and absorbed radiation doses to the whole body, organs, and selected regions of interest for [^{111}In]-FPI-2107 and [^{225}Ac]-FPI-2068
Dosimetry	• Determine the effect of predose administration of FPI-2053 on the radiation dosimetry of [^{111}In]-FPI-2107 (whole body, organs, and selected regions of interest) • Estimate the effect of predose administration of FPI-2053 on the radiation dosimetry of [^{225}Ac]-FPI-2068 (whole body, organs, and selected regions of interest)	• Changes in uptake of [^{111}In]-FPI-2107 and projected RAD of [^{225}Ac]-FPI-2068 by imaging following predose administration of FPI-2053 compared to uptake of [^{111}In]-FPI-2107 imaging alone
	Secondary	
Efficacy	• Assess preliminary anti-tumour activity of [^{225}Ac]-FPI-2068	• ORR per RECIST 1.1 • TTR, DoR, PFS, DCR, and OS • Percentage changes in total ctDNA (VAF), compared to baseline
Pharmacodynamics	• Obtain preliminary data on the	• Tumour uptake of [^{111}In]-FPI-2107

	tumour uptake of [^{111}In]-FPI-2107	in selected regions of interest on SPECT/CT and/or planar images
PK	• Determine the PK of [^{111}In]-FPI-2107, FPI-2053, and [^{225}Ac]-FPI-2068, and the effect of predose administration of FPI-2053 on the PK of [^{111}In]-FPI-2107 and [^{225}Ac]-FPI-2068	• Plasma concentrations and PK parameters of [^{111}In]-FPI-2107 and [^{225}Ac]-FPI-2068, including but not limited to: clearance, AUC_{last}, C_{max}, and half-life • Changes in plasma concentrations and PK parameters (as indicated above) of [^{111}In]-FPI-2107 following FPI-2053 preadministration compared to [^{111}In]-FPI-2107 alone
Immunogenicity	• To assess the immunogenicity of [^{111}In]-FPI-2107, [^{225}Ac]-FPI-2068, and FPI-2053	• Presence of ADA for [^{111}In]-FPI-2107, [^{225}Ac]-FPI-2068, and FPI-2053
	Exploratory	
Safety / Dosimetry	• Assess the relationship between organ dosimetry based on imaging with [^{111}In]-FPI-2107 and any observed toxicity following administration of [^{225}Ac]-FPI-2068	• Correlation between organ dosimetry based on imaging with [^{111}In]-FPI-2107 and observed toxicities following administration of [^{225}Ac]-FPI-2068
Pharmacodynamics	• Assess the impact of [^{225}Ac]-FPI-2068 regimen on exploratory, blood-based biomarkers	• Changes in circulating biomarkers such as TCR repertoire following administration of [^{225}Ac]-FPI-2068 regimen
Pharmacodynamics	• Assess the relationship between baseline tumour or circulating biomarkers and response to [^{225}Ac]-FPI-2068	• Correlation between baseline tumour or circulating marker and change in tumour size
Dosimetry	• Assess the association between target expression in the baseline tumour by IHC and tumour uptake of ^{111}In-FPI-2107	• Correlation between the IHC expression of EGFR and c-MET in baseline tumour and projected RAD
Dosimetry	• Assess the association between RAD and tumour response	• Correlation between RAD and changes in tumour size

ADA, anti-drug antibody; AE, adverse event; AUC_{last}, area under the concentration time curve from 0 to the last quantifiable concentration; C_{max}, maximum concentration after dosing; c-MET, mesenchymal-epithelial transition factor; CT, computed tomography; ctDNA, circulating tumour DNA; DCR, disease control rate; DLT, dose-limiting toxicity; DoR, duration of response; ECG, electrocardiogram; EGFR, epidermal growth factor receptor; IHC, immunohistochemistry; ORR, objective response rate; OS, overall survival; PFS, progression free survival; PK, pharmacokinetics; RAD, radiation absorbed dose; RECIST, Response Evaluation Criteria in Solid Tumours; RP2D, recommended Phase 2 dose; SPECT, single-photon emission computed tomography; TCR, T-cell receptor; TTR, time to response; VAF, variant allelic frequency.

4 STUDY DESIGN

4.1 Overall Design

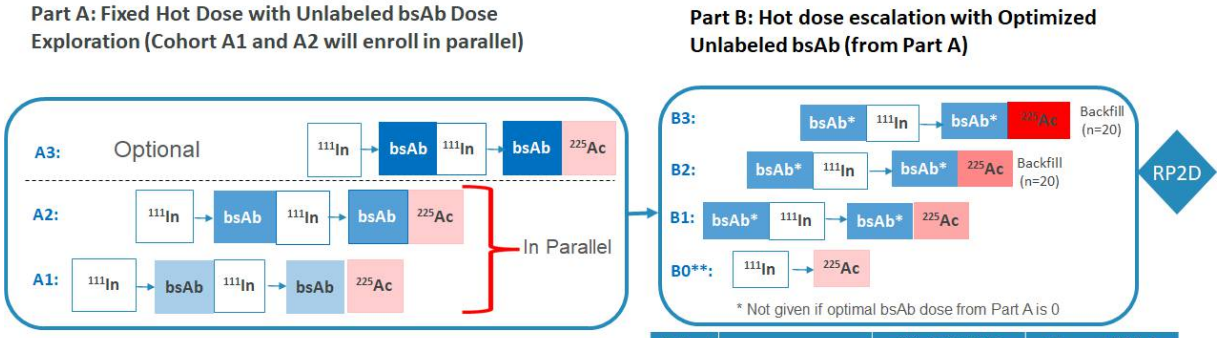
This is a first-in-human, Phase 1, non-randomised, multicentre, open-label clinical study designed to investigate the safety, tolerability, dosimetry, biodistribution, and PK of [^{225}Ac]-FPI-2068, [^{111}In]-FPI-2107, and the effect of predose administration of FPI-2053 on the PK and biodistribution of [^{225}Ac]-FPI-2068 and [^{111}In]-FPI-2107. In addition, the

pharmacodynamics, preliminary anti-tumour activity, and recommended Phase 2 dose (RP2D) of a [225Ac]-FPI-2068 regimen in participants with advanced, metastatic and/or recurrent solid tumours (HNSCC, NSCLC, mCRC, PDAC) that demonstrate uptake of the imaging agent as determined by SPECT/CT will be evaluated.

The study will be conducted in 2 parts:

- Part A: FPI-2053 dose exploration to determine the optimal predose administration of FPI-2053 with a fixed dose (15 kBq/kg) of [225Ac]-FPI-2068.
- Part B: [225Ac]-FPI-2068 dose escalation with the optimal dose of FPI-2053 as determined in Part A.

Figure 3 Study Schema



Cohort	Planned FPI-2053 Dose	[111In]-FPI-2107 Dose	[225Ac]-FPI-2068 Dose
A1	0.3 mg//kg	185 MBq	15 kBq/kg
A2	1 mg/kg		
A3	3 mg/kg		

Cohort	FPI-2053 Dose	[111In]-FPI-2107 Dose	Planned [225Ac]-FPI-2068 Dose
B0**	Optimal Dose Defined in Part A	185 MBq	15 kBq/kg
B1			25 kBq/kg
B2			40 kBq/kg
B3			70 kBq/kg

** B0 will open only if unlabeled bsAb not required based on Part A

111In, [111In]-FPI-2107; 225AC, [225Ac]-FPI-2068; bsAb, bispecific antibody (FPI-2053); RP2D, recommended Phase 2 dose.
Participants will be imaged with [111In]-FPI-2107 (with and/or without predose administration of FPI-2053) to determine participant eligibility and to estimate the maximum allowable cycles of [225Ac]-FPI-2068. The cumulative radiation dose of [225Ac]-FPI-2068 will be estimated for organs by cohort and individual participant. Colour intensity of blocks indicates dose levels (higher dose levels are darker).

Note:

- Cohort A1 and Cohort A2 will be initiated simultaneously and conducted in parallel.
- Individual participants will be allocated in an alternating manner to Cohort A1 or Cohort A2 after the General Screening Period but before the Imaging Screening Period (Figure 4), unless one of the cohorts is filled, in which case the recruitment will proceed sequentially until 3 participants have been treated with [225Ac]-FPI-2068 in each cohort. The first participant in Cohort A2 will be treated with [225Ac]-FPI-2068 only after the first participant in Cohort A1 has undergone a minimum of one week of safety observation.

- Following review of safety, PK, biodistribution, and dosimetry data from Cohorts A1 and A2 by the Sponsor and the SRC, Cohort A3 may be initiated if deemed necessary. The SRC will also determine when to initiate Part B.
- Part B will commence once the optimal dose of FPI-2053 is determined in Part A.
- Part A may be discontinued due to safety concerns. Cohorts within Part A may also be discontinued at the discretion of SRC based on criteria such as high (> 80%) imaging screen failure rate, low (< 5 Gy) projected cumulative tumour absorbed dose, and projected total organ absorbed doses that exceed CSP-specified limits in a significant number of participants.
- The study will employ a modified toxicity probability interval-2 (mTPI-2) design (see Section 6.7.4) to estimate MTD in Part B.
- Participants will be eligible to receive investigational treatment ([^{225}Ac]-FPI-2068 with or without FPI-2053 per assigned cohort) in Parts A or B if they meet all general screening and imaging criteria.
- The RP2D will be determined from Part B based on all available safety, efficacy, PK, and dosimetry information.

At least 3 evaluable participants are required at the optimal dose of FPI-2053 to be taken forward to Part B. At least three, and up to nine, evaluable participants are required for each dose cohort in Part B as per the mTPI-2 design (unless unacceptable toxicity is seen before three evaluable participants). The actual number of dose levels and participants enrolled during dose escalation will depend upon the number of DLTs in each cohort, the dosimetry at each dose level, and the overall safety profile observed, including the emergence of late-onset toxicities, as the study progresses.

Cohorts A1 and A2 will be initiated simultaneously and conducted in parallel. It is estimated that up to 110 participants may be enrolled. It is estimated that 9 participants will be enrolled in Part A, approximately 18 participants in Part B, 20 participants in backfill, and 60 participants at the RP2D.

The estimated study treatment duration for participants is approximately 12 months.

It is estimated that the clinical study will take approximately 4 years to complete.

4.1.1 Backfill Cohorts

If a preliminary signal of activity is observed, backfill cohorts of one or more dose level at any dose level not exceeding the projected MTD will be initiated per predefined efficacy criteria and at SRC discretion. The backfill cohorts will allow the safety, PK, dosimetry, pharmacodynamic measures, and preliminary anti-tumour activity to be assessed to a greater extent to assist selection of the RP2D. It is anticipated that one or two dose levels of approximately 20 evaluable participants per dose level may be backfilled, based on observed

anti-tumour activity such as one or more of the following:

- ≥ 1 confirmed partial response (PR)
- ≥ 2 unconfirmed PRs
- ≥ 1 unconfirmed PR and decrease in circulating tumour DNA (ctDNA) by 50% and ≥ 25 Gy cumulative absorbed dose in any tumour lesion

A backfill cohort may be further expanded to approximately 60 participants if ongoing safety and dosimetry support the decision and anti-tumour activity such as the following is observed in the first 20 participants:

- ≥ 4 confirmed PR
- ≥ 5 unconfirmed and/or confirmed PR

4.1.2 Cohort Discontinuation

In the event that the Sponsor and the SRC agree that, based on the totality of the data, continued evaluation of a given cohort is not advisable, enrolment to that cohort may be discontinued.

4.1.3 Radiation Dosimetry

Participants will receive an injection of [^{111}In]-FPI-2107 during the Imaging Screening Period to assess eligibility per local assessment and to estimate the maximum allowable cumulative dose of [^{225}Ac]-FPI-2068, with or without FPI-2053. Significant target expression is defined as at least one measurable lesion with uptake ≥ 2 times greater than skeletal muscle following [^{111}In]-FPI-2107 administration and SPECT/CT imaging. Only two SPECT/CT images need to be obtained between 24 and 96 hours post [^{111}In]-FPI-2107 injection. Planar imaging will be acquired at 4 time points for dosimetry calculation after [^{111}In]-FPI-2107 administration. Please refer to the Site Imaging Manual for timing of the scans, as precise timing may be revised over the course of the study.

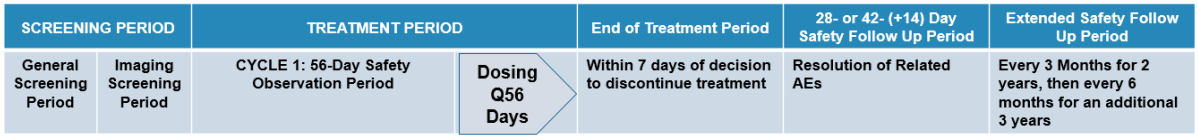
Participants may receive their first cycle of [^{225}Ac]-FPI-2068, with or without FPI-2053, after confirmation of successful completion of the imaging screening with [^{111}In]-FPI-2107 including organ dosimetry and sufficient target expression by the imaging vendor(s). Please refer to the imaging manual for details. All subsequent cycles of [^{225}Ac]-FPI-2068 will be based on individual dosimetry and will not exceed the participant's estimated cumulative radiation dose limit to specified organs. Eligible participants will receive up to 3 cycles of [^{225}Ac]-FPI-2068.

4.1.4 Study Periods

The study is divided into 5 periods: (1) General Screening Period, (2) Imaging Screening Period, (3) Treatment Period, (4) End of Treatment and 28- or 42- (+ 14 days) Day Safety

Follow-Up Period, and (5) Extended Safety Follow-Up Period:

Figure 4 Study Periods



Q56, every 56 days.
The length of each cycle within the treatment period will encompass a minimum of 56 days.

1. *General Screening Period:* All screening procedures **except baseline imaging** are to be performed during the General Screening Period. Participants must satisfy all general screening requirements (inclusion/exclusion) before undergoing baseline imaging.
2. *Imaging Screening Period:* The areas to be imaged with SPECT/CT are to be selected by the Investigator and/or appropriate delegate at the clinical sites and must include bone marrow, kidneys, lungs, and liver. [^{111}In]-FPI-2107 will be administered at a fixed dose of 185 MBq and the participant will undergo SPECT/CT imaging after administration followed by planar imaging. It is currently planned to obtain two SPECT/CT images and four planar images over approximately 5 days following administration of [^{111}In]-FPI-2107 (with or without preadministration of FPI-2053). Following completion of the general screening procedures, and confirmation of preliminary eligibility, the baseline imaging screen will be performed as follows:
   a) **Part A:** Imaging agent [^{111}In]-FPI-2107 will be administered followed by SPECT/CT and planar imaging to be performed over 4 days. After an appropriate washout period of 6 to 8 days, participants will be administered FPI-2053, followed by [^{111}In]-FPI-2107 and will once again undergo SPECT/CT and planar imaging. The interval between the administration of FPI-2053 and [^{111}In]-FPI-2107 will be 30 minutes to 2 hours.
   b) **Part B:** Participants will be administered FPI-2053 (at the optimal dose as defined in Part A; if applicable) followed by [^{111}In]-FPI-2107. The interval between the administration of FPI-2053 and [^{111}In]-FPI-2107 will be 30 minutes to 2 hours. The participant will then undergo SPECT/CT and planar imaging.
3. *Treatment Period:* All participants must undergo an appropriate washout period of 14 to 17 days following [^{111}In]-FPI-2107 administration in the screening period. After this washout period, if the participant is deemed eligible, based on imaging, and if they continue to satisfy the general screening requirements, they can receive their first treatment dose, as outlined below. The start of the Treatment Period will be marked by the first administration of [^{225}Ac]-FPI-2068, with or without FPI-2053 (Cycle 1,

Day 1). The Treatment Period will extend from Cycle 1, Day 1 to the End of Treatment visit.

a) **Part A:** FPI-2053, followed by a fixed dose of [^{225}Ac]-FPI-2068 on Day 1 of the Treatment Period on a 56 day (+ 28 days) cycle for a maximum of 3 cycles. The interval between the administration of FPI-2053 and [^{225}Ac]-FPI-2068 will be 30 minutes to 2 hours.

b) **Part B:** FPI-2053 (if applicable), followed by escalating doses of [^{225}Ac]-FPI-2068 on Day 1 of the Treatment Period on a 56-day (+ 28 days) cycle for a maximum of 3 cycles. The interval between the administration of FPI-2053 and [^{225}Ac]-FPI-2068 will be 30 minutes to 2 hours.

All subsequent cycles of [^{225}Ac]-FPI-2068 will be based on individual dosimetry and will not exceed the participant's estimated cumulative radiation dose limit to specified organs (see Section 6.7.3 and Table 15 for retreatment criteria). If a planned dose level exceeds the total allowable cumulative dose, the participant may receive a reduced dose. Refer to Section 4.3.3 for further guidance on cumulative radiation dose limits.

Prior to the administration of [^{225}Ac]-FPI-2068, all AEs related to [^{111}In]-FPI-2107 or FPI-2053 should be resolved to Grade 1 or baseline. A delay of 28 days is acceptable from the time of the last [^{111}In]-FPI-2107 (± FPI-2053) administration to the administration of [^{225}Ac]-FPI-2068 if an AE related to [^{111}In]-FPI-2107 or FPI-2053 requires longer time for resolution. In circumstances (e.g., intercurrent illness, etc.) where a delay of [^{225}Ac]-FPI-2068 administration may be necessary, the Sponsor and/or Medical Monitor must be consulted to discuss whether the participant can receive [^{225}Ac]-FPI-2068. In this scenario, Sponsor and/or Medical Monitor agreement is required prior to [^{225}Ac]-FPI-2068 administration. Laboratory results confirming bone marrow and organ function, within retreatment criteria requirements must be documented within 48 hours prior to each cycle of [^{225}Ac]-FPI-2068 administration.

Refer to Sections 8.1.4 through 8.1.7 for the assessment details and timepoints performed, and for the biospecimens and information collected during the Treatment Period.

4. *End of Treatment and 28- or 42-Day (+ 14 days) Safety Follow-Up Period:* Participants who do not receive any [^{225}Ac]-FPI-2068 (i.e., those who do not enter the Treatment Period) will have a Day 28 (± 3 days) safety visit as their last study visit. Participants who receive treatment with [^{225}Ac]-FPI-2068 will have a safety visit on Day 42 (+ 14 days) before entering the Extended Safety Follow-up Period.
5. *Extended Safety Follow-up Period:* Because cumulative radiation exposure may be associated with an increased risk of delayed onset of radiation-induced toxicity, participants will undergo additional safety assessments at 3-month intervals. The Extended Safety Follow-up Period will begin 3 months following the last dose of

[^{225}Ac]-FPI-2068, and will continue every 3 months for 2 years, then every 6 months for an additional 3 years up to 5 years, or until the participant withdraws from the study (see Section 7.2). Refer to Section 8.1.8 for the assessment details and timepoints performed, and for the biospecimens and information collected during the Extended Safety Follow-up Period.

4.1.5 Dose Levels

Table 7 Planned Dose Levels (Part A) – Dose Exploration with FPI-2053 and [^{111}In]-FPI-2107, Followed by FPI-2053 and [^{225}Ac]-FPI-2068

Cohort	FPI-2053 [a]	[^{111}In]-FPI-2107 (imaging)	[^{225}Ac]-FPI-2068
1	0.3 mg/kg	185 MBq	15 kBq/kg
2	1 mg/kg	185 MBq	
3	3 mg/kg	185 MBq	

PK, pharmacokinetics; SRC, Safety Review Committee.
[a] Individual participants will be allocated in an alternating manner to Cohorts A1 and A2 until 3 participants have been treated in each cohort. The SRC will review safety, PK, biodistribution, and dosimetry data from Cohorts A1 and A2, prior to Cohort A3 being initiated if deemed necessary. The SRC will decide when to initiate Part B based on the totality of the data from Part A.

Table 8 Potential Dose Levels (Part B) - [^{225}Ac]-FPI-2068 Dose Escalation with Optimised FPI-2053 Dose

Cohort	FPI-2053	[^{111}In]-FPI-2107 (imaging)	[^{225}Ac]-FPI-2068 [a]
0	0	185 MBq	15 kBq/kg
1	Optimal Dose Defined in A	185 MBq	25 kBq/kg
2	Optimal Dose Defined in A	185 MBq	40 kBq/kg
3	Optimal Dose Defined in A	185 MBq	70 kBq/kg

AE, adverse event; MTD, maximum tolerated dose; PK, pharmacokinetics; SRC, Safety Review Committee.
[a] The SRC may choose to dose escalate at a lower incremental step than outlined in the table based on a full review of available safety data, including type, frequency, and grade of AEs and laboratory assessments, as well as PK and dosimetry, if applicable. If the MTD is not reached after the highest planned dose level, dose escalation may continue to higher doses if deemed safe by the SRC and per dose escalation rules. Each additional dose level will not exceed ~35% increase relative to the previous dose level.

4.1.6 Study Conduct Mitigation During Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis

The guidance given below supersedes instructions provided elsewhere in this CSP and should be implemented only during cases of civil crisis, natural disaster, or public health crisis (e.g., during quarantines and resulting site closures, regional travel restrictions, and considerations if site personnel or study participants become infected with SARS-CoV-2 or similar pandemic infection) which would prevent the conduct of study-related activities at

study sites, thereby compromising the study site staff or the participant's ability to conduct the study. The Investigator or designee should contact the study Sponsor to discuss whether the mitigation plans below should be implemented.

To ensure continuity of the clinical study during a civil crisis, natural disaster, or public health crisis, changes may be implemented to ensure the safety of study participants, maintain compliance with GCP, and minimise risks to study integrity.

Where allowable by local health authorities, ethics committees, healthcare provider guidelines (e.g., hospital policies) or local government, these changes may include the following options:

- Obtaining reconsent for the mitigation procedures (note, in the case of verbal reconsent, the ICF should be signed at the participant's next contact with the study site).
- Rescreening: Additional rescreening for screen failure and to confirm eligibility to participate in the clinical study can be performed for previously screened participants. The Investigator should confirm this with the designated study physician.
- Telemedicine visit: Remote contact with the participants using telecommunications technology including phone calls, virtual or video visits, and mobile health devices.

For further details on study conduct during civil crisis, natural disaster, or public health crisis, refer to Appendix F.

4.2 Scientific Rationale for Study Design

This is a first-in-human study primarily designed to evaluate the safety and tolerability of [^{225}Ac]-FPI-2068 in monotherapy following the corresponding imaging with or without FPI-2053 at increasing doses in participants with advanced solid malignancies known to have a coexpression of EGFR and c-MET, such as HNSCC, NSCLC, mCRC, and PDAC, where an unmet need for a safe and effective radiation treatment modality exists. The study will also characterise the PK of [^{225}Ac]-FPI-2068 (with and without predosing of FPI-2053) and explore potential biological activity by assessing pharmacodynamic and exploratory biomarkers, and anti-tumour activity. The results from this study will form the basis for decisions on future studies.

Predosing with unlabelled antibody to improve biodistribution of the radiolabelled drug conjugate has been tested previously in clinical and nonclinical studies with other antibody-based radiotherapeutics (e.g., CD20, PSMA, EGFR, HER2, HER3). The same approach will be utilised in this study to optimise dose selection of [^{225}Ac]-FPI-2068 with or without predose administration of FPI-2053. If it is determined that predose FPI-2053 should be incorporated in the [^{225}Ac]-FPI-2068 dosing regimen, the same FPI-2053 dose will be administered prior to both [^{111}In]-FPI-2107 and [^{225}Ac]-FPI-2068 in Part B.

4.3 Justification for Starting Dose

4.3.1 [^{111}In]-FPI-2107

The proposed dose for [^{111}In]-FPI-2107 for use as a SPECT/CT imaging agent is 185 MBq (5 mCi), containing up to 5 mg of targeting protein. This mass dose represents an approximate 70-fold safety margin to FPI-2054 (bsAb conjugate) NOAEL at 5 mg/kg (when co-dosed with 100 mg/kg FPI-2053) identified in the GLP toxicology study conducted in cynomolgus monkeys. The administered radioactivity dose (185 MBq [5 mCi]) of indium-111 is consistent with the approved doses of indium-111 containing diagnostic agents such as OctreoScan and ProstaScint.

4.3.2 FPI-2053

The rationale for the starting doses for FPI-2053 of 0.3 and 1.0 mg/kg (to be co-dosed with [^{111}In]-FPI-2107 or [^{225}Ac]-FPI-2068) is based on modelling and simulation, in conjunction with the safety margin calculated from the NOAEL of the mass dose 100 mg/kg in cynomolgus monkeys from the GLP toxicology study.

A population PK model was developed to describe the PK of FPI-2053 in cynomolgus monkeys describing dual target mediated drug disposition. The model was extrapolated to humans from monkey PK data. The linear PK parameters were scaled using allometry, while the antibody affinity was obtained experimentally, and antigen density from literature. Antigen internalisation and conjugated/unconjugated binding assumptions were assumed to be the same as those derived in cynomolgus monkey. It is expected that these doses of FPI-2053 will be in the non-linear PK range.

The proposed dose levels for FPI-2053 are 0.3, 1, and 3 mg/kg. The starting doses of 0.3 and 1.0 mg/kg represent a greater than 100-fold margin to the NOAEL of 100 mg/kg FPI-2053 (see Table 9) when co-dosed with 5 mg/kg FPI-2054 identified in pivotal GLP study.

Table 9 Proposed Dose Levels and Exposure Margins for FPI-2053

Dose of FPI-2053 (mg/kg)	AUC_{cyno} (µg hr/mL)	AUC_{cyno} (µg.d/mL)	Predicted human AUC_h (µg.d/mL)	Safety margin (AUC_{cyno}/ $AUC_{h)}$	$C_{max, cyno}$ (µg/mL)	Predicted human C_{max} (µg/mL)	Safety margin ($C_{max, cyno}$/ $C_{max\ h)}$
0.3	192000	8000	7.9	1000	2260	5.6	400
1.0			33	240		18	120
3.0			170	47		56	40

AUC, area under the curve; AUCcyno, area under the curve in cynomolgus monkey; AUCh, area under the curve in human; Cmax, maximum concentration after dosing; Cmax cyno, maximum concentration after dosing in cynomolgus monkey; Cmax h, maximum concentration after dosing in human; GLP, Good Laboratory Practice. PK, pharmacokinetics.
AUC and C_{max} from cynomolgus monkey based on Day 1 PK profiles from a 5 week GLP toxicology Study 1589.04 (IV bolus). Human predictions are based on a 1 hour IV infusion.

4.3.3 [^{225}Ac]-FPI-2068

The rationale for the starting dose of 15 kBq/kg is based on the estimated radiation absorbed doses to critical organs projected from the cynomolgus monkey dosimetry study with [^{111}In]-FPI-2107, in conjunction with the safety margin calculated from the NOAEL of the mass dose 5 mg/kg of FPI-2054 in cynomolgus monkeys from the GLP toxicology study (see Table 10 and Table 11) and the PK projections based on the model described above.

The planned starting dose of [^{225}Ac]-FPI-2068 in mass dose terms are 200-fold lower than the NOAEL dose in a non-GLP toxicity study in non-human primates. Based on the upper end of the mass dose range, the AUC and C_{max} margins to the NOAEL dose are > 100-fold (see Table 12). Furthermore, the results of a cynomolgus monkey SPECT/CT biodistribution and dosimetry study were analysed to project adult human radiation absorbed doses of [^{225}Ac]-FPI-2068. These projections suggest that the proposed starting dose of 15 kBq/kg [^{225}Ac]-FPI-2068 with or without FPI-2053 coadministration will result in per-cycle absorbed doses to the critical organs and red marrow representing margins of 2.9 and 6.3-fold, of the International Commission on Radiological Protection (ICRP) limit with higher margins to kidney, liver, and lung ICRP limits.

Table 10 Projected Radiation Absorbed Doses to Critical Organs Following Administration of [^{225}Ac]-FPI-2068 per Single 15 kBq/kg Dose With or Without a Saturating Dose of FPI-2053

Organ/tissue	ICRP organ limit (Gy) [a]	Absorbed dose per 15 kBq/kg cycle of [^{225}Ac]-FPI-2068 (Sv)		Margin (organ limit/absorbed dose)	
		[^{225}Ac]-FPI-2068 [b, c]	[^{225}Ac]-FPI-2068 + FPI-2053 [b, d]	[^{225}Ac]-FPI-2068	[^{225}Ac]-FPI-2068 + FPI-2053
Kidney	23	0.36	0.54	64	43
Liver	31	3.6	1.5	8.5	20
Lung	16.5	0.11	0.35	147	47
Red marrow	2	0.32	0.69	6.3	2.9

ICRP, International Commission on Radiological Protection; Sv, sievert.

[a] ICR Publication 118, 2012

[b] Assuming 70kg bodyweight and RBE = 5.

[c] Based on projected absorbed doses for FPI-2068 for adult human kidney = 341 mSv/MBq, liver = 3470 mSv/MBq, lung = 106 mSv/MBq, red marrow = 303 mSv/MBq.

[d] Based on projected absorbed doses for FPI-2068 for adult human predosed with a saturating dose of unlabelled FPI-2053 (10 mg/kg in NHPs) kidney = 514 mSv/MBq, liver = 1430 mSv/MBq, lung = 333mSv/MBq, red marrow = 657 mSv/MBq.

Table 11 Projected Radiation Absorbed Doses to Critical Organs Following Administration of [^{225}Ac]-FPI-2068 Following 3 Cycles of 15 kBq/kg With or Without a Saturating Dose of FPI-2053

Organ/tissue	ICRP organ limit (Gy) [a]	Absorbed dose after 3 cycles of 15 kBq/kg [^{225}Ac]-FPI-2068 (Sv)		Margin (organ limit/absorbed dose)	
		[^{225}Ac]-FPI-2068 [b, c]	[^{225}Ac]-FPI-2068 + FPI-2053 [b, d]	[^{225}Ac]-FPI-2068	[^{225}Ac]-FPI-2068 + FPI-2053
Kidney	23	1.1	1.6	21	14
Liver	31	11	4.5	2.8	6.8
Lung	16.5	0.34	1.0	49	15
Red marrow	2	0.95	2.1	2.1	0.97

ICRP, International Commission on Radiological Protection; Sv, sievert.

[a] ICR Publication 118, 2012

[b] Assuming 70kg bodyweight and RBE = 5.

[c] Based on projected absorbed doses for FPI-2068 for adult human kidney = 341 mSv/MBq, liver = 3470 mSv/MBq, lung = 106 mSv/MBq, red marrow = 303 mSv/MBq.

[d] Based on projected absorbed doses for FPI-2068 for adult human predosed with a saturating dose of unlabelled FPI-2053 (10 mg/kg in NHPs) kidney = 514 mSv/MBq, liver = 1430mSv/MBq, lung = 333mSv/MBq, red marrow = 657 mSv/MBq.

Table 12 [^{225}Ac]-FPI-2068 Safety Margins According to Mass Dose Range

[^{225}Ac]-FPI-2068 (kBq/kg)	[^{225}Ac]-FPI-2068 mass dose range (µg/kg)	AUC_{cyno} (µg hr/mL)	AUC_{cyno} (µg d/mL)	Predicted human AUC_{lower} (µg d/mL)	Predicted human AUC_{upper} (µg d/mL)	Safety margin [a] (AUC_{cyno} / $AUC_{h)}$	$C_{max, cyno}$ (µg/mL)	Predicted human $C_{max, lower}$ (µg/mL)	Predicted human $C_{max, upper}$ (µg/mL)	Safety margin [a] ($C_{max, cyno}$ / $C_{max, h)}$
15	4.5-37.5	6360	265	0.15	1.3	200	89.4	0.11	0.84	106
25	7.5-62.5			0.25	2.2	120		0.18	1.4	63
40	12-100			0.40	3.5	75		0.28	2.3	39
70	21-175			0.70	6.2	43		0.49	3.9	22

AUC, area under the curve; AUCcyno, area under the curve in cynomolgus monkey; AUCh, area under the curve in human; Cmax, maximum concentration after dosing; $C_{max, cyno}$, maximum concentration after dosing in cynomolgus monkey; $C_{max\ h}$, maximum concentration after dosing in human; $C_{max, lower}$, maximum concentration after dosing lower limit; $C_{max, upper}$, maximum concentration after dosing upper limit; GLP, Good Laboratory Practice. PK, pharmacokinetics.

[a] Margins calculated based on upper limit of mass dose range

Mass dose range of [^{225}Ac]-FPI-2068 based on manufacturing target specific activity range of 0.814-3.145 MBq/mg and a 10-day shelf-life. AUC and C_{max} of FPI-2054 from cynomolgus monkey based on Day 1 PK profiles from a 5 week GLP toxicology Study 1589.04 (IV bolus).

Prior to treatment with [^{225}Ac]-FPI-2068, participants will be imaged with [^{111}In]-FPI-2107 (with and/or without predose administration of FPI-2053) to determine participant eligibility per local review. Prior to the administration of [^{225}Ac]-FPI-2068, individual dosimetry assessments and tumour-to-background-ratio (TBR) will be conducted centrally and reviewed with the Investigator to confirm eligibility and estimate the maximum allowable cycles of [^{225}Ac]-FPI-2068. All subsequent cycles of [^{225}Ac]-FPI-2068 will be based on assigned dose level and individual dosimetry such that an individual participant's cumulative radiation absorbed dose will not exceed limits of 23 Gy for kidneys, 31 Gy for liver, 16.5 Gy for lungs, and for Part A only, 2 Gy for red bone marrow. If a participant reaches a cycle in which the planned administered dose exceeds prespecified individualised cumulative radiation dose limits, the participant may receive a reduced administration such that the specified cumulative limit is not reached.

4.4 End of Study Definition

A participant is considered to have completed the study if they have completed all phases of the study including the last visit as per the Schedule of Activities (SoA) in Section 8.1.

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the Schedule of Activities for the last participant in the study globally.

There will be a data cut-off defined as when the last participant dies or 2 years after the final participant discontinues investigational product, whichever is sooner. The primary data analysis, including the OS and PFS analysis will be performed, and a Clinical Study Report (CSR) written based on this data set. Any participants still alive at the time of data cut-off will continue in long-term safety follow-up. The clinical database may be closed at the time of data cut-off and subsequent safety data collected on paper. A safety addendum to the CSR to include the long-term safety data may be prepared.

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Informed Consent

1. Capable of giving signed informed consent as described in Appendix A which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this CSP.
2. Provision of signed and dated written ICF prior to any mandatory study specific procedures, sampling, and analyses.

Age

3. Must be 18 years of age or older at the time of signing the ICF.

Type of Participant and Disease Characteristics

4. Histologically and/or cytologically confirmed solid tumour (either HNSCC, PDAC, CRC, or NSCLC) that is metastatic or locally advanced, inoperable (where surgery is not indicated due to disease extension, comorbidities, or other technical reasons) or recurrent.

5. TBR ≥ 2:1, relative to paravertebral spinal muscle, in at least one measurable extrahepatic lesion, as determined by SPECT/CT scan at any of the specified timepoints following the administration of [^{111}In]-FPI-2107.
6. Disease that has progressed despite prior treatment, and for which additional effective standard therapy is not available or is contraindicated, not tolerable, or the participant refuses standard therapy.
7. Measurable disease as defined by Response Evaluation Criteria in Solid Tumours (RECIST) Version 1.1. Lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.
8. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1.
9. Able to provide tumour tissue for analysis. If archival tissue obtained within the last 12 months is not available, a fresh biopsy will be required for immunohistochemistry (IHC) and biomarker analyses. Availability of tissue must be confirmed prior to administration of FPI-2053 or [^{111}In]-FPI-2107; however, the participant may receive study treatment prior to any analysis of the tissue.
10. Adequate organ function as indicated by the following laboratory values (all laboratory tests must be performed within 14 days prior to the first dose of investigational agent):
    a) Haematological:
        i. *Absolute neutrophil count (ANC) ≥ 1500/mm^3 (≥ 1.5 × 10^9/L)
        ii. *Platelet count ≥ 100,000/mm^3 (≥ 100 × 10^9/L)
        iii. *Haemoglobin ≥ 9.0 g/dL (≥ 90 g/L)
        iv. International normalised ratio 0.8 to upper limit of normal (ULN) or ≤ 3 for participants receiving anticoagulant therapy such as coumadin or heparin

        *Haematological criteria cannot be met with ongoing or recent blood transfusions (within 7 days prior to the scheduled first dose of study treatment) or require growth factor support (within 21 days prior to the scheduled first dose of study treatment).
    b) Cardiac:
        i. Resting QTcF: ≤ 450 msec for men and ≤ 470 msec for women
    c) Renal:
        i. Creatinine clearance ≥ 60 mL/min/1.73 m^2 (calculated by Cockcroft-Gault formula)
    d) Hepatic:
        i. AST and ALT ≤ 3.0 × ULN (≤ 5 × ULN in participants with known liver metastasis)
        ii. Serum total bilirubin ≤ 1.5 × ULN (≤ 3 x ULN in participants with Gilbert's disease).
11. In the judgement of the Investigator, the participant is expected to be compliant and have a high probability of completing the study.

12. Anticipated life expectancy ≥3 months.

Reproduction

13.

a) All women of childbearing potential (WCBP) must agree to use at least two forms of contraception, one of which must be a highly effective method, or agree to remain abstinent, for the duration of study participation and for 6 months following both [^{111}In]-FPI-2107 and the final dose of [^{225}Ac]-FPI2068. See Appendix C for definitions of highly effective forms of contraception and WCBP.

b) Male participants should be asked to avoid unprotected sex with women of child-bearing potential for the duration of study participation and for 6 months following both [^{111}In]-FPI-2107 and the final dose of [^{225}Ac]-FPI-2068. The effects of [^{111}In]-FPI-2107 and [^{225}Ac]-FPI-2068 on spermatogenesis and fertility in humans are not known. Participants should avoid procreation for 6 months after completion of study treatment and should refrain from donating sperm from the start of dosing until 6 months after discontinuing study treatment. See Appendix C for definitions of effective forms of contraception.

c) All WCBP must have a negative pregnancy test result during screening and prior to all imaging ([^{111}In]-FPI2107 ± FPI-2053) and treatment [^{225}Ac]-FPI-2068 ± FPI-2053) timepoints.

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1 As judged by the Investigator, any evidence of the malignancy which, in the Investigator's opinion, makes it undesirable for the participant to participate in the study.

2 Contraindications to or inability to perform the imaging procedures required in this study (e.g., inability to lay flat for the image acquisitions, etc.).

3 Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (≥ once per month).

4 Previous or concurrent cancer that is distinct from the cancer under investigation in primary site or histology, except cervical carcinoma in situ, treated cutaneous basal cell carcinoma or squamous cell carcinoma, and superficial bladder tumours. Any cancer curatively treated >2 years prior to the first dose of [^{111}In]-FPI-2107 is permitted.

5 History of organ transplantation, including stem cell transplantation; or prior treatment with chronic immunosuppressants.

6 History of myocardial infarction or New York Heart Association Class II-IV congestive heart failure within 6 months of the administration of the first dose of [^{111}In]-FPI-2107), Common Terminology Criteria for Adverse Events (CTCAE) Grade 2 or worse conduction defect (e.g., right or left bundle branch block) or uncontrolled hypertension.

7 Concurrent severe and/or uncontrolled illness not related to cancer and/or social situation that would limit compliance with study requirements, including but not limited to:

a) Psychiatric illness, substance abuse

b) Serious chronic gastrointestinal conditions associated with diarrhoea.

c) Ongoing or active known infection, including HIV infection, hepatitis B or hepatitis C virus.

d) Has significant pulmonary dysfunction, including pneumonitis, interstitial lung disease (ILD), idiopathic pulmonary fibrosis, cystic fibrosis, or severe chronic obstructive pulmonary disease.

i. Has had a history of non-infectious ILD/pneumonitis that required oral or IV steroids, or supplemental oxygen. Participants with a history of radiation pneumonitis which has clinically and radiologically resolved and not requiring treatment with steroids may be eligible. The Investigator must carefully evaluate benefit-risk assessment on a case basis and discuss it with the Sponsor Study Physician prior to the participant's enrolment.

e) Diabetes mellitus with fasting serum glucose ≥ 160 mg/dL or random ≥ 250 mg/dL and glycated haemoglobin (HbA1c) > 8% (> 64 mmol/mol).

Prior/Concomitant Therapy

8 Prior systemic radiopharmaceutical therapy.

9 Anti-cancer therapy, such as chemotherapy, immunotherapy, hormonal therapy, targeted therapy, or investigational agents within five half-lives or 4 weeks, whichever is shorter, prior to administration of the first dose of [^{111}In]-FPI-2107:

a) Ongoing toxicities from prior treatment(s) must have resolved to ≤ CTCAE Grade 1, except for alopecia.

b) Concurrent systemic high-dose corticosteroids (in dosing exceeding 10 mg once a day of prednisone or equivalent) is excluded except when used intermittently in an antiemetic regimen, or as part of a premedication regimen.

10 External beam radiation therapy (EBRT) within 28 days prior to the first dose of [^{111}In]-FPI-2107:

   a) Prior EBRT limits must not have exceeded 1.7 Gy to the kidney, 17 Gy to the liver, and 0.5 Gy to the lung. The projected total absorbed dose to the kidney, liver, lung, and red bone marrow, when added to the previous cumulative dose for those organs, will not exceed the individual organ limits, as defined in Section 4.3.

   b) Prior radiation > 20 Gy to more than one-third of the pelvis.

11 Major surgical procedure within 28 days prior to administration of the first dose of [^{111}In]-FPI-2107:

12 *Received any type of vaccine (e.g., live, live-attenuated, killed, viral vector or messenger RNA [mRNA] vaccine) within 30 days prior to the first dose of FPI-2053 or [^{111}In]-FPI-2107.

* Killed, viral vector, and mRNA vaccines may be allowed after completion of the DLT-period upon agreement between the Investigator, Sponsor, and Medical Monitor.

Prior/Concurrent Clinical Study Experience

13 Participation in another clinical study with an investigational product administered in the last 4 weeks or 5 half-lives, whichever is shorter.

14 Known or suspected allergies or contraindications to the Investigational Medicinal Product (IMP) or any component of the investigational drug formulation.

Diagnostic Assessments

15 Known untreated or active central nervous system (CNS) metastases and/or carcinomatous meningitis:

   a) To be eligible for the study treatment, participants must have stable, well controlled disease for ≥ 1 month, as confirmed by magnetic resonance imaging (MRI) or CT scan, and CNS metastases must be well controlled by low dose steroids, anti-epileptics, or other symptom-relieving medications.

16 Clinically relevant proteinuria (e.g., urinary dipstick analysis for proteins is 3 + [300 mg/dL] or 4 + [1000 mg/dL], or daily urinary protein excretion > 500 mg).

Other Exclusions

17 Involvement in the planning and/or conduct of the study (applies to both Fusion Pharmaceuticals staff and/or staff at the study site).

18 Judgment by the Investigator that the participant should not take part in the study if the participant is unlikely to comply with study procedures, restrictions, and requirements.

19 *Previous enrolment in the present study.

*Note that individuals who do not meet the criteria for participation in this study (general screen failure) may be rescreened. Only one general rescreening is allowed per participant in the study. Participants who complete imaging assessment but are not eligible for treatment will not be permitted to repeat the imaging screening.

20 Currently pregnant (confirmed with positive pregnancy test) or breastfeeding.

5.3 Lifestyle Considerations

The following restrictions apply while the participant is receiving study intervention and for the specified times before and after:

- Participants must follow the contraception requirements outlined in Appendix C.
- Participants should not donate blood or blood components while participating in this study and through 180 days after receipt of the final dose of study intervention.
- Restrictions relating to concomitant therapies are described in Section 6.6.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. The term applies to both general screen failures and imaging screen failures. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE). All imaging data for participants who complete imaging assessment but are not eligible for treatment must be recorded and retained as outlined in Section 8.3, the Imaging Charter, and the Site Imaging Manual.

Individuals who do not meet the criteria for participation in this study (general screen failure) may be rescreened. Only one general rescreening is allowed per participant in the study. Participants who complete imaging assessment but are not eligible for treatment will not be permitted to repeat the imaging screening. Rescreened participants should be assigned the same participant number as for the initial screening.

6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s) or placebo intended to be administered to or medical device(s) utilised by a study participant according to the CSP.

Please refer to the Pharmacy Manual and the IB for detailed information on the IMPs.

6.1 Study Intervention(s) Administered

6.1.1 Investigational Medicinal Products

6.1.1.1 Investigational Medicinal Products Information

Please refer to the Pharmacy Manual for full details regarding the IMP preparation and administration.

[^{111}In]-FPI-2107 and [^{225}Ac]-FPI-2068

The [^{111}In]-FPI-2107 and [^{225}Ac]-FPI-2068 solutions for injection should be administered to the participant, undiluted, via slow (over 3 to 5 minutes) IV injection. [^{111}In]-FPI-2107 and [^{225}Ac]-FPI-2068 will be drawn up from a vial into individual syringes. The specific volume to be drawn will be calculated on the day of preparation.

No bacteriostatic agent is present in the products; therefore, adherence to aseptic technique is required. An IV tubing administration set with a 3-way stopcock is recommended during injection of [^{111}In]-FPI-2107 and [^{225}Ac]-FPI-2068 to ensure IV delivery of the products and to ensure proper priming and flushing.

The injection tubing should be primed with at least 10 mL normal saline prior to use. [^{111}In]-FPI-2107 and [^{225}Ac]-FPI-2068 should not be diluted or administered with any other IV fluids, combined with other drugs, or administered through an injection set that was used for any purpose other than IP administration. Following injection of [^{111}In]-FPI-2107 or [^{225}Ac]-FPI-2068, the IV line should be flushed with at least 10 mL normal saline as needed to ensure delivery of the full dose. Following IP administration, the injection line should be removed from the participant and not used for any other procedures.

The radioactivity of the injection syringe before and after administration of [^{111}In]-FPI-2107 and [^{225}Ac]-FPI-2068 will be measured in the dose calibrator to determine the exact dose administered. These measurements will be recorded in the electronic case report form (eCRF).

FPI-2053

The FPI-2053 concentrate for infusion should be diluted in normal saline and administered to the participant via a 60-minute IV infusion. If there are interruptions, the total allowed time must not exceed 4 hours with the infusion bag kept at room temperature, otherwise a new dose must be prepared from new vials. The total time from needle puncture of the vial to the start of administration must not exceed 24 hours at 2°C to 8°C, or 4 hours at room temperature. If the final product is stored at both refrigerated and ambient temperatures, the total time must not exceed 24 hours, otherwise a new dose must be prepared from new vials. FPI-2053 does not contain preservatives; any unused portion of the vial must be discarded immediately after use.

No bacteriostatic agent is present in the product; therefore, adherence to aseptic technique is required. An IV tubing administration set with a 3-way stopcock is recommended during infusion of FPI-2053 to ensure IV delivery of the products and to ensure proper priming and flushing. Infusions must be administered through an IV administration set with a 0.2 or

0.22 μm filter.

The infusion tubing should be primed with at least 10 mL normal saline prior to use. FPI-2053 should not be administered with any other IV fluids, combined with other drugs, or administered through an infusion set that was used for any purpose other than IP administration. Following infusion of FPI-2053, the IV line should be flushed with at least 10 mL normal saline as needed to ensure delivery of the full dose. Following IP administration, the infusion line should be removed from the participant and not used for any other procedures.

6.1.1.2 Dosage

[^{111}In]-FPI-2107

The dose of [^{111}In]-FPI-2107 is 185 MBq (5 mCi) at the time of administration. All participants will receive the same dose of [^{111}In]-FPI-2107.

The volume to be administered to a given participant should be calculated using the:

- fixed administered dose of 185 MBq (5 mCi)
- radioactivity concentration of the product at time of calibration (the activity concentration and time and date of calibration are provided on the vial and lead pig label).

FPI-2053

The proposed doses of FPI-2053 are 0.3, 1, and 3 mg/kg.

The volume to be administered to a given participant should be calculated using:

- participant's body weight (kg)
- dosage level (in kBq/kg body weight)

[^{225}Ac]-FPI-2068

For Part A (first radiation dose level, 15 kBq/kg with and without unlabelled bsAb), dosimetry estimates of all previous and planned therapeutic administrations of [^{225}Ac]-FPI-2068 do not exceed a cumulative exposure of 23 Gy for kidneys, 31 Gy for liver, 2 Gy for red bone marrow, and 16.5 Gy for lungs. Additionally, the absorbed radiation dose to the kidneys, liver, and lungs from prior EBRT treatment must be taken into account and considered part of the cumulative dose to the organs when determining the number of cycles of treatment that a participant can receive. Eligible participants will receive up to 3 cycles of [^{225}Ac]-FPI-2068.

For Part B, dosimetry estimates of all previous and planned therapeutic administrations of [^{225}Ac]-FPI-2068 do not exceed a cumulative exposure of 23 Gy for kidneys, 31 Gy for liver, and 16.5 Gy for lungs. The absorbed radiation dose to the kidneys, liver, and lungs from prior EBRT treatment must be taken into account and considered part of the cumulative dose to the organs when determining the number of cycles of treatment that a participant can receive.

Eligible participants will receive up to 3 cycles of [^{225}Ac]-FPI-2068.

If a planned dose level exceeds the total allowable cumulative dose, the participant may receive a reduced dose.

The dose level of [^{225}Ac]-FPI-2068 will be determined by the assigned dose level (see Table 7 and Table 8).

The volume to be administered to a given participant should be calculated using the:

- participant's body weight (kg)
- dosage level (in kBq/kg body weight)
- radioactivity concentration of the product at time of calibration (the activity concentration at time of calibration and the date of calibration are provided on the vial and lead pig label)

Table 13 Investigational Products

Intervention name	**[^{111}In]-FPI-2107**	**FPI-2053**	**[^{225}Ac]-FPI-2068**
Type	Biologic	Biologic	Biologic
Dose formulation	Solution for injection	Concentrate for infusion	Solution for injection
Unit dose strength(s)	74–111 MBq/mL (at time of calibration)	100 mg/vial	0.407–0.629 MBq/mL (at time of calibration)
Dosage level(s)	185 MBq (5 mCi) [a, b]	Proposed 0.3, 1, and 3 mg/kg Q8W [c]	Proposed 15, 25, 40, and 70 kBq/kg Q8W [b]
Route of administration	IV injection	IV infusion	IV injection
Use	Experimental	Experimental	Experimental
IMP or NIMP	IMP	IMP	IMP
Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor	Provided centrally by the Sponsor
Packaging and labelling	Study intervention will be labelled in accordance with GMP Annex 13 and per country regulatory requirement	Study intervention will be labelled in accordance with GMP Annex 13 and per country regulatory requirement	Study intervention will be labelled in accordance with GMP Annex 13 and per country regulatory requirement
Aliases	None	None	None

GMP, Good Manufacturing Practice; IMP, investigational medicinal product; IND, investigational new drug; IV, intravenous; NIMP, non-IMP; Q8W, every 8 weeks.

[a] [^{111}In]-FPI-2107 is only given during the imaging screening period. All participants will receive 2 doses of [^{111}In]-FPI-2107 unless the optimal dose of FPI-2053 from Part A is 0, in which case participants in Part B will receive one dose.

[b] Administered dose tolerances for [^{111}In]-FPI-2107 and [^{225}Ac]-FPI-2068 are outlined in the Pharmacy Manual.

[c] The proposed FPI-2053 dose levels of 0.3, 1, and 3 mg/kg will be used in Part A. The FPI-2053 dose level in Part B will be determined in Part A.

6.1.1.3 Monitoring of Dose Administration

Participants will be monitored during administration of [^{111}In]-FPI-2107, FPI-2053, or [^{225}Ac]-FPI-2068, and for 30 minutes after administration for each cycle. Participants will then be monitored as clinically indicated thereafter. Vital signs and electrocardiogram (ECG) will be measured according to the schedules described in Section 8.4.2 and Section 8.4.3, respectively. In the event of an infusion-related reaction (IRR), see Table 15 for the TMGs and retreatment criteria.

As with any biologics product, allergic reactions to dose administration are possible. Therefore, appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and study personnel must be trained to recognise and treat anaphylaxis.

6.1.2 Non-investigational Products

6.1.2.1 Premedication for IRR

No premedication for the prevention of IRR prior to the first administration of [^{225}Ac]-FPI-2068, [^{111}In]-FPI-2107 or FPI-2053 is permitted (i.e., primary prophylaxis). Any planned premedication with acetaminophen (paracetamol), histamine (H1 and H2)-receptor antagonists, with subsequent administrations of [^{225}Ac]-FPI-2068, [^{111}In]-FPI-2107 or FPI-2053 following an IRR (i.e., secondary prophylaxis) is permitted. Steroids should not be used as routine premedication for Grade 1 or 2 IRRs. If more than 1 participant during the course of the study develops a Grade $\geq$ 3 IRR during the first infusion, the SRC may recommend premedication for all subsequent participants to be implemented for the first infusion as follows: paracetamol/acetaminophen (500 to 1000 mg orally) and diphenhydramine (25 to 50 mg orally or IV; or an alternative antihistamine at an adequate dose), should be administered approximately 30 minutes prior to administration of [^{225}Ac]-FPI-2068, [^{111}In]-FPI-2107 or FPI-2053. H2-receptor antagonists (e.g., ranitidine) may be added if clinically indicated.

6.2 Preparation/Handling/Storage/Accountability

- The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention.
- Only participants enrolled in the study may receive study interventions and only authorised site staff may supply or administer study interventions. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the Investigator and authorised site staff.

- The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
- Accountability, reconciliation, and destruction of the study intervention will be conducted in accordance with the relevant site SOPs. Unused study intervention is to be destroyed at the exhaustion, expiry, or end of study usage.
- Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual.

6.2.1 Investigational Medicinal Products Receipt, Handling, and Storage

The Investigator is responsible for ensuring that the IMPs (FPI-2053, [^{111}In]-FPI-2107, and [^{225}Ac]-FPI-2068) are correctly received, handled, stored, used, and disposed of in accordance with regulatory guidelines, the CSP, the IB, and the Pharmacy Manual.

6.2.2 Participant Protection

All handling of radiopharmaceuticals must be carried out in restricted areas by persons trained and authorised in the safe use, handling, and administration of radiopharmaceuticals to humans. Care must be taken to minimise contamination of clothing and skin of personnel with the use of disposable gloves and protective clothing. Hands must be washed after handling any radioactive materials. All handling of radioactive material must follow site Standard Operating Procedures and the regulations and radionuclide licenses issued by the local nuclear regulatory authorities. Before, during, and after administration of [^{111}In]-FPI-2107 and [^{225}Ac]-FPI-2068, sites should follow the regulations set forth by the competent nuclear regulatory agency with jurisdiction over the site.

The participant and caregivers will be given instructions regarding hygiene precautions after receiving the drug to minimise risk of potential radiation exposure of the 3rd party.

For further information refer to the Pharmacy Manual.

6.3 Dose Calibration Setting

Reference standards will be supplied to allow each site to calibrate equipment including dose calibrators for indium-111 and actinium-225 prior to the first participant enrolment as detailed in the Site Imaging Manual.

6.4 Measures to Minimise Bias: Randomisation and Blinding

This is an open-label, non-randomised study; no blinding is required. Participants will be allocated to Part A Cohorts 1 or 2 in an alternating manner.

6.5 Study Intervention Compliance

Participants are to receive IMP in accordance with the dose range specified in the CSP. If a

participant received a dose outside the specified range, the Investigator should contact the Sponsor and/or Medical Monitor immediately, monitor the participant for any TEAE/SAE(s), and document the event in the eCRF.

The administration of all study intervention should be recorded in the appropriate sections of the eCRF. Any changes from the dosing schedule, dose interruptions, dose reductions, and dose discontinuations should be recorded in the eCRF. The reason should also be documented.

Use of doses in excess of that specified in the CSP is considered to be an overdose. Refer to Section 8.6 for procedures in case of overdose.

When participants are dosed at the site, they will receive study intervention directly from the Investigator or designee, under medical supervision. The date, and time if applicable, of dose administered in the clinic will be recorded in the source documents and recorded in the eCRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

6.6 Concomitant Therapy

All concurrent medical conditions and complications of the underlying malignancy will be treated at the discretion of the Investigator according to standard of care and institutional practice guidelines and procedures. If there is a clinical indication for any medication or vaccination specifically prohibited during the study, discontinuation from study treatment may be required.

Participants should receive analgesics, antiemetics, antibiotics, antipyretics, and blood products, as necessary. Any medication, including vaccines, over-the-counter or prescription medicines, vitamins, and/or herbal supplements that the participant received within 30 days prior to signing informed consent or receives during the study must be recorded including reason for use, dates of administration including start and end dates, and dosage information including dose and frequency.

Concomitant medications will be collected according to the timepoints outlined in the SoAs (see Section 8.1). If a participant is currently receiving bisphosphonates for treatment of osteoporosis, treatment-induced bone loss, or metastases to bone, the participant must have started treatment with the bisphosphonates at least 4 weeks prior to the first dose of study treatment.

The IMP excretion is partially hepatic; it is at the Investigator’s discretion to treat participants with laxatives to accelerate excretion from the intestine.

Prior and concomitant therapies will be coded using WHO Drug Version 01 March 2022 or higher.

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrolment or

receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The Study Physician should be contacted if there are any questions regarding concomitant or prior therapy.

Participants must abstain from taking prescription or non-prescription drugs (including vitamins and dietary or herbal supplements) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) before the start of study intervention until completion of the follow-up visit, unless, in the opinion of the Investigator, Medical Monitor, and Sponsor, the medication will not interfere with the study.

Acetaminophen, at doses of ≤ 2 g/day, is permitted for use at any time during the study. Other concomitant medication may be considered on a case-by-case basis by the Investigator in consultation with the Sponsor and Medical Monitor if required.

Table 14 Permitted Concomitant Medications

Supportive medication/class of drug	Usage
Premedication for management of diarrhoea, nausea, and vomiting	Permitted after but not before the first dose of study intervention
Blood transfusions	Permitted at any time during the study after Cycle 1, Day 1 May not be used to meet inclusion criteria within 7 days prior to the scheduled first dose of study intervention [a]
Erythropoietin	Prophylactic erythropoietin should not be started within 21 days prior to the scheduled first dose of study intervention in order to meet inclusion criteria, nor should it be used during Cycle 1 of the study; however, it may be started after Cycle 1
G-CSF	G-CSF should not be started within 21 days prior to the scheduled first dose of study intervention in order to meet inclusion criteria, nor should it be used prophylactically during Cycle 1; however, it may be considered after Cycle 1
Megestrol acetate	Permitted for appetite stimulation
Bisphosphonates	Permitted for treatment of osteoporosis, treatment-induced bone loss, or metastases to bone; the participant must have started treatment with the bisphosphonates at

Supportive medication/class of drug	Usage
	least four weeks prior to the first dose of study treatment
Concomitant medications or treatments (e.g., acetaminophen in doses exceeding 2 g/day or diphenhydramine) deemed necessary to provide adequate prophylactic or supportive care, except for those medications identified as "prohibited," as listed in Section 6.6.1	To be administered as prescribed by the Investigator
Best supportive care (including antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control, and pain management [including palliative radiotherapy to non-target lesions, etc.])	Should be used when necessary

[a] Haematological criteria cannot be met with ongoing or recent blood transfusions (within seven days prior to the scheduled first dose of study treatment) or require growth factor support (within 21 days prior to the scheduled first dose of study treatment).

G-CSF, granulocyte colony stimulating factor.

6.6.1 Prohibited Treatment

The following treatments are not allowed during the study treatment and for 28 days post last dose of study intervention:

- Any concurrent anticancer therapy, including but not limited to, chemotherapy, radiotherapy, hormonal therapy, immunotherapy, or locoregional therapy
- Immunosuppressive therapies, including continuous high-dose corticosteroids (except when used: intermittently in an antiemetic regimen; for the management of study intervention-related adverse events; in participants with contrast allergies; or for CNS metastases management), methotrexate, azathioprine, and tumour necrosis factor-α blockers. Use of inhaled, topical, and intranasal corticosteroids is permitted.
- Any vaccine within 30 days prior to the first dose of FPI-2053 or [^{111}In]-FPI-2107 (see Exclusion Criterion 12 in Section 5)
  - Killed, viral vector, and mRNA vaccines may be allowed after completion of the DLT-period upon agreement between the Investigator, Sponsor, and Medical Monitor.
- Live or attenuated vaccines are prohibited
- Other investigational agents for any disease indication
- Herbal and natural remedies which may have immune-modulating effects.

6.6.2 Medications to be Used with Caution

The potential of [^{225}Ac]-FPI-2068 to be associated with drug-drug interactions has not been established. It is anticipated that the major route of excretion will be via the kidneys; therefore, medications which might affect renal function should be avoided or used with caution as assessed by the Investigator. These medications include but are not limited to the following:

Drugs causing prerenal damage:

- Drugs that cause excessive gastrointestinal losses, either through diarrhoea or vomiting, also cause volume depletion and may precipitate acute kidney injury (AKI).
- Nonsteroidal anti-inflammatory drugs (NSAIDs), even in short courses, can cause AKI as a result of renal under perfusion.
- Angiotensin-converting enzyme (ACE) inhibitors can also cause a deterioration in renal function. However, this is concerning only in participants with compromised renal perfusion, particularly those with renal artery stenosis.
- Care should be taken when an ACE inhibitor and NSAID are prescribed together, as this combination may precipitate an acute deterioration in renal function.

Drugs causing intrarenal damage:

- Intrarenal damage may result in a direct toxic effect on the kidneys or hypersensitivity reactions.
- Most drugs that cause damage within the kidneys do so as a result of hypersensitivity reactions, which involve either glomerular or interstitial damage.
- Drugs that have been reported to cause glomerulonephritis include penicillamine, gold, captopril, phenytoin, and some antibiotics, including penicillins, sulfonamides, and rifampicin.
- Drugs that may cause interstitial nephritis include penicillins, cephalosporins, sulfonamides, thiazide diuretics, furosemide, NSAIDs, and rifampicin.
- There are several drugs that cause direct toxicity to the renal tubules (acute tubular necrosis); e.g., aminoglycosides, amphotericin, and ciclosporin.

Drugs causing postrenal damage (urinary tract obstruction):

- High-dose sulfonamides, acetazolamide or methotrexate may cause crystalluria and could therefore cause urinary tract obstruction.
- Anticholinergics (e.g., tricyclic antidepressants) and alcohol may cause urinary tract obstruction due to retention of urine in the bladder.

Other nephrotoxic drugs:

- Cephalosporins: cephaloridine, one of the first cephalosporins introduced, has been associated with direct renal toxicity and is no longer in clinical use. Other cephalosporins are much less likely to produce renal damage but third generation cephalosporins (e.g., cefixime) have (very rarely) been reported to cause nephrotoxicity.

Analgesics:

- NSAIDs may cause AKI due to hypoperfusion and interstitial nephritis, as well as analgesic nephropathy (chronic interstitial nephritis and papillary necrosis).
- Analgesic nephropathy has been most seen with combination analgesic products that contain aspirin and/or paracetamol.

6.7 Dose Modification

6.7.1 [^{111}In]-FPI-2107

The [^{111}In]-FPI-2107 185 MBq (5 mCi) dose will not be modified during the study.

6.7.2 FPI-2053

Intraparticipant dose modifications for FPI-2053 will not occur during the study.

6.7.3 [^{225}Ac]-FPI-2068

For a participant to be eligible to receive repeat dosing with [^{225}Ac]-FPI-2068, they must meet the retreatment criteria defined in Table 15 within 56 days (+ 4 weeks) from their previous [^{225}Ac]-FPI-2068 administration. If retreatment criteria are not met, the treatment administration may be held for up to 28 days. If treatment-related toxicities are not resolved within this window, then the participant will discontinue study treatment. Adjustments to these guidelines may occur if agreed by the Investigator, Sponsor, and Medical Monitor.

Table 15 Toxicity Management Guidelines and Retreatment Criteria

Event	Characteristic	Grade	Management recommendation
Anaemia, leucopenia, or neutropenia	Haemoglobin ≤ 9g/dL WBC < 3×10^9/L ANC < 1.5×10^9/L	≥ 2	Hold [^{225}Ac]-FPI-2068 (with or without FPI-2053) until improvement to Grade 1 or baseline. Dose may be held for up to 4 weeks beyond the next planned dose per CSP (i.e., beyond 56 days). Manage as deemed appropriate by Investigator. Use of growth factors is permitted but should be discontinued once the AE resolves to Grade 1 or baseline. Transfusions may be given as clinically indicated for anaemia.
Thrombocytopenia	Platelets: > 50×10^9/L and < 75×10^9/L	2	Hold [^{225}Ac]-FPI-2068 (with or without FPI-2053) until improvement to Grade 1 or baseline, retreat at the same dose level. Manage as deemed appropriate by Investigator. Transfusions may be given as clinically indicated for thrombocytopenia.
	Platelets: < 50×10^9/L	3 and 4	Hold [^{225}Ac]-FPI-2068 (with or without FPI-2053) until improvement to Grade 1 or baseline, reduce by one dose level. Manage as deemed appropriate by Investigator. Transfusions may be given as clinically indicated for thrombocytopenia.
Increased serum creatinine	CrCl 30-59 mL/min/1.73 m^2	2	Hold [^{225}Ac]-FPI-2068 (with or without FPI-2053) until improvement to Grade 1 or baseline. If resolved in ≤ 7 days, then maintain dose level for the next cycle. If resolved in > 7 days, then reduce by one dose level for the next cycle. Manage as deemed appropriate by Investigator.
	CrCl 15-29 mL/min/1.73 m^2	3	Treatment should be permanently discontinued.

Event	Characteristic	Grade	Management recommendation
	CrCl < 15-29 mL/min/1.73 m^2; dialysis or renal transplant indicated	4	Treatment should be permanently discontinued.
Increased AST or ALT	> 5.0 - 20 x ULN if baseline was normal; > 5.0 baseline if baseline was abnormal	3	Hold [^{225}Ac]-FPI-2068 (with or without FPI-2053) until improvement to Grade 1 or baseline or ≤ Grade 2 if liver metastases are present. If resolved in ≤ 7 days, then maintain dose level for the next cycle. If resolved in > 7 days, then reduce by one dose level for the next cycle.
	> 20.0 × ULN if baseline was normal; > 20.0 × baseline if baseline was abnormal	4	Treatment should be permanently discontinued.
Increased total bilirubin	> 3.0 - 10.0 × ULN if baseline was normal; > 3.0 - 10.0 × baseline if baseline was abnormal	3	Hold [^{225}Ac]-FPI-2068 (with or without FPI-2053) until improvement to Grade 1 or baseline. If resolved in ≤ 7 days, then reduce by one dose level for the next cycle. If resolved in > 7 days, then permanently discontinue study drug
	> 10.0 × ULN if baseline was normal; > 10.0 × baseline if baseline was abnormal	4	Treatment should be permanently discontinued.
Non-haematologic AEs		3	Hold [^{225}Ac]-FPI-2068 (with or without FPI-2053) until improvement to Grade 1 or baseline. If resolved < 7 days, then maintain dose level for the next cycle. If resolved > 7 days, then reduce by one dose level for the next

Event	Characteristic	Grade	Management recommendation
			cycle.
		4	Treatment should be permanently discontinued.
Infusion-related reaction		1	The infusion rate may be decreased by 50% or temporarily interrupted until resolution of the event. Monitor closely and manage per institutional standard at the discretion of Investigator. If no other reactions appear, the subsequent infusion rate could be resumed at the initial planned rate.
		2	Temporarily interrupt study intervention administration. If the event resolves or improves, infusion can be restarted at a 50% reduced infusion rate. Consider discontinuation if recurrent Grade 2 despite premedication and 50% reduced infusion rate. Acetaminophen and/or antihistamines may be administered per institutional standard at the discretion of the Investigator. Steroids should not be used for routine premedication of Grade ≤ 2 infusion-related reactions. Consider appropriate premedication prior to subsequent doses (see Section 6.1.2).
		3-4	Discontinue study intervention. Manage severe infusion-related reactions per institutional standards (e.g., IM epinephrine, followed by IV diphenhydramine and famotidine, and IV glucocorticoid IV fluid therapy, oxygen inhalation etc).
ILD/pneumonitis		Any grade	Please follow the dose modifications specific to each severity grade. Closely monitor participants for signs and symptoms of pneumonitis or ILD (e.g., new onset or worsening shortness of

Event	Characteristic	Grade	Management recommendation
			breath or cough). Consider the following to exclude alternative aetiologies: • Chest CT (preferably high resolution CT) and pulmonologist consultation as clinically indicated • Chest X-ray • Pulmonary function tests (spirometry, DLCO) • Physical examination • Monitor oxygen saturation via pulse oximetry • Laboratory work-up as indicated
		1	**Note: if participants remain asymptomatic, then the event should be considered as Grade 1, even if treatment with corticosteroids is given.** Hold all study intervention for 21 days, immediately upon detection. If pulmonary function tests at 21 days after Grade 1 pneumonitis/ILD detection are not showing clinically meaningful deterioration and in the absence of symptoms and stable SpO_2, all study intervention can be resumed at the same dose level. Repeat spirometry and DLCO after 21 days from detection. Consider additional imaging (e.g., HRCT scan) if feasible. Monitor for symptoms onset and oxygen saturation as clinically indicated. Consider starting systemic corticosteroids per institutional guidelines. If symptoms appear follow Grade 2 guidelines.
		2	Permanently discontinue study intervention. Promptly start and treat with systemic steroids per institutional guidelines.

Event	Characteristic	Grade	Management recommendation
			Monitor symptoms closely. Re-image as clinically indicated. Consider additional work-up for alternative aetiologies as described above. Escalate care as clinically indicated.
		3-4	Permanently discontinue study intervention. Hospitalisation required. Promptly initiate high-dose corticosteroids treatment per institutional guidelines. Re-image as clinically indicated. Consider additional work-up for alternative aetiologies as described above. Consider other immunosuppressants (e.g., infliximab or mycophenolate) per local practice.
Radiation dose estimates	Planned activity does not exceed cumulative limits of 23 Gy for kidneys, 31 Gy for liver, 16.5 Gy for lungs, and for Part A only, 2 Gy for red bone marrow.	NA	Dosimetry estimate of the previously administered and planned cumulative administered activity of [^{225}Ac]-FPI-2068 (with or without FPI-2053), based on individual uptake as assessed by [^{111}In]-FPI-2107 imaging (with or without FPI-2053). Additionally, the absorbed radiation dose to the kidney, liver, and lung from prior EBRT treatment must be taken into account and considered part of the cumulative dose to the organs when determining the number of cycles of treatment that a participant can receive. If a planned dose level may exceed the total allowable cumulative dose, the participant may receive a reduced administration such that the specified cumulative limit is not reached.

AE, adverse event; ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; CrCl, creatinine clearance; CT, computed tomography; DLCO, diffusing capacity of the lungs for carbon monoxide; EBRT, external beam radiation therapy; HRCT, high resolution computed tomography; ILD, interstitial lung disease; IM, intramuscular(ly); IV, intravenous(ly); NA, not applicable; SpO_2, pulse oximetry; ULN, upper limit of normal; WBC, white blood cell count.

If moderate or severe AEs are consistently observed across participants in a cohort or if unacceptable pharmacological effects, reasonably attributable to study intervention in the opinion of the Investigator are observed in more than 30% of the participants in a cohort, then dose escalation will be temporarily halted and no further participants will be dosed until a full safety review of the study has taken place by the SRC. Relevant reporting and discussion with the Study Physician, relevant site personnel, and the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) will take place before resumption of dosing.

The above criteria will apply even if measured PK parameters are below the prespecified PK stopping criteria, and every effort will be made to take a blood sample at the time of the AE for PK analysis.

In case a dose reduction is necessary, the study intervention will be administered as outlined in Table 15.

6.7.4 Starting Dose, Dose Escalation Scheme, and Stopping Criteria

Part A Cohort 1 and Cohort 2 will be initiated simultaneously and enrol in parallel. Participants will be assigned in an alternating manner. The first participant in Cohort A2 will be treated with [^{225}Ac]-FPI-2068 only after the first participant in Cohort A1 has undergone a minimum of one week of safety observation. Dosing of [^{225}Ac]-FPI-2068 in Part A will be 15 kBq/kg/cycle and be administered at this dose for up to a maximum of 3 cycles. If FPI-2053 is to be administered prior to [^{225}Ac]-FPI-2068 or FPI-2107 then the interval between the administration of FPI-2053 and FPI-2068 or [^{111}In]-FPI-2107 will be 30 minutes to 2 hours. Following review of safety, PK, biodistribution, and dosimetry data from Cohorts A1 and A2 by the Sponsor and the SRC, Cohort A3 may be initiated if deemed necessary.

In Part B there will be a minimum of 56 days between completion of dosing in the last evaluable participant, for a dose escalation decision, from one cohort and the start of dosing in the subsequent cohort.

There may be ongoing participants who become evaluable after the dose escalation decision (i.e., dosing may start in the next cohort whilst these participants are ongoing).

Intra-participant dose escalation is not permitted.

The dose for subsequent cohorts or a decision to stop recruitment will be agreed by the SRC after review of the data from each cohort (see Section 6.7.8).

In Part B a minimum of three and a maximum of nine participants will be enrolled at a given dose level.

Part B, dose escalation to the next dose level will be conducted using the mTPI-2 algorithm with a target DLT rate of 30% and an equivalence interval (25%, 35%). A minimum of 3 participants must complete the DLT-evaluation period before making an escalation decision. Dose escalation will consist of four planned dose levels. Intermediate dose levels may be

explored if warranted by emerging safety, PK, pharmacodynamic, biomarker, and efficacy data. Dose escalation and de-escalation will follow the mTPI-2 algorithm schema below:

- A minimum of 3 evaluable participants are required in each dose level unless unacceptable toxicity is encountered in the first 2 subjects prior to enrolment of the third participant, which would require dose de-escalation per the mTPI-2 design.
- If a de-escalation decision is made, choice of de-escalation to the previous dose level will be at the discretion of the SRC. In the eventuality that a decision is made to de-escalate back to a dose escalation level that was previously deemed safe, and into which participants have since been enrolled at that dose level, these participants will now be included in further dose escalation decisions following mTPI-2 rules.
- If a stay ("S") decision is made, additional participants will be enrolled for a given dose level (typically in groups of 2 to 4 participants).
- Administration of the first dose of investigational product will be staggered by a minimum of 24 hours between the first and second participants in each dose escalation cohort.
- At the discretion of the Sponsor, dose escalation may be stopped before an MTD is reached. In this case, the dose for evaluation in any future dose expansion study may be chosen based on an assessment of PK, pharmacodynamics, safety, or efficacy data.
- The MTD will be determined by isotonic transformation of posterior mean DLT rates observed during dose escalation using the mTPI-2 method (Ji et al, 2010).

The mTPI-2 algorithm employs a simple beta-binomial Bayesian model. The posterior density of the toxicity probability is divided into multiple intervals with equal length. These intervals are categorised as underdosing, proper dosing, and overdosing in terms of toxicity. The underdosing interval corresponds to a dose escalation, overdosing corresponds to a dose de-escalation, and proper dosing corresponds to staying at the current dose. Given an interval and a probability distribution, the unit probability mass of that interval is defined as the probability of the interval divided by the length of the interval. The design for the dose escalation phase of the study uses a target DLT rate of 30% and an equivalence interval (25%, 35%) for dose escalation/de-escalation decisions as well as MTD determination. A dose level will be considered unsafe, with no additional participants enrolled at that dose level, if it has an estimated 95% or more probability of exceeding the target DLT rate of 30% (i.e., P [DLT > 30% data] ≥ 95%) with at least 3 participants treated and evaluated at that dose level. In Table 16, dose escalation/de-escalation decision rules are computed based on the above information.

Table 16 mTPI-2 Decision Rules

Number	Number of participants treated at current dose level

Table 16 mTPI-2 Decision Rules

Number	Number of participants treated at current dose level								
	1	2	3	4	5	6	7	8	9
0	S[a]	S[a]	E	E	E	E	E	E	E
1	S[b]	S[b]	S	S	E	E	E	E	E
2		DU	D	D	D	S	S	S	E
3			DU	DU	D	D	D	D	S
4				DU	DU	DU	D	D	D
5					DU	DU	DU	DU	DU
6						DU	DU	DU	DU
7							DU	DU	DU

D, de-escalate to the next lower dose level; DLT, dose limiting toxicity; DU, current dose is unacceptably toxic; E, escalate to the next higher dose level; EI, equivalence interval; mTPI, modified toxicity probability interval; S, stay at the current dose level.

[a] Changed from "E" to "S" as a minimum of 3 evaluable participants are needed to make a dose escalation decision.

[b] Changed from "D" to "S" as a minimum of 3 evaluable participants are needed to make a dose escalation decision.

Target toxicity (%) is 30% and EI (25%, 35%); Sample size cap for each dose level will be nine participants.

Source(s): Modified from (Ji et al, 2010; Guo et al, 2017).

6.7.4.1 Stopping Criteria

The study will be suspended if any death or two Grade 4, non-haematologic adverse reactions within the same organ system are observed. These should be at least potentially related to the investigational products, and not related to disease progression or intercurrent illness. Continuation of the study may occur if deemed appropriate by the SRC and may require a protocol amendment. Participants on treatment at time of suspension may continue if they are tolerating treatment well, and if continuing treatment is considered appropriate for the toxicity in question based upon the treating physician's medical judgement. Dose reduction may also be considered.

6.7.5 Definition of Maximum Tolerated Dose

The MTD will be selected from all investigated dose levels that have not been previously declared to be unsafe with a dose unacceptable decision according to the mTPI-2 decision rules (see Table 16). With this constraint, the MTD will be determined as the dose level with the DLT estimate closest to the target toxicity level of 30%.

In the case of dose levels with estimated toxicity of equal distance (tied dose levels) from the target toxicity of 30%, the following approach will be used (Ji et al, 2010): among all tied dose levels the highest dose level with target toxicity ≤ 30% will be selected, unless all tied dose levels have estimated toxicity > 30%, in which case the lowest dose level will be selected.

6.7.6 Definition of a DLT Evaluable Participant

A DLT evaluable participant is defined as a participant who receives [^{225}Ac]-FPI-2068 and either completes the DLT observation period without a DLT or experiences a DLT at any time during the DLT observation period. Participants who are unable to complete the 56-day DLT observation period, for reasons other than DLT (e.g., rapid disease progression or death) will be replaced; therefore, additional participants may be enrolled.

6.7.7 Definition of a DLT

The DLT observation period will be 56 days during the first cycle of therapeutic treatment, and subsequent cycles will be administered every 56 days.

The cycle length is set at 56 days in order to balance the need to monitor toxicities and associated resolution time with the need to re-treat participants with advanced disease. This duration is deemed appropriate based upon the rate of radioactive decay and expected biological clearance of [^{225}Ac]-FPI-2068 following administration to participants.

A DLT is defined by the occurrence of any of the toxicities listed below within the first cycle of treatment excluding toxicities clearly related to disease progression or intercurrent illness.

6.7.7.1 Events considered DLTs

Haematologic AEs

Neutropenia

- Grade 4 neutropenia (< 500/mm^3 or < 0.5 x 10^9/L) lasting longer than 7 days despite optimal treatment
- Any febrile neutropenia as defined by CTCAE Version 5.0:
    - Grade 3 is defined as an absolute neutrophil count (ANC) < 1000/mm^3 with a single temperature of > 38.3°C (101°F) or a sustained temperature of ≥ 38.3°C (100.4°F) for more than 1 hour
    - Grade 4 is defined as ANC < 1000/mm^3 with a single temperature of > 38.3°C (101°F) or a sustained temperature of ≥ 38°C (100.4°F) for more than 1 hour, with life-threatening consequences and urgent intervention indicated

Thrombocytopenia

- Grade 4 thrombocytopenia (< 25,000/mm^3 or < 25 × 10^9/L) of any duration
- Grade 3 thrombocytopenia (< 50,000-25,000/mm^3 or < 50-25 × 10^9/L) lasting > 7 days.
- ≥ Grade 3 thrombocytopenia of any duration with ≥ Grade 2 haemorrhage.

Anaemia

- Grade 4 anaemia (life-threatening consequences and urgent intervention indicated) of any duration

Non-haematologic AEs

- All cases of laboratory abnormalities that meet Hy's Law criteria
    - AST or ALT ≥ 3 × ULN and
    - total bilirubin ≥ 2 × ULN and
    - alkaline phosphatase < 2 × ULN and
    - no other reason for liver injury
- ≥ Grade 3 non-haematologic toxicities except for the following:
    - Grade 3 nausea, vomiting or diarrhoea for less than 72 hours with adequate antiemetic and other supportive care
    - Grade 3 fatigue for less than 1 week
    - Grade 3 or higher electrolyte abnormality that lasts up to 72 hours, is not clinically complicated, and resolves spontaneously or responds to conventional medical intervention
    - Grade 3 or higher amylase or lipase that is not associated with symptoms or clinical manifestations of pancreatitis
    - Alopecia
- Any other toxicity that in the opinion of the Investigator represents a clinically significant hazard to the participant.
- Any death not clearly due to the underlying disease or extraneous causes.

Notes:

- A repeat test may be required for confirmation of an isolated abnormality in the absence of clinical signs, symptoms, or other abnormal investigation, i.e., a suspected spurious value.
- If a participant withdraws from the study for any other reason than a DLT during the first cycle, that participant will be replaced.

6.7.8 Safety Review Committee

A SRC will be convened to provide review of the accumulating safety data during the conduct of the study. The SRC will be responsible for making recommendations for dose escalation or dose de-escalation decisions and making recommendations regarding further conduct of the

study during all phases of the study including suspension or stopping of the study. The SRC will review the totality of all available clinical, laboratory, safety, PK, and all other relevant data prior to adjudicating on dose escalation/de-escalation decisions based on the dose escalation rules (see Table 16). The data listed above will be extracted and confirmed for accuracy by the Sponsor ahead of the SRC review.

The SRC will consist of the Investigators, the Sponsor's medical representatives, including pharmacovigilance, Patient Safety Physician, and the Medical Monitor. The Study Clinical Pharmacology Scientist, Study Statistician, Patient Safety Scientist, Study Delivery Leader, Clinical Trial Manager, and Clinical Scientist may also be invited as appropriate. At a minimum, the Investigators will include at least one representative from the following disciplines: medical oncology, radiation oncology, and nuclear medicine; these individuals may be selected from across the participating centres, i.e., not requiring each site to have all three areas of expertise represented on the SRC. The decision to proceed to the next dose level/cohort or to suspend or stop dose escalation will be based on the review of safety data. The SRC membership will be recorded in the SRC Charter.

The SRC will conduct regular, planned reviews of the safety data to evaluate the safety of the study drugs regimen to safeguard participants' safety. Refer to the SRC Charter for further details regarding roles, responsibilities, composition of the SRC, the purpose and timing of the SRC meetings, and the data and decision-making process to be used by the SRC.

Following review of safety, PK, biodistribution, and dosimetry data from Cohorts A1 and A2 by the Sponsor and the SRC, Cohort A3 may be initiated if deemed necessary. The SRC will also determine when to initiate Part B.

The SRC will make recommendations on imaging requirements, such as timing of image acquisition or decisions to drop imaging assessments. They may also recommend to enrol additional participants at a given dose level if it is deemed necessary to evaluate safety, and they may make decisions to explore alternative (e.g., intermediate) dose levels. Once all three participants in a given dose cohort have been monitored for safety for 56 days, the SRC will convene and will provide guidance for management of the next cohort. Dose exploration will not proceed at or beyond a dose level where the DLT rate exceeds 30%.

The SRC may also recommend investigation of alternative dose regimens, modification of the dosing interval, or changes to the maximum number of doses. Such cohorts may be executed in parallel to the ongoing dose escalation cohorts provided that the safety profile and potential activity at a given dose level justifies this approach.

If ≥ 30% of participants at any given dose level (dose escalation and backfill cohorts combined) experience DLTs, enrolment at this dose level may be paused, and available safety data of all participants treated at this dose level and previous any relevant RP2D decisions will be reviewed by the SRC.

6.7.9 Dose Modifications

If a participant experiences a clinically significant and/or unacceptable toxicity including a DLT not attributable to the disease or disease-related processes under investigation, dosing will be interrupted, delayed, or the dose reduced and supportive therapy administered as required (see Table 15).

6.8 Intervention after the End of the Study

No intervention is planned after the end of the study.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Intervention

It may be necessary for a participant to permanently discontinue (definitive discontinuation) study intervention prior to completion of the Treatment Period. If study intervention is permanently discontinued, the participant will remain in the study to be evaluated for follow-up- assessments. See the SoA for the End of Treatment and Extended Follow-up period (see Table 25) for data to be collected at the time of discontinuation of study intervention and follow-up, and for any further evaluations that need to be completed.

Note that discontinuation from study intervention is NOT the same as withdrawal from the study (see Section 7.1.1).

The participant should continue attending subsequent study visits and data collection should continue according to the CSP. If the participant does not agree to continue in-person study visits, a modified follow-up must be arranged to ensure the collection of endpoints and safety information. This could be a telephone contact with the participant at the Extended Safety Follow-up visit, a contact with a relative or treating physician, or information from medical records. The approach taken should be recorded in the medical records. A participant who agrees to modified follow-up is not considered to have withdrawn consent or to have withdrawn from the study.

Participants will continue to receive repeat cycles of treatment at the dose level and schedule of administration at which they were enrolled:

- up to a maximum of three cycles or
- until individual participant-specific cumulative radiation dose limits to specified organs based on [^{111}In]-FPI-2107 imaging are reached (see Section 4.3).

Participants must also be discontinued from study treatment in the following situations:

- Unacceptable AE or inability to tolerate study therapy
- Delay in dosing of 28 days, without approval of Sponsor or Medical Monitor

- Documented, confirmed radiographic progressive disease (PD) (as assessed per RECIST 1.1)
  - Participants may remain on study treatment following confirmed radiographic PD if, in the opinion of the Investigator and with the agreement of the Sponsor and/or Medical Monitor, they continue to derive clinical benefit from the study treatment and if the following criteria are met:
    - Absence of symptoms and signs indicating clinically significant progression of disease;
    - No decline in performance status; and
    - Absence of symptomatic rapid disease progression requiring urgent medical intervention (e.g., symptomatic pleural effusion, spinal cord compression).
  - Participants must provide written consent to remain on study treatment following confirmed radiographic PD
- Participant or Investigator decision; the participant is free at any time to discontinue treatment, without prejudice to further treatment
- Noncompliance with the CSP (Investigator or participant) placing the participant at significant safety risk as judged by the Investigator, Medical Monitor or Sponsor
- Pregnancy (see Section 8.5.10)
- Death
- Sponsor termination of study for reasons including, but not limited to, unfavourable risk/benefit or change in drug development plan
- Unexpected, significant or unacceptable risk to the participants enrolled in the study
- Participant incorrectly initiated on study treatment
  - When the reason does not impact safety consider the risk/benefit to the participant of stopping treatment

7.1.1 Temporary Discontinuation of Study Intervention

It may be necessary for a participant to temporarily discontinue study intervention during the Treatment Period. If study intervention is temporarily discontinued, it must be restarted within 28 days of the start of the next cycle.

7.2 Participant Withdrawal from the Study

Note that withdrawal from the study is NOT the same as discontinuation from study intervention (see Section 7.1).

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the Investigator for safety, behavioural, compliance, or administrative reasons. This is expected to be uncommon.
- A participant who considers withdrawing from the study must be informed by the Investigator about modified follow-up options (e.g., telephone contact, a contact with a relative or treating physician, or information from medical records).
- At the time of withdrawal from the study, if appropriate, an End of Treatment visit may be conducted as shown in the End of Treatment and Extended Follow-up Period SoA (see Section 8.1.8). The End of Treatment visit should be conducted within 7 days of the decision to permanently discontinue treatment with [^{225}Ac]-FPI-2068. If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, it should be confirmed if he/she still agrees for existing samples to be used in line with the original consent. If he/she requests withdrawal of consent for use of samples, destruction of any samples taken and not tested should be carried out in line with what was stated in the informed consent and local regulation. The Investigator must document the decision on use of existing samples in the site study records and inform the Global Study Team.

7.3 Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits, as defined in Section 8, and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

- Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants enrolled, including those who did not get investigational product. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix A.

8 STUDY ASSESSMENTS AND PROCEDURES

- Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the Medical Monitor and/or Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of the ICF may be utilised for screening or baseline purposes provided the procedures met the CSP-specified criteria and were performed within the time frame defined in the SoA.
- In all parts of the study, up to approximately 550 mL of blood will be required during the general and imaging screening periods, and the first cycle of the treatment period. The total volume to be collected over the course of the study will depend on the study treatment (whether or not the participant is predosed with FPI-2053), the duration the participant remains on treatment, and the length of follow-up.

8.1 Schedule of Activities

Study procedures and their timing are presented below as individual SoA tables for each study part and study period. At the End of Treatment, all participants must follow the procedures and timings outlined in the SoA table in Section 8.1.8.

- Part A – Dose Exploration with Unlabelled bsAb
    - Screening Period (see Section 8.1.1)
    - Treatment Period

  - Cycle 1 (see Section 8.1.4)
  - Cycle ≥ 2 (see Section 8.1.7)
  - PK, ECG, and biomarker sampling (see Section 8.1.9)
- Part B – Hot Dose Escalation with Unlabelled bsAb
  - Screening Period (see Section 8.1.2)
  - Treatment Period
  - Cycle 1 (see Section 8.1.5)
  - Cycle ≥ 2 (see Section 8.1.7)
  - PK, ECG, and biomarker sampling (see Section 8.1.10)
- Part B – Hot-only Dose Escalation
  - Screening Period (see Section 8.1.3)
  - Treatment Period (see Section 8.1.6)
  - PK, ECG, and biomarker sampling (see Section 8.1.11)

8.1.1 Screening Period – Part A (Dose Exploration with Unlabelled bsAb)

The SoA for the screening period in Part A is presented as two tables. Table 17 presents the SoA from the General Screening Period until 4 days after the first [^{111}In]-FPI-2107 injection (i.e., on the day of the first dosimetry scan). Table 18 presents the SoA from after the washout period following the first dosimetry scan until 4 days after the second [^{111}In]-FPI-2107 injection (i.e., second dosimetry scan with FPI-2053 and [^{111}In]-FPI-2107) or, if the participant does not continue in the study and does not receive [^{225}Ac]-FPI-2068, until the 28 Day Safety Visit.

Table 17 Schedule of Activities – Screening Period and First Dosimetry– Part A (Dose Exploration with Unlabelled bsAb)

Assessments/procedures [a]	General Screening D-39 to ~D-26	[^{111}In]-FPI-2107 Imaging Screening Period					Details in Section/Appendix
		[^{111}In]-FPI-2107 Day 1		24 h (± 6 h) Post-inj.	48 h (± 6 h) Post-inj.	72-96 h (± 6 h) Post-inj	
		Pre-inj.	Inj.				
Informed consent, demographics	X						A 3
Eligibility criteria	X						5.1 & 5.2
Medical history	X						5.1 & 5.2
Concomitant medications	X	X	X	X	X	X	6.6
AE monitoring	Continuous monitoring						8.5
Haematology (whole blood)	X	X		X			8.4.4
Coagulation tests	X	X					8.4.4
Clinical chemistry (serum or plasma)	X	X		X			8.4.4
Thyroid panel	X						8.4.4
Urinalysis	X						8.4.4
Pregnancy test (blood or urine in accordance with institutional practice)	X	X					8.4.4
Complete physical examination	X						8.4.1
Symptom-directed physical examination		X	X				8.4.1

Assessments/procedures [a]	General Screening D-39 to ~D-26	[^{111}In]-FPI-2107 Imaging Screening Period					Details in Section/Appendix
		[^{111}In]-FPI-2107 Day 1		24 h (± 6 h) Post-inj.	48 h (± 6 h) Post-inj.	72-96 h (± 6 h) Post-inj	
		Pre-inj.	Inj.				
ECOG Performance Status	X						8.4.5
Height	X						8.4.1
Weight	X	X					8.4.1
Vital signs	X	X [b]	X [b]	X	X		8.4.2
Ophthalmologic examination	X						8.4.6.2
ECG (12-lead)	Table 26						8.4.3
[^{111}In]-FPI-2107 administration			X				6.1
Whole body planar scintigraphy [c]			X				8.3.2
SPECT/CT imaging [d, e]				X			8.3.1
CT or MRI for RECIST 1.1 Response Assessments [f]	X						8.2
Blood for TCR analysis	Table 26						8.8.1.1
Blood for RNA analysis	Table 26						8.8.1.1
Plasma for ctDNA analysis	Table 26						8.8.1.2
Serum for tumour marker measurement (e.g., CA-19-9, CEA, etc.)	X						8.8.1.3
PK samples	Table 26						8.7.1
ADA samples	Table 26						8.7.2
Archival sample (within 12 months) or fresh biopsy	X						8.8.1.4

ADA, anti-drug antibody; AE, adverse event; bsAb, bispecific monovalent antibody; CA-19-9, carbohydrate antigen-19-9; CEA, carcinoembryonic antigen; CT, computed tomography; ctDNA, circulating tumour DNA; D, day; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; inj., injection; MRI, magnetic resonance imaging; PK, pharmacokinetics; RECIST, Response Evaluation Criteria in Solid Tumours; RNA, ribonucleic acid; SPECT, single-photon emission computed tomography; TCR, T-cell receptor.

[a] If clinically indicated, any procedure or assessment may be done as an unscheduled visit.

[b] Vital signs to be collected at pre-injection (± 5 minutes), end of injection (± 5 minutes), and 4 hours (± 30 minutes) post injection on day of [^{111}In]-FPI-2107.

[c] Planar imaging will be acquired at 4 time points for dosimetry calculation after [^{111}In]-FPI-2107 administration. Please refer to the Site Imaging Manual for timing of the scans, as precise timing may be revised over the course of the study.

[d] SPECT/CT should include relevant body area(s) with known tumour involvement as determined by the Investigator and/or nuclear medicine physician, as well as bone marrow, liver, kidney, and lung.

[e] Only two SPECT/CT images need to be obtained between 24 and 96 hours post [^{111}In]-FPI-2107 injection; please refer to the Site Imaging Manual for timing of the scans, as precise timing may be revised over the course of the study.

[f] The same assessment modality (CT or MRI as appropriate) should be used at baseline and throughout the study.

Table 18 Schedule of Activities – Screening Period and Second Dosimetry– Part A (Dose Exploration with Unlabelled bsAb)

Assessments/procedures [a]	[^{111}In]-FPI-2107 Imaging Screening Period							Details in Section/Appendix
	FPI-2053		[^{111}In]-FPI-2107 Inj.	24 h (± 6 h) Post-inj. of [^{111}In]-FPI-2107	48 h (± 6 h) Post-inj. of [^{111}In]-FPI-2107	72-96 h (± 6 h) Post-inj. of [^{111}In]-FPI-2107	28-Day Safety Visit [b]	
	Pre-inj.	Inj.						
Concomitant medications	X	X	X	X	X	X	X	6.6
AE monitoring	Continuous monitoring							8.5
Haematology (whole blood)	X			X			X	8.4.4
Coagulation tests	X							8.4.4
Serum or plasma chemistry	X			X			X	8.4.4
Thyroid panel	X							8.4.4
Urinalysis	X						X	8.4.4
Pregnancy test (blood or urine in accordance with institutional practice)	X						X	8.4.4
Complete physical examination	X						X	8.4.1
Symptom-directed physical examination			X	X				8.4.1
ECOG Performance Status	X						X	8.4.5
Weight	X							8.4.1
Vital signs	X		X [c]	X	X		X	8.4.2
Ophthalmologic examination							X	8.4.6.2
ECG (12-lead)	Table 26							8.4.3
FPI-2053 administration		X						6.1
[^{111}In]-FPI-2107 administration			X					6.1

Assessments/procedures [a]	[^{111}In]-FPI-2107 Imaging Screening Period							Details in Section/Appendix
	FPI-2053		[^{111}In]-FPI-2107 Inj.	24 h (± 6 h) Post-inj. of [^{111}In]-FPI-2107	48 h (± 6 h) Post-inj. of [^{111}In]-FPI-2107	72-96 h (± 6 h) Post-inj. of [^{111}In]-FPI-2107	28-Day Safety Visit [b]	
	Pre-inj.	Inj.						
Whole body planar scintigraphy [d]			X					8.3.2
SPECT/CT imaging [e, f]				X				8.3.1
PK samples	Table 26							8.7.1
ADA Samples	Table 26							8.7.2

ADA, anti-drug antibody; AE, adverse event; bsAb, bispecific monovalent antibody; CT, computed tomography; D, day; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; inj., injection; PK, pharmacokinetics; SPECT, single-photon emission computed tomography.

[a] If clinically indicated, any procedure or assessment may be done as an unscheduled visit.

[b] Participants who only received FPI-2053 or [^{111}In]-FPI-2107 should have a Day 28 (± 3 days) safety visit as their last study visit (safety laboratory tests, physical examination, vital signs, AE assessment, and concomitant medications).

[c] Vital signs to be collected at pre-injection (± 5 minutes), end of injection (± 5 minutes), and 4 hours (± 30 minutes) post injection on day of [^{111}In]-FPI-2107.

[d] Planar imaging will be acquired at 4 time points for dosimetry calculation after [^{111}In]-FPI-2107 administration. Please refer to the Site Imaging Manual for timing of the scans, as precise timing may be revised over the course of the study.

[e] SPECT/CT should include relevant body area(s) with known tumour involvement as determined by the Investigator and/or nuclear medicine physician, as well as bone marrow, liver, kidney, and lung.

[f] Only two SPECT/CT images need to be obtained between 24 and 96 hours post [^{111}In]-FPI-2107 injection; please refer to the Site Imaging Manual for timing of the scans, as precise timing may be revised over the course of the study.

8.1.2 Screening Period – Part B (Hot Dose Escalation with Optimized Unlabelled bsAb)

Table 19 Schedule of Activities – Screening Period – Part B (Hot Dose Escalation with Unlabelled bsAb)

Assessments/procedures [a]	General Screening D-28 to ~D-15	[^{111}In]-FPI-2107 Imaging Screening Period							Details in Section/Appendix
		FPI-2053		[^{111}In]-FPI-2107 Inj.	24 h (± 6 h) Post-inj. of [^{111}In]-FPI-2107	48 h (± 6 h) Post-inj. of [^{111}In]-FPI-2107	72-96 h (± 6 h) Post-inj. of [^{111}In]-FPI-2107	28-Day Safety Visit [b]	
		Pre-inj.	Inj.						
Informed consent, demographics	X								A 3
Eligibility criteria	X								5.1 & 5.2
Medical history	X								5.1 & 5.2
Concomitant medications	X	X	X	X	X	X	X	X	6.6
AE monitoring	Continuous monitoring								8.5
Haematology (whole blood)	X	X			X			X	8.4.4
Coagulation tests	X	X							8.4.4
Clinical chemistry (serum or plasma)	X	X			X			X	8.4.4
Thyroid panel	X								8.4.4
Urinalysis	X							X	8.4.4
Pregnancy test (blood or urine in accordance with institutional practice)	X	X						X	8.4.4
Complete physical examination	X							X	8.4.1
Symptom-directed physical		X		X	X				8.4.1

Assessments/procedures [a]	General Screening D-28 to ~D-15	[^{111}In]-FPI-2107 Imaging Screening Period							Details in Section/Appendix
		FPI-2053		[^{111}In]-FPI-2107 Inj.	24 h (± 6 h) Post-inj. of [^{111}In]-FPI-2107	48 h (± 6 h) Post-inj. of [^{111}In]-FPI-2107	72-96 h (± 6 h) Post-inj. of [^{111}In]-FPI-2107	28-Day Safety Visit [b]	
		Pre-inj.	Inj.						
examination									
ECOG Performance Status	X							X	8.4.5
Height	X								8.4.1
Weight	X	X							8.4.1
Vital signs	X	X		X [c]	X	X		X	8.4.2
Ophthalmologic examination	X								8.4.6.2
ECG (12-lead)	Table 27								8.4.3
FPI-2053 administration			X						6.1
[^{111}In]-FPI-2107 administration				X					6.1
Whole body planar scintigraphy [d]				X					8.3.2
SPECT/CT imaging [e, f]					X				8.3.1
CT or MRI for RECIST 1.1 Response Assessments [g]	X								8.2
Blood for TCR analysis	Table 27								8.8.1.1
Blood for RNA analysis	Table 27								8.8.1.1
Plasma for ctDNA analysis	Table 27								8.8.1.2
Serum for tumour marker measurement (e.g., CA-19-9,	X								8.8.1.3

Assessments/procedures [a]	General Screening D-28 to ~D-15	[111In]-FPI-2107 Imaging Screening Period							Details in Section/Appendix
		FPI-2053		[111In]-FPI-2107 Inj.	24 h (± 6 h) Post-inj. of [111In]-FPI-2107	48 h (± 6 h) Post-inj. of [111In]-FPI-2107	72-96 h (± 6 h) Post-inj. of [111In]-FPI-2107	28-Day Safety Visit [b]	
		Pre-inj.	Inj.						
CEA, etc.)									
PK samples	Table 27								8.7.1
ADA samples	Table 27								8.7.2
Archival sample (within 12 months) or fresh biopsy	X								8.8.1.4

ADA, anti-drug antibody; AE, adverse event; bsAb, bispecific monovalent antibody; CA-19-9, carbohydrate antigen-19-9; CEA, carcinoembryonic antigen; CT, computed tomography; ctDNA, circulating tumour DNA; D, day; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; inj., injection; MRI, magnetic resonance imaging; PK, pharmacokinetics; RECIST, Response Evaluation Criteria in Solid Tumours; RNA, ribonucleic acid; SPECT, single-photon emission computed tomography; TCR, T-cell receptor.

[a] If clinically indicated, any procedure or assessment may be done as an unscheduled visit.

[b] Participants who only received FPI-2053 and [111In]-FPI-2107 should have a Day 28 (± 3 days) safety visit as their last study visit (safety laboratory tests, physical examination, vital signs, AE assessment, and concomitant medications).

[c] Vital signs to be collected at pre-injection (± 5 minutes), end of injection (±5 minutes), and 4 hours (± 30 minutes) post injection on day of [111In]-FPI-2107.

[d] Planar imaging will be acquired at 4 time points for dosimetry calculation after [111In]-FPI-2107 administration. Please refer to the Site Imaging Manual for timing of the scans, as precise timing may be revised over the course of the study.

[e] SPECT/CT should include relevant body area(s) with known tumour involvement as determined by the Investigator and/or nuclear medicine physician, as well as bone marrow, liver, kidney, and lung.

[f] Only two SPECT/CT images need to be obtained between 24 and 96 hours post [111In]-FPI-2107 injection; please refer to the Site Imaging Manual for timing of the scans, as precise timing may be revised over the course of the study.

[g] The same assessment modality (CT or MRI as appropriate) should be used at baseline and throughout the study.

8.1.3 Screening Period – Part B – Hot-only Dose Escalation (in the Event that Part A Results Indicate that Dose Escalation Without Pre-administration of FPI-2053 is Recommended)

Table 20 Schedule of Activities – Screening Period – Part B, Hot-only Dose Escalation (if Applicable)

Assessments/procedures [a]	General Screening D-28 to ~D-15	[^{111}In]-FPI-2107 Imaging Screening Period						Details in Section/Appendix
		[^{111}In]-FPI-2107 D1		24 h (±6 h) Post-inj. of [^{111}In]-FPI-2107	48 h (±6 h) Post-inj. of [^{111}In]-FPI-2107	72-96 h (±6 h) Post-inj. of [^{111}In]-FPI-2107	28-Day Safety Visit [b]	
		Pre-inj.	Inj.					
Informed consent, demographics	X							A 3
Eligibility criteria	X							5.1 & 5.2
Medical history	X							5.1 & 5.2
Concomitant medications	X	X	X	X	X	X	X	6.6
AE monitoring	Continuous monitoring							8.5
Haematology (whole blood)	X	X		X			X	8.4.4
Coagulation tests	X	X						8.4.4
Clinical chemistry (serum or plasma)	X	X		X			X	8.4.4
Thyroid panel	X							8.4.4
Urinalysis	X						X	8.4.4
Pregnancy test (blood or urine in accordance with institutional practice)	X	X					X	8.4.4
Complete physical examination	X						X	8.4.1
Symptom-directed physical examination		X	X					8.4.1

Assessments/procedures [a]	General Screening D-28 to ~D-15	[^{111}In]-FPI-2107 Imaging Screening Period						Details in Section/Appendix
		[^{111}In]-FPI-2107 D1		24 h (±6 h) Post-inj. of [^{111}In]-FPI-2107	48 h (±6 h) Post-inj. of [^{111}In]-FPI-2107	72-96 h (±6 h) Post-inj. of [^{111}In]-FPI-2107	28-Day Safety Visit [b]	
		Pre-inj.	Inj.					
ECOG Performance Status	X						X	8.4.5
Height	X							8.4.1
Weight	X	X						8.4.1
Vital signs	X	X [c]	X [c]	X	X		X	8.4.2
Ophthalmologic examination	X						X	8.4.6.2
ECG (12-lead)	Table 28							8.4.3
[^{111}In]-FPI-2107 administration			X					6.1
Whole body planar scintigraphy [d]			X					8.3.2
SPECT/CT imaging [e, f]				X				8.3.1
CT or MRI for RECIST 1.1 Response Assessments [g]	X							8.2
Blood for TCR analysis	Table 28							8.8.1.1
Blood for RNA analysis	Table 28							8.8.1.1
Plasma for ctDNA analysis	Table 28							8.8.1.2
Serum for tumour marker measurement (e.g., CA-19-9, CEA, etc.)	X							8.8.1.3
PK samples	Table 28							8.7.1
ADA samples	Table 28							8.7.2
Archival sample (within 12	X							8.8.1.4

Assessments/procedures [a]	General Screening D-28 to ~D-15	[^{111}In]-FPI-2107 Imaging Screening Period						Details in Section/Appendix
		[^{111}In]-FPI-2107 D1		24 h (±6 h) Post-inj. of [^{111}In]-FPI-2107	48 h (±6 h) Post-inj. of [^{111}In]-FPI-2107	72-96 h (±6 h) Post-inj. of [^{111}In]-FPI-2107	28-Day Safety Visit [b]	
		Pre-inj.	Inj.					
months) or fresh biopsy								

ADA, anti-drug antibody; AE, adverse event; CA-19-9, carbohydrate antigen-19-9; CEA, carcinoembryonic antigen; CT, computed tomography; ctDNA, circulating tumour DNA; D, day; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; inj., injection; MRI, magnetic resonance imaging; PK, pharmacokinetics; RECIST, Response Evaluation Criteria in Solid Tumours; RNA, ribonucleic acid; SPECT, single-photon emission computed tomography; TCR, T-cell receptor.

[a] If clinically indicated, any procedure or assessment may be done as an unscheduled visit.

[b] Participants who only received [^{111}In]-FPI-2107 should have a Day 28 (± 3 days) safety visit as their last study visit (safety laboratory tests, physical examination, vital signs, AE assessment, and concomitant medications).

[c] Vital signs to be collected at pre-injection (± 5 minutes), end of injection (± 5 minutes), and 4 hours (± 30 minutes) post injection on day of [^{111}In]-FPI-2107.

[d] Planar imaging will be acquired at 4 time points for dosimetry calculation after [^{111}In]-FPI-2107 administration. Please refer to the Site Imaging Manual for timing of the scans, as precise timing may be revised over the course of the study.

[e] SPECT/CT should include relevant body area(s) with known tumour involvement as determined by the Investigator and/or nuclear medicine physician, as well as bone marrow, liver, kidney, and lung.

[f] Only two SPECT/CT images need to be obtained between 24 and 96 hours post [^{111}In]-FPI-2107 injection; please refer to the Site Imaging Manual for timing of the scans, as precise timing may be revised over the course of the study.

[g] The same assessment modality (CT or MRI as appropriate) should be used at baseline and throughout the study.

8.1.4 Treatment Period - Part A (Dose Exploration with Unlabelled bsAb) - Cycle 1

Table 21 Schedule of Assessments - Treatment Period - Part A (Dose Exploration with Unlabelled bsAb) - Cycle 1

Assessments/procedures [a]	[225Ac]-FPI-2068 Cycle 1 [b]								Details in Section/Appendix
	Day 1			Day 8 (± 1 D)	Day 15 (± 2 D)	Day 22 (±2 D)	Day 29 (± 3 D)	Day 36 (± 3 D)	
	FPI-2053		[225Ac]-FPI-2068						
	Pre-inj.	Inj.							
Eligibility criteria [c]	X								5.1 & 5.2
Concomitant medications and procedures	X			X	X	X	X	X	6.6
AE monitoring [d]	Continuous monitoring								8.5
Haematology (whole blood)	X			X	X	X	X	X	8.4.4
Coagulation tests	As clinically indicated								8.4.4
Clinical chemistry (serum or plasma)	X			X	X	X	X	X	8.4.4
Thyroid panel	As clinically indicated								8.4.4
Urinalysis	X					X			8.4.4
Pregnancy test (blood or urine, in accordance with institutional practice)	X								8.4.4
Complete physical examination	X								8.4.1
Symptom-directed physical examination		X	X	X	X	X	X	X	8.4.1
ECOG Performance Status	X								8.4.5
Weight	X								8.4.1
Vital signs	X	X	X	X	X	X	X	X	8.4.2
Ophthalmologic examination	As clinically indicated								8.4.6.2
ECG (12-lead)	Table 26								8.4.3
FPI-2053 administration		X							6.1

Assessments/procedures [a]	[225Ac]-FPI-2068 Cycle 1 [b]								Details in Section/Appendix
	Day 1			Day 8 (± 1 D)	Day 15 (± 2 D)	Day 22 (±2 D)	Day 29 (± 3 D)	Day 36 (± 3 D)	
	FPI-2053		[225Ac]-FPI-2068						
	Pre-inj.	Inj.							
[225Ac]-FPI-2068 administration			X						6.1
CT or MRI for RECIST 1.1 Response Assessments [e]	Every 8 weeks (± 1 week) after first [225Ac]-FPI-2068 dose								8.2
Blood for TCR analysis	Table 26								8.8.1.1
Blood for RNA analysis	Table 26								8.8.1.1
Plasma for ctDNA analysis	Table 26								8.8.1.2
Tumour biopsy (if applicable)				Day 8 to Day 11 [f]					8.8.2.1
PK samples	Table 26								8.7.1
ADA samples	Table 26								8.7.2

ADA, anti-drug antibody; AE, adverse event; bsAb, bispecific monovalent antibody; CT, computed tomography; ctDNA, circulating tumour DNA; D, day; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; FDG, fluorodeoxyglucose; inj., injection; MRI, magnetic resonance imaging; PET, positron emission tomography; PK, pharmacokinetics; RECIST, Response Evaluation Criteria in Solid Tumours; RNA, ribonucleic acid; TCR, T-cell receptor; TEAE, treatment-emergent adverse event.

[a] If clinically indicated, any procedure or assessment may be done as an unscheduled visit.

[b] Each cycle must be at least 56 days duration.

[c] Obtain within 48 hours prior to the injection and confirm that all tests are within the eligibility requirements.

[d] AEs reported after [111In]-FPI-2107 administration will be reported as TEAEs. All TEAEs related to [111In]-FPI-2107 should be resolved to < Grade 1 or to baseline within 14-days post-[111In]-FPI-2107 administration and prior to [225Ac]-FPI-2068 administration.

[e] A consistent modality of scanning (CT, MRI) should be used for the participant throughout the course of the study. Participants who experience a PR should have their response confirmed 4-6 weeks following documentation of the initial response. CT scan or MRI of chest, abdomen, and pelvis (and other organs if medically indicated) can be obtained for those with non-avid FDG-PET/CT scan. Tumour assessment scans are only required at 2, 4, 6 months (±1 week) and then every 3 months (±2 weeks) until progression or start of new systemic anti-cancer treatment.

[f] If a tumour sample can be safely obtained, every effort should be made to collect a core biopsy between Day 8 and Day 11 in Cycle 1 or Cycle 2 of the Treatment Period.

8.1.5 Treatment Period - Part B (Hot Dose Escalation with Unlabelled bsAb) – Cycle 1

Table 22 Schedule of Assessments - Treatment Period - Part B (Hot Dose Escalation with Unlabelled bsAb) – Cycle 1

Assessments/procedures [a]	[225Ac]-FPI-2068 Cycle 1 [b]								Details in Section/Appendix
	Day 1			Day 8 (± 1 D)	Day 15 (± 2 D)	Day 22 (± 2 D)	Day 29 (± 3 D)	Day 36 (± 3 D)	
	FPI-2053		[225Ac]-FPI-2068						
	Pre-inj.	Inj.							
Eligibility criteria [c]	X								5.1 & 5.2
Concomitant medications and procedures	X			X	X	X	X	X	6.6
AE monitoring [d]	Continuous monitoring								8.5
Haematology (whole blood)	X			X	X	X	X	X	8.4.4
Coagulation tests	As clinically indicated								8.4.4
Clinical chemistry (serum or plasma)	X			X	X	X	X	X	8.4.4
Thyroid panel	As clinically indicated								8.4.4
Urinalysis	X					X			8.4.4
Pregnancy test (blood or urine, in accordance with institutional practice)	X								8.4.4
Complete physical examination	X								8.4.1
Symptom-directed physical examination		X	X	X	X	X	X	X	8.4.1
ECOG Performance Status	X								8.4.5
Weight	X								8.4.1
Vital signs	X	X	X	X	X	X	X	X	8.4.2
Ophthalmologic examination	As clinically indicated								8.4.6.2
ECG (12-lead)	Table 27								8.4.3
FPI-2053 administration		X							6.1

Assessments/procedures [a]	[225Ac]-FPI-2068 Cycle 1 [b]								Details in Section/Appendix
	Day 1			Day 8 (± 1 D)	Day 15 (± 2 D)	Day 22 (± 2 D)	Day 29 (± 3 D)	Day 36 (± 3 D)	
	FPI-2053		[225Ac]-FPI-2068						
	Pre-inj.	Inj.							
[225Ac]-FPI-2068 administration			X						6.1
CT or MRI for RECIST 1.1 Response Assessments [e]	Every 8 weeks (± 1 week) after first [225Ac]-FPI-2068 dose								8.2
Blood for TCR analysis	Table 27								8.8.1.1
Blood for RNA analysis	Table 27								8.8.1.1
Plasma for ctDNA analysis	Table 27								8.8.1.2
Tumour biopsy (if applicable) [f]				Day 8 to Day 11					8.8.2.1
PK samples	Table 27								8.7.1
ADA samples	Table 27								8.7.2

ADA, anti-drug antibody; AE, adverse event; bsAb, bispecific monovalent antibody; CT, computed tomography; ctDNA, circulating tumour DNA; D, day; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; FDG, fluorodeoxyglucose; inj., injection; MRI, magnetic resonance imaging; PK, pharmacokinetics; PET, positron emission tomography; RECIST, Response Evaluation Criteria in Solid Tumours; RNA, ribonucleic acid; TCR, T-cell receptor; TEAE, treatment-emergent adverse event.

[a] If clinically indicated, any procedure or assessment may be done as an unscheduled visit.

[b] Each cycle must be at least 56 days duration.

[c] Obtain within 48 hours prior to the injection and confirm that all tests are within the eligibility requirements.

[d] All TEAEs related to [111In]-FPI-2107 should be resolved to < Grade 1 or to baseline prior to [225Ac]-FPI-2068 administration.

[e] A consistent modality of scanning (CT, MRI) should be used for the participant throughout the course of the study. Participants who experience a PR should have their response confirmed 4-6 weeks following documentation of the initial response. CT scan or MRI of chest, abdomen, and pelvis (and other organs if medically indicated) can be obtained for those with non-avid FDG-PET/CT scan. Tumour assessment scans are only required at 2, 4, 6 months (±1 week) and then every 3 months (±2 weeks) until progression or start of new systemic anti-cancer treatment.

[f] If a tumour sample can be safely obtained, every effort should be made to collect a core biopsy between Day 8 and Day 11 in Cycle 1 or Cycle 2 of the Treatment Period.

8.1.6 Treatment Period - Part B – Hot-only Dose Escalation (in the Event that Results from Part A Indicate that Dose Escalation Without Pre-administration of FPI-2053 is Recommended)

Table 23 Schedule of Assessments - Treatment Period - Part B – Hot-only Dose Escalation (if Applicable)

Assessments/procedures [a]	[^{225}Ac]-FPI-2068 Cycle 1 [b]							[^{225}Ac]-FPI-2068 Cycle 2 and beyond [b]			Details in Section/Appendix
	Day 1		Day 8 (± 1 D)	Day 15 (± 2 D)	Day 22 (± 2 D)	Day 29 (± 3 D)	Day 36 (± 3 D)	Day 1 (± 3D)		Day 15 and Day 29 (± 3 D)	
	Pre-inj.	Post-inj.						Pre-inj.	Post-inj.		
Eligibility/retreatment criteria [c] (see Table 15)	X							X			5.1, 5.2 & 6.7
Concomitant medications and procedures	X		X	X	X	X	X	X		X	6.6
AE monitoring [d]	X	Continuous monitoring									8.5
Haematology (whole blood)	X		X	X	X	X	X	X		X	8.4.4
Coagulation tests	As clinically indicated										8.4.4
Clinical chemistry (serum or plasma)	X		X	X	X	X	X	X		X	8.4.4
Thyroid panel								X			8.4.4
Urinalysis	X				X			X			8.4.4
Pregnancy test (blood or urine, in accordance with institutional practice)	X							X			8.4.4
Complete physical examination	X										8.4.1
Symptom-directed physical examination		X	X	X	X	X	X	X	X	X	8.4.1
ECOG Performance Status	X							X			8.4.5
Weight	X							X			8.4.1

Assessments/procedures [a]	[225Ac]-FPI-2068 Cycle 1 [b]							[225Ac]-FPI-2068 Cycle 2 and beyond [b]			Details in Section/Appendix
	Day 1		Day 8 (± 1 D)	Day 15 (± 2 D)	Day 22 (± 2 D)	Day 29 (± 3 D)	Day 36 (± 3 D)	Day 1 (± 3D)		Day 15 and Day 29 (± 3 D)	
	Pre-inj.	Post-inj.						Pre-inj.	Post-inj.		
Vital signs	X	X	X	X	X	X	X	X	X	X	8.4.2
Ophthalmologic examination	As clinically indicated										8.4.6.2
ECG (12-lead)	Table 28										8.4.3
[225Ac]-FPI-2068 administration		X							X		6.1
CT or MRI for RECIST 1.1 Response Assessments [e]								Every 8 weeks, or as clinically indicated			8.2
Serum for tumour marker measurement (e.g., CA-19-9, CEA, etc.)								X [f]			8.8.1.3
Blood for TCR analysis	Table 28										8.8.1.1
Blood for RNA analysis	Table 28										8.8.1.1
Plasma for ctDNA analysis	Table 28										8.8.1.2
Tumour biopsy (if applicable)			Day 8 to Day 11 [g]								8.8.2.1
PK samples	Table 28										8.7.1
ADA samples	Table 28										8.7.2

ADA, anti-drug antibody; AE, adverse event; CA-19-9, carbohydrate antigen-19-9; CEA, carcinoembryonic antigen; CT, computed tomography; ctDNA, circulating tumour DNA; D, day; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; inj., injection; MRI, magnetic resonance imaging; PK, pharmacokinetics; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumours; RNA, ribonucleic acid; TCR, T-cell receptor; TEAE, treatment-emergent adverse event.

[a] If clinically indicated, any procedure or assessment may be done as an unscheduled visit.
[b] Each cycle must be at least 56 days duration.
[c] Obtain within 48 hours prior to the injection and confirm that all tests are within the eligibility requirements.
[d] All TEAEs related to [111In]-FPI-2107 should be resolved to < Grade 1 or to baseline prior to [225Ac]-FPI-2068 administration.

[e] A consistent modality of scanning (CT, MRI) should be used for the participant throughout the course of the study. Participants who experience a PR should have their response confirmed 4-6 weeks following documentation of the initial response. CT scan or MRI of chest, abdomen, and pelvis (and other organs if medically indicated) can be obtained for those with non-avid FDG-PET/CT scan. Tumour assessment scans are only required at 2, 4, 6 months (±1 week) and then every 3 months (±2 weeks) until progression or start of new systemic anti-cancer treatment.

[f] Tumour markers to be obtained, if applicable, at approximately the same time as radiologic tumour assessments (± 7 days).

[g] If a tumour sample can be safely obtained, every effort should be made to collect a core biopsy between Day 8 and Day 11 in Cycle 1 or Cycle 2 of the Treatment Period.

8.1.7 Treatment Period – Part A and Part B ≥ Cycle 2

Table 24 Schedule of Assessments - Treatment Period – Part A and Part B ≥ Cycle 2

Assessments/procedures [a]	Cycle 2 and beyond – Treatment Period [b]					Details in Section/Appendix
	Day 1			Day 15 (± 2 D)	Day 29 (± 3 D)	
	FPI-2053		[225Ac]-FPI-2068			
	Pre-Inj.	Inj.				
Retreatment criteria (see Table 15) [c]	X					6.7
Concomitant medications and procedures	Continuous monitoring					6.6
AE monitoring	Continuous monitoring					8.5
Haematology (whole blood)	X			X	X	8.4.4
Coagulation tests	As clinically indicated					8.4.4
Clinical chemistry (serum or plasma)	X			X	X	8.4.4
Thyroid panel	X					8.4.4
Urinalysis	X				X	8.4.4
Pregnancy test (blood or urine, in accordance with institutional practice)	X					8.4.4
Symptom directed physical examination [d]	X			X	X	8.4.1
ECOG Performance Status	X				X	8.4.5
Weight	X				X	8.4.1
Vital signs [d]	X		X	X	X	8.4.2
Ophthalmologic examination	As clinically indicated					8.4.6.2
ECG (12-lead)	Table 26 (Part A), Table 27 (Part B)					8.4.3
FPI-2053 administration		X				6.1
[225Ac]-FPI-2068 administration [e, f]			X			6.1
CT or MRI for RECIST 1.1 Response Assessments [g]	Every 8 weeks (± 1 week) after first [225Ac]-FPI-2068 dose					8.2

Assessments/procedures [a]	Cycle 2 and beyond – Treatment Period [b]					Details in Section/Appendix
	Day 1			Day 15 (± 2 D)	Day 29 (± 3 D)	
	FPI-2053		[225Ac]-FPI-2068			
	Pre-Inj.	Inj.				
Serum for tumour marker measurement (e.g., CA-19-9, CEA, etc.) [h]	X				X	8.8.1.3
Blood for TCR analysis	Table 26 (Part A), Table 27 (Part B)					8.8.1.1
Blood for RNA analysis	Table 26 (Part A), Table 27 (Part B)					8.8.1.1
Plasma for ctDNA analysis	Table 26 (Part A), Table 27 (Part B)					8.8.1.2
Tumour biopsy (if applicable) [i]				Day 8 to Day 11		8.8.2.1
PK samples	Table 26 (Part A), Table 27 (Part B)					8.7.1
ADA samples	Table 26 (Part A), Table 27 (Part B)					8.7.2

ADA, anti-drug antibody; AE, adverse event; CA-19-9, carbohydrate antigen-19-9; CEA, carcinoembryonic antigen; CT, computed tomography; ctDNA, circulating tumour DNA; D, day; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; inj., injection; MRI, magnetic resonance imaging; PK, pharmacokinetics; RECIST, Response Evaluation Criteria in Solid Tumours; RNA, ribonucleic acid; TCR, T-cell receptor; TEAE, treatment-emergent adverse event.

[a] If clinically indicated, any procedure or assessment may be done as an unscheduled visit.

[b] [225Ac]-FPI-2068 is administered as a multi-dose regimen. Cycles 2 and 3 to be administered over 56 + 28 days during the Treatment Period.

[c] Obtain within 48 hours prior to the injection and confirm that all tests are within the eligibility requirements.

[d] Vital signs to be collected prior to PK sample draw, at pre-injection, end of injection, and 4 hours post injection on day of [225Ac]-FPI-2068 prior to FPI-2053 administration.

[e] All TEAEs related to [225Ac]-FPI-2068 should be resolved to < Grade 1 or to baseline prior to [225Ac]-FPI-2068 administration.

[f] To occur within approximately 2 hours after FPI-2053 administration.

[g] A consistent modality of scanning (CT, MRI) should be used for the participant throughout the course of the study. Participants who experience a PR should have their response confirmed 4-6 weeks following documentation of the initial response. CT scan or MRI of chest, abdomen, and pelvis (and other organs if medically indicated) can be obtained for those with non-avid FDG-PET/CT scan. Tumour assessment scans are only required at 2, 4, 6 months (±1 week) and then every 3 months (±2 weeks) until progression or start of new systemic anti-cancer treatment.

[h] Tumour markers to be obtained, if applicable, at approximately the same time as radiologic tumour assessments (± 7 days).

[i] If a tumour sample can be safely obtained, every effort should be made to collect a core biopsy between Day 8 and Day 11 in Cycle 1 or Cycle 2 of the treatment period. A core biopsy does not need to be collected in Cycle 2 if one has already been collected in Cycle 1.

8.1.8 End of Treatment and Extended Follow-up Period

Table 25 Schedule of Assessments - End of Treatment and Extended Follow-up Period

Assessments/procedures [a]	End of Treatment [b] ± 3 days	42 -Day (+ 14 days) Safety Follow-Up [c] After the last dose (± 3 days)	Extended Safety Follow-up (after the last dose) Every 3 months (± 2 weeks) for 2 years then every 6 months for 3 years	Details in Section/Appendix
Subsequent anti-cancer treatment	X	X	X	9.4.2
AE monitoring	X	X	X [d]	8.5
Concomitant medications and procedures	X	X		6.6
Haematology (whole blood) with blood smear (pathology)	X	X	X	8.4.4
Clinical chemistry (serum or plasma)	X	X	X	8.4.4
Thyroid panel		X		8.4.4
Urinalysis		X		8.4.4
Pregnancy test (blood or urine, in accordance with institutional practice)	X			8.4.4
Complete physical examination	X			8.4.1
Symptom-directed physical examination		X		8.4.1
ECOG Performance Status	X	X		8.4.5
Weight	X			8.4.1
Ophthalmologic examination	X			8.4.6.2
CT or MRI for RECIST 1.1 Response Assessments	X [d]		X [e]	8.2
Serum for tumour marker measurement (e.g., CA-19-9, CEA, etc.) [g]	X		X [h]	8.8.1.3
Blood for TCR analysis	X		X	8.8.1.1

Assessments/procedures [a]	End of Treatment [b] ± 3 days	42 -Day (+ 14 days) Safety Follow-Up [c] After the last dose (± 3 days)	Extended Safety Follow-up (after the last dose) Every 3 months (± 2 weeks) for 2 years then every 6 months for 3 years	Details in Section/Appendix
Blood for RNA analysis	X		X	8.8.1.1
Plasma for ctDNA analysis	X		X	8.8.1.2
PK sample	X			8.7.1
ADA samples	X	X		8.7.2
Tumour biopsy [i]	X			8.8.2.1
Survival follow-up			X	8.2.2

ADA, anti-drug antibody; AE, adverse event; CA-19-9, carbohydrate antigen-19-9; CEA, carcinoembryonic antigen; CT, computed tomography; ctDNA, circulating tumour DNA; ECOG, Eastern Cooperative Oncology Group; MRI, magnetic resonance imaging; PK, pharmacokinetics; RECIST, Response Evaluation Criteria in Solid Tumours; RNA, ribonucleic acid; TCR, T-cell receptor.

[a] If clinically indicated, any procedure or assessment may be conducted as an unscheduled visit.
[b] The End of Treatment visit should be conducted within 7 days of the decision to permanently discontinue treatment with [^{225}Ac]-FPI-2068.
[c] The Follow-up Visits should be scheduled within CSP-defined timeframe (e.g., 42-56 days) based on the date of the last dose of IMP.
[d] Only related AEs to be collected in the Extended Follow-Up Period.
[e] Radiologic tumour assessment only for participants who came off treatment for reasons other than disease progression.
[f] Radiologic tumour assessments to be performed during Extended Follow-up only if participants discontinued treatment for reasons other than radiologic tumour progression and are only required until disease progression is documented.
[g] Tumour markers to be obtained, if applicable, at approximately the same time as the radiologic tumour assessments (± 7 days).
[h] Tumour markers will be collected during the Extended Safety Follow-up period only from participants who discontinued treatment for reasons other than radiologic tumour progression and are only required until disease progression is documented or until a participant starts subsequent anti-cancer treatment.
[i] Optional tumour biopsy may be collected at the End of Treatment visit only if the participant has confirmed disease progression.

8.1.9 PK, ECG, and Biomarker Sample Timepoints: Part A (Dose Exploration with Unlabelled bsAb)

Table 26 PK, ECG, and Biomarker Sample Timepoints: Part A (Dose Exploration with Unlabelled bsAb)

Visit/timepoint		PK	Triplicate 12-lead ECG [a]	Blood for RNA and TCR analysis	Plasma for ctDNA analysis	ADA samples
Details in Section/Appendix		8.7.1	8.4.3	8.8.1.1	8.8.1.2	8.7.2
General Screening			During visit day		During visit day	
[^{111}In]-FPI-2107 Imaging Screening Period						
Day of [^{111}In]-FPI-2107 administration	Predose [^{111}In]-FPI-2107 injection (within 2 h prior)	X	X	X	X	X
	End of [^{111}In]-FPI-2107 injection	+ 5 min	X			
	1 hr post injection	± 10 min	X			
	2 h post injection	± 15 min	X			
	4 h post injection	± 30 min	X			
	8 h post injection [b]	± 30 min [c]	X			
Planar scintigraphy and SPECT/CT timepoints	24 h (± 6 h) post injection	Within 2 h prior	X			
	48 h (± 6 h) post injection	Within 2 h prior	X			
	72-96 h (± 6 h) post injection	Within 2 h prior	X			
28-day Safety Visit [d]						X
Screening Period with predose FPI-2053 followed by [^{111}In]-FPI-2107						
Day of [^{111}In]-FPI-2107	Predose FPI-2053 administration (within 2 h prior)	X	X	X	X	X

Visit/timepoint		PK	Triplicate 12-lead ECG [a]	Blood for RNA and TCR analysis	Plasma for ctDNA analysis	ADA samples
administration	End of FPI-2053 administration	+ 5 min	X			
	Predose [^{111}In]-FPI-2107 administration	- 5 min	X			
	End of [^{111}In]-FPI-2107 administration	+ 5 min	X			
	1 hr post administration	± 10 min	X			
	2 h post administration	± 15 min	X			
	4 h post administration	± 30 min	X			
	8 h post administration [b]	± 30 min [c]	X			
Planar scintigraphy and SPECT/CT timepoints	24 h (± 6 h) post injection	Within 2 h prior	X			
	48 h (± 6 h) post injection	Within 2 h prior	X			
	72-96 h (± 6 h) post injection	Within 2 h prior	X			
Cycle 1 – Treatment Period predose FPI-2053 followed by [^{225}Ac]-FPI-2068						
Day of [^{225}Ac]-FPI-2068 administration	Predose FPI-2053 administration (within 2 h prior)	X	X	X	X	X
	End of FPI-2053 administration	+ 5 min	X			
	Predose [^{225}Ac]-FPI-2068 administration	- 5 min	X			
	End of [^{225}Ac]-FPI-2068	+ 5 min	X			

Visit/timepoint		PK	Triplicate 12-lead ECG [a]	Blood for RNA and TCR analysis	Plasma for ctDNA analysis	ADA samples
	administration					
	1 hr post administration	± 10 min	X			
	2 h post administration	± 15 min	X			
	4 h post administration	± 30 min	X			
	8 h post administration [b]	± 30 min	X			
Day 8 (7 days [± 6 h] post injection)		During visit day	During visit day			X
Day 15 (14 days [± 2 days] post injection)		During visit day	During visit day	During visit day	During visit day	
Day 22 (21 days [± 2 days] post injection)		During visit day	During visit day			X
Day 29 (28 days [± 3 days] post injection)		During visit day	During visit day			
Day 57 (56 days [± 3 days] post injection, if Cycle 2 is delayed)		During visit day	During visit day	X [e]	X [e]	X [e]
Cycles 2 and beyond Treatment Period						
Day of [^{225}Ac]-FPI-2068 administration	Predose FPI-2053 administration (within 2 h prior)	X	X	X	X	X
	End of FPI-2053 administration	+ 5 min	X			
	Predose [^{225}Ac]-FPI-2068 administration	- 5 min	X			
	End of [^{225}Ac]-FPI-2068	+ 5 min	X			

Visit/timepoint		PK	Triplicate 12-lead ECG [a]	Blood for RNA and TCR analysis	Plasma for ctDNA analysis	ADA samples
	administration					
Day 15 (14 days [± 2 days] post injection)				During visit day	During visit day	
Day 57 (56 days [± 3 days] post injection, if next cycle is delayed)				X [e]	X [e]	X [e]

ADA, anti-drug antibody; bsAb, bispecific monovalent antibody; CT, computed tomography; ctDNA, circulating tumour DNA; ECG, electrocardiogram; PK, pharmacokinetics; RNA, ribonucleic acid; SPECT, single-photon emission computed tomography; TCR, T-cell receptor.

[a] ECG may be performed, if clinically indicated, at any other visit/timepoint. ECGs must be performed prior to collection of the PK sample at the same timepoint.

[b] Not required initially, but if early PK data indicates that it is necessary, the 8-hour PK timepoint will be collected.

[c] If 8 h post injection PK sample is drawn.

[d] The 28 or 42-day (+ 14 days) Safety Visit only occurs if the participant does not proceed to the treatment phase (i.e., only receives FPI-2053 and [^{111}In]-FPI-2107).

[e] Blood samples for RNA, ctDNA, and ADA assessments at End of Treatment taken only if participant does not progress to next cycle.

8.1.10 PK, ECG, and Biomarker Time Points: Part B (Hot Dose Escalation with Unlabelled bsAb)

Table 27 PK, ECG, and Biomarker Time Points: Part B (Hot Dose Escalation with Unlabelled bsAb)

Visit/timepoint		PK	Triplicate 12-lead ECG [a]	Blood for RNA and TCR analysis	Plasma for ctDNA analysis	ADA samples
Details in Section/Appendix		8.7.1	8.4.3	8.8.1.1	8.8.1.2	8.7.2
General Screening			During visit day		During visit day	
Screening Period with predose FPI-2053 followed by [^{111}In]-FPI-2107						
Day of [^{111}In]-FPI-2107	Predose FPI-2053 administration (within 2 h prior)	X	X	X	X	X
	End of FPI-2053 administration	+ 5 min	X			
	Predose [^{111}Ac]-FPI-2107 administration	- 5 min	X			
	End of [^{111}In]-FPI-2107 administration	+ 5 min	X			
	1 hr post administration	± 10 min	X			
	2 h post administration	± 15 min	X			
	4 h post administration	± 30 min	X			
	8 h post administration [b]	± 30 min [c]	X			
Planar scintigraphy and SPECT/CT timepoints	24 h (± 6 h) post injection	Within 2 h prior	X			
	48 h (± 6 h) post injection	Within 2 h prior	X			
	72-96 h (± 6 h) post injection	Within 2 h prior	X			
28-day Safety Visit [d]						X
Cycle 1 – Treatment Period with predose FPI-2053 followed by [^{225}Ac]-FPI-2068						
Day of [^{225}Ac]-FPI-2068 Injection	Predose FPI-2053 (within 2 h prior)	X	X	X	X	X
	End of FPI-2053 administration	+ 5 min	X			
	Predose [^{225}Ac]-FPI-2068	- 5 min	X			

Visit/timepoint		**PK**	**Triplicate 12-lead ECG** [a]	**Blood for RNA and TCR analysis**	**Plasma for ctDNA analysis**	**ADA samples**
	End of [^{225}Ac]-FPI-2068 administration	+ 5 min	X			
	1 h post administration	± 10 min	X			
	2 h post administration	± 15 min	X			
	4 h post administration	± 30 min	X			
	8 h post administration [b]	± 30 min [c]	X [c]			
Day 8 (7 days [± 6 h] post injection)		During visit day	During visit day			X
Day 15 (14 days [± 2 days] post injection)		During visit day	During visit day	During visit day	During visit day	
Day 22 (21 days [± 2 days] post injection)		During visit day	During visit day			X
Day 29 (28 days [± 3 days] post injection)		During visit day	During visit day			
Day 57 (56 days [± 3 days] post injection, if Cycle 2 is delayed)		During visit day	During visit day	X [e]	X [e]	X [e]
Cycles 2 and beyond Treatment Period (until last planned cycle) with predose FPI-2053 followed by [^{225}Ac]-FPI-2068						
Day of [^{225}Ac]-FPI-2068 administration	Predose FPI-2053 administration (within 2 h prior)	X	X	X	X	X
	End of FPI-2053 administration	+ 5 min	X			
	Predose [^{225}Ac]-FPI-2068 administration	- 5 min	X			
	End of [^{225}Ac]-FPI-2068 administration	+ 5 min	X			
Day 15 (14 days [± 2 days] post injection)				During visit day	During visit day	
Day 57 (56 days [± 3 days] post injection, if next cycle is delayed)				X [e]	X [e]	X [e]

ADA, anti-drug antibody; bsAb, bispecific monovalent antibody; CT, computed tomography; ctDNA, circulating tumour DNA; ECG, electrocardiogram; PK, pharmacokinetics; RNA, ribonucleic acid; SPECT, single-photon emission computed tomography; TCR, T-cell receptor.

[a] ECG may be performed, if clinically indicated, at any other visit/timepoint. ECGs must be performed prior to collection of the PK sample at the same timepoint.

[b] Not required initially, but if early PK data indicates that it is necessary, the 8-hour PK timepoint will be collected.

[c] If 8 h post injection PK sample is drawn.

[d] The 28 or 42-day (+ 14 day) Safety Visit only occurs if the participant does not proceed to the treatment phase (i.e., only receives FPI-2053 and [^{111}In]-FPI-2107).
[e] Blood samples for RNA, ctDNA, and ADA assessments at End of Treatment taken only if participant does not progress to next cycle.

8.1.11 PK, ECG, and Biomarker Sample Timepoints: Part B – Hot-only Dose Escalation (in the Event that Results from Part A Indicate that Dose Escalation Without Pre-administration of FPI-2053 is Recommended)

Table 28 PK, ECG, and Biomarker Sample Timepoints: Part B, Hot-only Dose Escalation (if Applicable)

Visit/timepoint		**PK**	**Triplicate 12-lead ECG** [a]	**Blood for RNA and TCR analysis**	**Plasma for ctDNA analysis**	**ADA samples**
Details in Section/Appendix		8.7.1	8.4.3	8.8.1.1	8.8.1.2	8.7.2
General Screening			During visit day		During visit day	
[^{111}In]-FPI-2107 Imaging Screening Period						
Day of [^{111}In]-FPI-2107 administration	Predose [^{111}In]-FPI-2107 injection (within 2 h prior)	X	X	X	X	X
	End of [^{111}In]-FPI-2107 injection	+ 5 min	X			
	1 hr post injection	± 10 min	X			
	2 h post injection	± 15 min	X			
	4 h post injection	± 30 min	X			
	8 h post injection [b]	± 30 min [c]	X			
Planar scintigraphy and SPECT/CT timepoints	24 hrs (± 6 h) post injection	Within 2 h prior	X			
	48 h (± 6 h) post injection	Within 2 h prior	X			
	72-96 h (± 6 h) post injection	Within 2 h prior	X			
28-day Safety Visit [d]						X

Visit/timepoint		PK	Triplicate 12-lead ECG [a]	Blood for RNA and TCR analysis	Plasma for ctDNA analysis	ADA samples
Cycle 1 – Treatment Period [^{225}Ac]-FPI-2068						
Day of [^{225}Ac]-FPI-2068 administration	Predose (within 2 h prior)	X	X	X	X	X
	End of [^{225}Ac]-FPI-2068 injection	+ 5 min	X			
	1 hr post injection	± 10 min	X			
	2 hr post injection	± 15 min	X			
	4 h post injection	± 30 min	X			
	8 h post injection [b]	± 30 min [c]	X			
Day 8 (7 days [± 6 h] post injection)		During visit day	During visit day			X
Day 15 (14 days [± 2 days] post injection)		During visit day	During visit day	During visit day	During visit day	
Day 22 (21 days [± 2 days] post injection)		During visit day	During visit day			X
Day 29 (28 days [± 3 days] post injection)		During visit day	During visit day			
Day 57 (56 days [± 3 days] post injection, if Cycle 2 is delayed)		During visit day	During visit day	X [e]	X [e]	X [e]
Cycles 2 and beyond Treatment Period (until last planned cycle)						
Day of [^{225}Ac]-FPI-2068 administration	Predose (within 2 h prior)	X	X	X	X	X
	End of [^{225}Ac]-FPI-2068 administration	+ 5 min	X			
Day 15 (14 days [± 2 days] post injection)				During visit day	During visit day	

Visit/timepoint	PK	Triplicate 12-lead ECG [a]	Blood for RNA and TCR analysis	Plasma for ctDNA analysis	ADA samples
Day 57 (56 days [± 3 days] post injection, if next cycle is delayed)			X [e]	X [e]	X [e]

ADA, anti-drug antibody; CT, computed tomography; ctDNA, circulating tumour DNA; ECG, electrocardiogram; PK, pharmacokinetics; RNA, ribonucleic acid; SPECT, single-photon emission computed tomography; TCR, T-cell receptor.

[a] ECG may be performed, if clinically indicated, at any other visit/timepoint. ECGs must be performed prior to collection of the PK sample at the same timepoint.

[b] Not required initially, but if early PK data indicates that it is necessary, the 8-hour PK timepoint will be collected.

[c] If 8 h post injection PK sample is drawn.

[d] The 28 or 42-day (+ 14 day) Safety Visit only occurs if the participant does not proceed to the treatment phase (i.e., only receives [^{111}In]-FPI-2107).

[e] Blood samples for RNA, ctDNA, and ADA assessments at End of Treatment taken only if participant does not progress to next cycle.

8.2 Efficacy Assessments

8.2.1 Tumour Assessments

Tumour assessments will be based on RECIST v1.1 (Eisenhauer et al, 2009) and will be performed approximately every 8 weeks (± 1 week) after the first [^{225}Ac]-FPI-2068 dose, or as clinically indicated (see Section 8.1).

Standard radiographic imaging using RECIST v1.1 is used to assess both response (in participants with measurable disease) and progression. An objective response (OR) as per RECIST v1.1 criteria requires confirmation of PR and complete response (CR) and must occur no fewer than 4 weeks after initial documentation of PR or CR. Disease progression will be defined as per RECIST v1.1.

Tumour Evaluations

All tumour assessments should include the following evaluations: physical examination and cross-sectional imaging using computed tomography (CT) or magnetic resonance imaging (MRI) scan.

Physical Examination

Lesions detected by physical examination will only be considered measurable if superficial, e.g., skin nodules, and palpable lymph nodes and spleen. Documentation by colour photography including ruler is recommended for estimating the size of skin lesions.

Imaging

Chest, abdomen, and pelvic CT/MRI scans are required for all participants. Central nervous system (CNS) imaging is optional unless disease is known to be present at baseline.

The preferred method of systemic disease assessment is CT with contrast; if CT with contrast is contraindicated, CT without contrast is preferred over MRI. The preferred method for CNS imaging is MRI; if CT scan is performed, CT with contrast is required. The same method should be followed for all subsequent tumour assessments.

- CT scans
    - CT scans should be performed with contiguous cuts in slice thickness of 5 mm or less. Spiral CT should be performed using a 5-mm contiguous reconstruction algorithm.
    - CT scans of hepatic tumours should be collected in the hepatic arterial, portal venous, and delayed phases (Lencioni and Llovet, 2010).
- MRI scans
    - MRI scan is acceptable for measurement of lesions provided that the same anatomical plane is used for serial assessments. If possible, the same imaging device should be used for serial evaluations.

- MRI scans of hepatic tumours should be performed in the precontrast, hepatic arterial, portal venous and delayed phases (Lencioni and Llovet, 2010).

8.2.2 Overall Survival

Assessments for survival will be conducted every 3 months for the first 2 years then every 6 months following treatment discontinuation. Survival information may be obtained via telephone contact with the participant, participant's family, by contact with the participant's current physician, or local death registries. Additional assessments, including subsequent anticancer therapy, are to be recorded.

8.3 Dosimetry Assessments

Dosimetry assessments will be performed according to the SoAs (see Section 8.1).

Internal dosimetry estimates will be obtained for each participant from the scintigraphy images and SPECT/CT using the Medical Internal Radiation Dose technique and the OLINDA/EXM internal dosimetry software. A total radiation dose estimate will be computed for each participant both for [^{111}In]-FPI-2107 and for [^{225}Ac]-FPI-2068 with and without FPI-2053. For [^{225}Ac]-FPI-2068, total radiation dose estimates on a per unit injected activity basis (mGy/MBq) and for the CSP-planned amount of injected [^{225}Ac]-FPI-2068 will be computed.

Participants may receive their first cycle of [^{225}Ac]-FPI-2068, with or without FPI-2053, after confirmation of successful completion of the imaging screening with [^{111}In]-FPI-2107 including organ dosimetry and sufficient target expression by the imaging vendor(s). Please refer to the imaging manual for details. All subsequent cycles of [^{225}Ac]-FPI-2068 will be based on individual dosimetry and will not exceed the participant's estimated cumulative radiation dose limit to specified organs.

The total radiation doses estimated for kidneys, liver, and lungs will be compared to published, radiation exposure data, based on ICRP prespecified limits (Stewart et al, 2012).

The critical organ radiation dose limits are kidneys ≤ 23 Gy (cumulative); liver ≤ 31 Gy (cumulative); red bone marrow ≤ 2 Gy (cumulative, Part A only) and lungs ≤ 16.5 Gy (cumulative). If any of the 4 organs' (3 organs' for Part B) estimated radiation doses (based on the planned administration) exceeds these limits, then the participant will not receive the planned full dose of [^{225}Ac]-FPI-2068. The total amount of injected activity necessary to approach but not exceed the organ dose limit will be computed. A new total radiation dose estimate will be computed for the participant using this dosimetry-limited injected activity quantity. The participant may receive this adjusted (reduced) dose of [^{225}Ac]-FPI-2068 following consultation and agreement between the Investigator, Sponsor, and Medical Monitor.

The detailed procedures for image acquisition and analysis, as well as the acquisition

timepoints, will be described in the Imaging Charter and in the Site Imaging Manual. Sponsor-identified independent radiologist(s) and physicist(s) will confirm EGFR/c-MET tumour uptake positivity and estimates of healthy organ and whole body dosimetry. These determinations will be shared with study Investigators prior to administration of each participant's first cycle of treatment.

8.3.1 SPECT/CT Scans

- SPECT/CT scan will be used to evaluate the radiation dosimetry of [^{111}In]-FPI-2107 and make projections for [^{225}Ac]-FPI-2068 and the effect of predose administration of FPI-2053 on radiation dosimetry.
- SPECT/CT scan will also to be used to determine eligibility for treatment with [^{225}Ac]-FPI-2068.
- Two SPECT/CT images will be obtained between 24 and 96 hours post-[^{111}In]-FPI-2107 injection; please refer to the Site Imaging Manual for timing of the scans, as precise timing may be revised over the course of the study.

8.3.2 Whole Body Planar Scintigraphy

- Planar imaging must be used to evaluate the radiation dosimetry of [^{111}In]-FPI-2107 and [^{225}Ac]-FPI-2068 and the effect of predose administration of FPI-2053 on radiation dosimetry.
- Four planar images will be obtained between 0 and 96 hours post-[^{111}In]-FPI-2107 injection; please refer to the Site Imaging Manual for timing of the scans, as precise timing may be revised over the course of the study.

8.4 Safety Assessments

Planned time points for all safety assessments are provided in the SoAs (see Section 8.1).

8.4.1 Physical Examinations

Physical examination will be performed at timepoints as specified in the SoAs (see Section 8.1). Situations in which physical examination results should be reported as AEs are described in Section 8.5.5.

- A complete physical examination will include assessments of the following; general appearance, respiratory, cardiovascular, abdomen skin, head, and neck (including ears, eyes, nose, and throat), lymph nodes, thyroid, muscular-skeletal (including spine and extremities), and neurological systems, and weight.
- A symptom-directed examination will include assessments of relevant organ systems related to any AE that the participant may be experiencing, as deemed appropriate by the Investigator.

- Height will be measured at screening only.
- Weight will be measured as part of complete physical examinations in addition to other timepoints outlined in the SoAs (see Section 8.1).

8.4.2 Vital Signs

Vital signs (body temperature, blood pressure, respiration rate, and heart [pulse] rate) will be performed at timepoints specified in the SoAs (see Section 8.1). Situations in which changes in vital signs should be reported as AEs are described in Section 8.5.5.

8.4.3 Electrocardiograms

All ECGs will be performed in triplicate (all 3 within a 5-minute time period, at least 1 minute apart) and the mean value of the triplicate measurement will be recorded as the baseline value.

All ECG recordings will be made with the participant in a supine position having rested in this position for at least 5 minutes before the start of the ECG.

All ECGs will be recorded at a speed of 25 mm/second with amplitude recording of 100 mm/mV. At least 3 full complexes must be recorded. A multi-channel ECG machine should be used (equals 3 leads recorded simultaneously) and there must be amplitude index calibration for each lead. Digital copies of ECGs may be held centrally by a central ECG provider and stored for potential independent analysis during, or at the end of, the study at the Sponsor's discretion. The central independent review will not replace the local review by the Investigator or other medically qualified designee.

Electronic software will be used to assess the following parameters: pulse rate, QRS, QT, and QTc time intervals (to be reported by Fridericia's formula [QTcF], where available, or by Bazett's formula [QTcB], where QTcF is not available) should be reported if available. All ECGs must be reviewed by the Principal Investigator or a medically qualified designee before the start of injection or infusion (for time points prior to the start of injection or infusion) and before the participant is permitted to leave the clinic (for post injection or infusion time points). In case of a clinically significant ECG abnormality (e.g., occurrence of de- or re-polarisation disorders, arrhythmic disorders), including QTcF prolongation of >500 milliseconds, a minimum of 2 additional 12-lead ECGs should be obtained over a brief interval (e.g., 30 minutes) to confirm the abnormality based on manual over-read by a medically qualified person. Such abnormalities and any obvious changes in ECG parameters from baseline will be assessed by the Principal Investigator for clinical significance. If clinically significant, the ECG abnormality should be recorded as an AE in the eCRF. Clinical interpretation and any associated management of participant related to ECG abnormalities will be done locally and will be based on interpretation by a medically qualified person at the site.

8.4.4 Clinical Safety Laboratory Assessments

Blood and urine samples for assessment of haematology, clinical chemistry, coagulation,

thyroid function, pregnancy test, and urinalysis will be taken at the visits indicated in the SoA (see Section 8.1).

Additional safety samples may be collected, if clinically indicated, at the discretion of the Investigator. The date, time of collection, and results (values, units and reference ranges) will be recorded on the appropriate eCRF.

The clinical chemistry, haematology, coagulation, and urinalysis will be performed at a local laboratory at or near to the Investigator site. Sample tubes and sample sizes may vary depending on laboratory method used and routine practice at the site.

The following laboratory variables will be measured.

Table 29 Laboratory Safety Variables

Assessment group	**Variables**	
Haematology (whole blood)	Hb	Platelet count
	Haematocrit	Reticulocytes
	RBC count	WBC count with differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils)
	Blood smear (pathology, only during the End of Treatment and Extended Follow-up period	
Clinical chemistry (serum or plasma)	Sodium	ALP [a]
	Potassium	LDH
	Chloride	GGT
	Bicarbonate	Total protein
	BUN	Albumin
	Serum creatinine	Calcium
	Glucose	Magnesium
	Total bilirubin [a, b, c]	Phosphate
	AST [a, b]	Amylase
	ALT [a, b]	Lipase
Coagulation	PT	aPTT
	INR	
Thyroid panel	Free T3	Free T4
	TSH	
Pregnancy test (blood or urine in accordance with institutional practice)	hCG or beta hCG	
Urinalysis (including dipstick)	U-Hb/erythrocytes/blood	U-pH
	U-protein/albumin	U-bilirubin

Assessment group	Variables	
	U-glucose	U-ketones
	U-microscopy including WBC/HPF and RBC/HPF [d]	

ALP, alkaline phosphatase; ALT, alanine aminotransferase; aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; BUN, blood urea nitrogen; Hb, haemoglobin; hCG, human chorionic gonadotropin; GGT, gamma-glutamyl transferase; HPF, high-power field; INR, international normalised ratio; LDH, lactate dehydrogenase; PT, prothrombin time; PTT, partial thromboplastin time; RBC, red blood cell; T3, triiodothyronine; T4, thyroxine; TSH, thyroid stimulating hormone; U, urine; ULN, upper limit of normal; WBC, white blood cell.

[a] Tests for AST, ALT, ALP, and total bilirubin must be conducted and assessed concurrently.

[b] In case a participant shows an AST **or** ALT ≥ 3 × ULN together with total bilirubin ≥ 2 × ULN please refer to Appendix E (Actions required in cases of increases in liver biochemistry and evaluation of Hy's Law'), for further instructions.

[c] If total bilirubin increases 1.5 × above the ULN (or 2 × above the baseline value in participants with documented Gilbert's syndrome), indirect bilirubin should be measured and any potential alternative aetiologies should be assessed.

[d] If clinically indicated.

8.4.5 ECOG Performance Status

ECOG PS will be assessed as stated in the SoAs, based on ECOG scale.

8.4.6 Other Safety Assessments

8.4.6.1 Pneumonitis/ILD Investigation

If new or worsening pulmonary symptoms (e.g., dyspnoea, cough or fever) suggestive of ILD/pneumonitis is observed, treatment with study intervention must be interrupted and a thorough investigation is required as described in detail in the toxicity management guidelines (TMGs) for [^{225}Ac]-FPI-2068 (see Table 15).

Evaluations could include:

- History (cough, shortness of breath, pyrexia) and examination (auscultation of lung fields)
- Tests to rule out infection
- Tests to rule out a cardiac event (ECG and troponin)
- High resolution CT (HRCT) scan of the chest
- Pulmonary function tests (spirometry, diffusing capacity of the lung for carbon monoxide) and pulse oximetry (SpO_2)
- Arterial blood gases if clinically indicated
- Pulmonologist consultation
- Bronchoscopy and bronchoalveolar lavage as clinically indicated and if feasible
- One blood sample for PK as soon as ILD/pneumonitis is suspected (Section 8.7.1)
- Additional blood samples for exploratory ILD biomarker analysis as soon as ILD/pneumonitis is suspected, if feasible (Section 8.8.2.3)

- Other tests/procedures could be considered, as clinically indicated, and to rule out alternate aetiology such as infection (e.g., lung biopsy if clinically indicated and feasible without additional harm to the wellbeing of the participant).

The results of the full diagnostic workup (including HRCT, blood and sputum culture, haematological parameters, etc.) must be captured in the eCRF. It is strongly recommended to perform a full diagnostic workup to exclude alternative causes such as lymphangitic carcinomatosis, infection, allergy, cardiogenic oedema, or pulmonary haemorrhage. In the presence of confirmatory HRCT scans where other causes of respiratory symptoms have been excluded, a diagnosis of pneumonitis/ILD should be considered and the TMGs (Table 15) should be followed.

Additionally, when pneumonitis/ILD is suspected during study treatment, the following markers should be measured where possible:

- ILD markers (KL-6, SP-D) and β-D-glucan
- Tumour markers: applicable tumour markers that are related to disease progression
- Additional clinical chemistry: C-reactive protein, lactate dehydrogenase

8.4.6.2 Ophthalmological Examinations

An ophthalmic assessment, including visual acuity testing, slit lamp examination, intraocular pressure measurement, fundoscopy, and fluorescein staining will be performed at screening and at the end of treatment visit. The assessment should also be performed any time during the study if a participant experiences any visual symptoms (including blurring of vision), with additional tests if clinically indicated. Any clinically significant findings, including those confirmed by an ophthalmologist, must be reported as an AE. Photographs should be taken to record any clinically significant findings. Ophthalmology examination results should be recorded in the eCRF.

8.5 AEs and SAEs

The Principal Investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

The definitions of an AE or SAE can be found in Appendix B.

AEs will be reported by the participant.

The Investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE.

8.5.1 Time Period and Frequency for Collecting AE and SAE Information

Data on AEs and SAEs will be collected from time of signature of the informed consent form, throughout the Treatment Period and including the 28 or 42-day (+ 14 days) safety follow-up

period. During the extended follow-up period, only data for SAEs will be collected.

SAEs will be recorded from the time of signing of the informed consent form.

If the Investigator becomes aware of an SAE with a suspected causal relationship to the IMP that occurs after the end of the clinical study in a participant treated by him or her, the Investigator shall, without undue delay, report the SAE to the Sponsor.

8.5.2 Follow-up of AEs and SAEs

Any AEs that are unresolved at the participant's last AE assessment in the study are followed up by the Investigator for as long as medically indicated, but without further recording in the eCRF. Fusion Pharmaceuticals retains the right to request additional information for any participant with ongoing AEs/SAEs at the end of the study, if judged necessary.

AE variables

The following variables will be collected for each AE;

- AE (verbatim)
- The date and time when the AE started and stopped (time is only required if the AE begins on a dosing day)
- CTCAE grade/changes in CTCAE grade
- Whether the AE is serious or not
- Investigator causality rating against the Investigational Product(s) (yes or no)
- Action taken with regard to Investigational Product(s)
- Outcome

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for SAE
- Date Investigator became aware of SAE
- AE is serious due to
- Date of hospitalisation
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to study procedure(s)
- Causality assessment to other medication

8.5.3 Causality Collection

The Investigator should assess causal relationship between investigational product and each AE, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?'

For SAEs, causal relationship should also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

A guide to the interpretation of the causality question is found in Appendix B to the CSP.

8.5.4 AEs Based on Signs and Symptoms

All AEs spontaneously reported by the participant or reported in response to the open question from the study site staff: 'Have you had any health problems since the previous visit/you were last asked?', or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

8.5.5 AEs Based on Examinations and Tests

The results from the CSP mandated laboratory tests and vital signs will be summarised in the CSR.

Deterioration as compared to baseline in CSP-mandated physical examinations, laboratory values, vital signs, and ECGs should therefore only be reported as AEs if they fulfil any of the SAE criteria, are the reason for discontinuation of treatment with the investigational product or are considered to be clinically relevant as judged by the Investigator (which may include but not limited to consideration as to whether treatment or non-planned visits were required or other action was taken with the study treatment, e.g., dose adjustment or drug interruption).

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting Investigator uses the clinical, rather than the laboratory term (e.g., anaemia versus low haemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Deterioration of a laboratory value, which is unequivocally due to disease progression, should not be reported as an AE/SAE.

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE unless unequivocally related to the disease under study.

8.5.6 Hy's Law

Cases where a participant shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥ 3 × ULN together with total bilirubin ≥ 2 × ULN may need to be reported as SAEs. Please refer to Appendix E for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law.

Refer to the TMGs in Section 6.7.2 for management of participants with elevations in liver biochemistry.

8.5.7 Disease Progression

Disease progression can be considered as a worsening of a participant's condition attributable to the disease for which the investigational product is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. The development of new, or progression of existing metastasis to the primary cancer under study should be considered as disease progression and not an AE. Events, which are unequivocally due to disease progression, should not be reported as an AE during the study.

8.5.8 Disease Under Study

Symptoms of disease under study are those which might be expected to occur as a direct result of participants' advanced solid tumour. Events which are unequivocally due to disease under study should not be reported as an AE during the study unless they meet SAE criteria or lead to discontinuation of the investigational product.

8.5.9 Reporting of SAEs

All SAEs have to be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). All SAEs will be recorded in the eCRF.

If any SAE occurs in the course of the study, then Investigators or other site personnel inform the appropriate Sponsor representatives within 1 day, i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated Sponsor representative works with the Investigator to ensure that all the necessary information is provided to the Sponsor's representative Patient Safety data entry site **within one calendar day** of initial receipt for fatal and life-threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up will be undertaken immediately. Investigators or other site personnel will inform Sponsor representatives of any follow-up information on a previously reported SAE within one calendar day, i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

Once the Investigators or other site personnel indicate an AE is serious in the electronic data capture (EDC) system, an automated email alert is sent to the designated Sponsor

representative.

If the EDC system is not available, then the Investigator or other study site staff reports a SAE to the appropriate Sponsor representative by telephone.

The Sponsor representative will advise the Investigator/study site staff how to proceed.

The reference document for definition of expectedness for the IMPs in this study can be found in the IB.

8.5.10 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to the Sponsor's representative except for:

- If the pregnancy is discovered before the study participant has received any study intervention

8.5.10.1 Maternal Exposure

If a participant becomes pregnant during the course of the study, the investigational products should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital anomalies/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital anomaly/birth defect) should be followed up and documented even if the participant was discontinued from the study.

If any pregnancy occurs in the course of the study, then the Investigator or other site personnel informs the appropriate Sponsor representatives within **1 day**, i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated Sponsor representative works with the Investigator to ensure that all relevant information is provided to the Sponsor's representative Patient Safety data entry site **within 1 or 5 calendar days** for SAEs (see Section 8.5.9) and **within 30 days** for all other pregnancies.

The same timelines apply when outcome information is available.

The PREGREP module in the eCRF is used to report the pregnancy and the paper-based PREGOUT module is used to report the outcome of the pregnancy.

8.5.10.2 Paternal Exposure

Male participants should refrain from fathering a child or donating sperm during the study and 6 months following the last dose.

Pregnancy of the participant's partners is not considered to be an AE. However, the outcome

of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital anomaly), occurring from the date of the first dose until 6 months after the last dose and as indicated by previous studies (nonclinical and clinical) should, if possible, be followed up and documented in the Pregnancy Report Form. Consent from the partner must be obtained before the Pregnancy Report Form is completed.

8.5.11 New Cancers

The development of a new cancer should be regarded as an SAE. New primary cancers are those that are not the primary reason for the administration of the study intervention and have been identified after the participant's inclusion in this study. They do not include metastases of the original cancer.

8.5.12 Deaths

All deaths that occur during the study intervention period, or within the CSP-defined follow-up period after the administration of the last dose of study intervention, must be reported as follows:

- Death clearly resulting from disease progression should be reported to the Study Monitor/Physician at the next monitoring visit and should be documented in the eCRF. It should not be reported as an SAE.
- Where death is not due (or not clearly due) to progression of the disease under study, the AE causing the death must be reported as an SAE within 24 hours. It should also be documented in the eCRF. The report should contain a comment regarding the coinvolvement of PD, if appropriate, and should assign main and contributory causes of death.
- Death with an unknown cause should always be reported as an SAE. It should also be documented in the eCRF. A postmortem may be helpful in the assessment of the cause of death, and if performed, a copy of the postmortem results should be forwarded to Fusion Pharmaceuticals Patient Safety or its representative within the usual time frames.

As this study includes an endpoint of OS, deaths occurring after the CSP-defined safety follow-up period (28 or 42-days [+ 14 days]) after the administration of the last dose of study intervention should be documented in the eCRF. If the death occurred as a result of an event that started after the defined safety follow-up period and the event is considered to be due to a late-onset toxicity to study intervention, then it should also be reported as an SAE.

8.5.13 Medication Error

If a medication error occurs in the course of the study, then the Investigator or other site personnel informs the appropriate Sponsor representatives within **1 calendar day**, i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated Sponsor representative works with the Investigator to ensure that all relevant information is provided to the Fusion Pharmaceuticals Patient Safety data entry site within **1** (Initial Fatal/Life-Threatening or follow-up Fatal/Life-Threatening) **or 5** (other serious initial and follow-up) **calendar days** if there is an SAE associated with the medication error (see Section 8.5.9) and **within 30 days** for all other medication errors.

For the purposes of this clinical study a medication error is an **unintended** failure or mistake in the treatment process for an IMP that either causes harm to the participant or has the potential to cause harm to the participant.

The full definition of a medication error can be found in Appendix B 4.

8.6 Overdose

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module.
- An overdose without associated symptoms is only reported on the Overdose eCRF module

If an overdose on a Sponsor study drug occurs in the course of the study, the Investigator or other site personnel inform appropriate Sponsor representatives immediately, but **no later than 24 hours** of when he or she becomes aware of it.

The designated Sponsor representative works with the Investigator to ensure that all relevant information is provided to the Sponsor's representative Patient Safety data entry site **within one or 5 calendar days** for overdoses associated with an SAE (see Section 8.5.9) and **within 30 days** for all other overdoses.

8.7 Human Biological Samples

Instructions for the collection and handling of biological samples will be provided in the study specific laboratory manual. Samples should be stored in a secure storage space with adequate measures to protect confidentiality. For further details on Handling of Human Biological Samples see Appendix D.

Samples will be stored for a maximum of 15 years from the date of the issue of the CSR in line with consent and local requirements, after which they will be destroyed/repatriated.

- PK samples will be disposed of after the bioanalytical report finalisation or 6 months after issuance of the draft bioanalytical report (whichever is earlier), unless consented for future analyses.
    - PK samples may be disposed of or anonymised by pooling. Additional analyses may be conducted on the anonymised, pooled PK samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR.

- Remaining anti-drug antibody (ADA) sample aliquots will be retained at Fusion Pharmaceuticals or its designee for a maximum of 15 years following issue of the CSR. Additional use includes, but is not limited to, further characterisation of any ADAs, confirmation and/or requalification of the assay as well as additional assay development work. The results from future analysis will not be reported in the CSR.

8.7.1 Pharmacokinetics

- Blood samples will be collected for measurement of serum concentrations of [^{111}In]-FPI-2107 and [^{225}Ac]-FPI-2068 as specified in the SoAs (see Section 8.1).
- Samples may be collected at additional time points during the study if warranted and agreed upon between the Investigator, Medical Monitor, and the Sponsor, e.g., for safety reasons. The timing of sampling may be altered during the course of the study based on newly available data (e.g., to obtain data closer to the time of peak or trough matrix concentrations) to ensure appropriate monitoring.
- Serum samples will be used to analyse the PK of [^{111}In]-FPI-2107 and [^{225}Ac]-FPI-2068. Samples collected for analyses of [^{111}In]-FPI-2107 and [^{225}Ac]-FPI-2068 serum concentrations may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.
- Samples will be collected, labelled, stored, and shipped as detailed in the laboratory manual.
- If feasible, a blood sample should be collected for PK analysis as soon as possible when a participant is suspected of having ILD/pneumonitis, if there are no other PK samples on the same day (see SoA Table 26, Table 27, and Table 28, and Section 8.4.6.1). PK samples should be taken only while the patient remains on treatment (e.g., within 56 days of the last dose).

8.7.1.1 Determination of Drug Concentration

Samples for determination of drug concentration by radioanalysis and by antibody determination using assays targeting total bsAb and conjugated bsAb assays will be assayed by bioanalytical test sites operated by or on behalf of Fusion Pharmaceuticals, using an appropriately validated bioanalytical method. Full details of the analytical methods used will be described in a separate bioanalytical report.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation, if performed, will be reported in a separate bioanalytical report.

8.7.2 Immunogenicity Assessments

Blood samples for determination of ADA in serum will be assayed by bioanalytical test sites

operated by or on behalf of the Sponsor, using an appropriately validated bioanalytical method. Full details of the methods used will be described in a separate report. ADA samples may also be further tested for characterisation of the ADA response. Samples will be collected, labelled, stored, and shipped as detailed in the laboratory manual.

8.7.3 Pharmacodynamics

For collection of biological samples for biomarker analysis, including ctDNA, see Section 8.8.

8.8 Human Biological Sample Biomarkers

By consenting to participate in the study the participant consents to the mandatory research components of the study. Samples for biomarker research are required and will be collected from all participants in this study as specified in the SoAs (see Section 8.1).

8.8.1 Collection of Mandatory Samples for Biomarker Analysis

Samples will be tested to determine the systemic pharmacodynamic parameters and biomarkers of clinical response to FPI-2068 when administered as monotherapy or with other anticancer agents to evaluate their association with changes in peripheral biomarkers, including but not, limited to variations in the allelic frequency of ctDNA, soluble and cellular analytes, and changes in gene expression as deemed appropriate. These biomarker measurements will support understanding of the mechanism of action and may guide further identification of participants who are most likely to respond to FPI-2068.

The participant's consent to the use of donated biological samples is mandatory. Details regarding specimen collection, processing, and testing will be provided in the laboratory manual.

The following samples are mandatory and will be collected from all participants (unless otherwise noted) at timepoints specified in the SoAs (see Section 8.1) for each study part:

- Whole blood for RNA and T-cell receptor sequencing (see Section 8.8.1.1)
- Plasma for ctDNA and circulating biomarkers (see Section 8.8.1.2)
- Serum for tumour marker analysis (see Section 8.8.1.3)
- Archival tumour samples for exploratory analysis (see Section 8.8.1.4).

8.8.1.1 Collection of Blood for RNA and T-cell receptor sequencing

A peripheral blood sample will be collected to provide PBMCs for TCR sequencing. Baseline and on-treatment whole blood for PBMCs will be collected predose at the timepoints indicated in the SoAs (see Section 8.1) for each study part.A peripheral blood sample will be collected in PAXgene tubes and stored frozen for RNA sample preparation. Baseline and on-treatment whole blood RNA will be collected predose at the timepoints indicated in the SoAs (see Section 8.1) for each study part.Testing may include (but is not limited to):

- Evaluation of the immune cellular repertoire to monitor T-cell clone expansion and/or T-cell activation
- Analyses of transcript and/or RNA expression and stored for future analyses.
- Messenger RNA levels of selected inflammatory/immune and cytokine pathways that may include, but are not limited to, IFN-γ, IFN-γ inducible genes, and effector T-cell or dendritic cell gene signatures will be measured in relation to their association with clinical outcome.

8.8.1.2 Collection of Plasma Samples for ctDNA

A peripheral blood sample will be collected to provide plasma for ctDNA. Baseline and on-treatment plasma for ctDNA will be collected predose and at timepoints indicated in the SoAs (see Section 8.1) for each study part. The final sample will be taken at disease progression.

Testing may include (but is not limited to):

- Whether there is sufficient ctDNA in plasma for mutational testing.
- Correlation of baseline ctDNA levels and kinetics of ctDNA changes with clinical outcome measures.
- Correlation between tumour and plasma mutational status.
- Genetic alterations as potential mechanisms of sensitivity or resistance to FPI-2068 treatment.
- Future diagnostic development.

8.8.1.3 Collection of Serum Samples for Tumour Marker Analysis

A peripheral blood sample will be collected to provide serum for tumour marker analysis. Baseline and on-treatment serum for tumour marker analysis will be collected predose and at timepoints indicated in the SoAs (see Section 8.1) for each study part.

Testing may include (but is not limited to):

- Carbohydrate antigen-19-9 (CA-19-9).
- Carcinoembryonic antigen (CEA)

8.8.1.4 Collection of Archival Tumour Samples

Provision of a tumour tissue sample (block or unstained slides) at baseline is mandatory for all participants. Expression of EGFR and MET will be evaluated from the baseline tumour samples using validated central laboratory IHC assays. Where a participant has multiple archival tissue samples with sufficient tumour content available, tissue from the most recent biopsy is preferred. If archival tissue obtained within the last 12 months is not available, a

fresh biopsy will be required for IHC and biomarker analyses. Availability of tissue must be confirmed prior to administration of FPI-2053 or [^{111}In]-FPI-2107; however, the participant may receive study treatment prior to any analysis of the tissue.

Additional exploratory analyses will be performed on the archival tumour tissue samples, including but not limited to genomic and or protein analysis of tumour tissue to identify markers of response and resistance to study intervention. The tumour samples may also be used for future diagnostic test development and/or validation.

8.8.2 Collection of Optional Biomarker Samples

The on-study provision of tumour tissue is encouraged only if clinically appropriate and not considered detrimental to participant care. The biopsied tumour must not be used as part of the RECIST v1.1 assessments. Participants will not be excluded from the study if these samples are not collected.

Refer to the Investigator laboratory manual for further details of on-study tumour tissue collection, shipping, and storage.

8.8.2.1 Collection of On-study Tumour Samples

Tumour Biopsy on Treatment

If a tumour sample can be safely obtained, every effort should be made to collect a core biopsy between Day 8 and Day 11 in Cycle 1 or Cycle 2 of the Treatment Period. Inability to obtain a biopsy will not be noted as a protocol deviation; however, a minimum of 6 paired biopsies must be obtained during the backfill cohort (Predose and Cycle 1 or Cycle 2 between Days 8 and 11).

Tumour Biopsy on Disease Progression

Where possible, a further on-study tumour biopsy sample from the progressing lesion should be taken at the time of documented RECIST v1.1 progression in participants that have provided the additional optional consent. Biopsies at progression may be particularly valuable when there is a marked phenotypic change in a particular lesion, and Investigators are encouraged to contact Fusion in these cases.

8.8.2.2 Collection of Blood for RNA

An optional whole blood sample may be collected in a PaxGene DNA tube to aid in somatic variant calling of tumour tissue samples. Where possible, this sample should be collected at the same time as the collection of any optional tumour biopsy sample.

8.8.2.3 Collection of Blood for ILD Investigational Biomarker Analysis

If feasible, additional blood samples for exploratory biomarker analysis should be taken as soon as possible when a participant is suspected of having ILD/pneumonitis (see SoA, Table 26, Table 27, and Table 28 and Section 8.4.6.1).

8.9 Optional Genomics Initiative Sample

Optional Genomics Initiative research is not applicable in this study.

8.10 Medical Resource Utilisation and Health Economics

Medical Resource Utilisation and Health Economics parameters are not evaluated in this study.

9 STATISTICAL CONSIDERATIONS

The statistical analyses will be performed by Fusion Pharmaceuticals or its delegated representatives (Contract Research Organisation [CRO]) under the direction of Fusion Pharmaceuticals. Statistical Methods will be detailed in the Statistical Analysis Plan (SAP).

9.1 Statistical Hypotheses

Not applicable.

9.2 Sample Size Determination

The primary objective of this study is to investigate the safety, tolerability, and dosimetry, and thereby estimate the MTD and determine the RP2D, of [^{225}Ac]-FPI-2068. Hence, the number of participants has been based on the desire to obtain adequate tolerability, safety, and PK data while exposing as few participants as possible to the investigational product and study procedures.

Approximately 150 participants will be screened to achieve approximately 125 safety-evaluable participants and approximately 110 efficacy-evaluable participants across all parts of the study. This assumes an approximate 20% and 10% general and imaging screen fail rate, respectively.

The total number of participants depends upon the number of dose escalations/de-escalations necessary. Approximately three participants in up to 3 dose cohorts are required in Part A. At least three, and up to nine, evaluable participants are required for each dose cohort (unless unacceptable toxicity is seen before three evaluable participants) in Part B. If a preliminary signal of activity is observed, backfill of one or more dose level at any dose level at or below the projected MTD (approximately 20 evaluable participants per dose level) is permissible per the predefined efficacy criteria outlined in Section 4.1.1. The actual number of dose levels and participants enrolled during dose escalation will depend upon the number of DLTs in each cohort, the dosimetry at each dose level, and the overall safety profile observed, including the emergence of late-onset toxicities, as the study progresses.

9.3 Populations for Analyses

For purposes of analysis, the study populations are defined as provided in Section 5. The analysis sets are described in Table 30.

Table 30 Analysis Sets

Analysis set	Description
Enrolled	All participants who signed the informed consent form
DLT evaluable	A participant who receives [^{225}Ac]-FPI-2068 and completes the DLT observation period without a DLT or a participant who experiences a DLT
Safety	All enrolled participants that receive any amount of [^{111}In]-FPI-2107 with or without [^{225}Ac]-FPI-2068
Efficacy evaluable	All participants who received at least one dose of [^{225}Ac]-FPI-2068 and either have at least one postbaseline efficacy assessment or discontinued from the study prematurely due to toxicity, disease progression, or death
PK	All participants who received at least one dose of [^{111}In]-FPI-2107 or [^{225}Ac]-FPI-2068 and have at least one reportable PK concentration

DLT, dose limiting toxicity; PK, pharmacokinetics.

9.4 Statistical Analyses

The SAP will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.1 General Considerations

This study will employ an mTPI-2 design. The mTPI-2 design employs a simple beta-binomial Bayesian model. The posterior density of the toxicity probability is divided into multiple intervals with equal length. These intervals are categorised as underdosing, proper dosing, and overdosing in terms of toxicity. The underdosing interval corresponds to a dose escalation, overdosing corresponds to a dose de-escalation, and proper dosing corresponds to staying at the current dose. The design for the dose escalation phase of the study uses a target DLT rate of 30% and an equivalence interval (25%, 35%) for dose escalation/de-escalation decisions as well as MTD determination. A dose level is considered unsafe, with no additional participants enrolled at that dose level, if it has an estimated 95% or more probability of exceeding the target DLT rate of 30% (i.e., P [DLT > 30% data] ≥ 95%).

All collected data will be reported using summary tables and figures, as appropriate. Data summaries will be presented separately by cohort and/or dose level, as applicable. Tabulations will be produced for appropriate disposition, demographic, baseline, PK, ADA, efficacy, and safety parameters.

Categorical variables will be summarised by frequency distributions (number and percentages of participants) and continuous variables will be summarised by descriptive statistics (mean, standard deviation, median, minimum, and maximum). For PK concentration and PK parameters, geometric mean and coefficient of variation will be reported. For time-to-event variables, percentages of participants experiencing that event will be presented and time-to-event endpoints will be estimated using the Kaplan-Meier method. Graphical displays will be

presented, as appropriate. All data will be provided in by-participant listings.

9.4.2 Efficacy Analyses

The secondary efficacy endpoints of ORR, time to response (TTR), duration of response (DoR), PFS, disease control rate (DCR), OS, and percentage change in total ctDNA (variant allelic frequency) from baseline will be summarised on the Efficacy Evaluable Analysis Set (i.e., all participants who received at least one dose of [^{225}Ac]-FPI-2068 and either have at least one postbaseline efficacy assessment or discontinued from the study prematurely due to toxicity, disease progression, or death).

ORR is defined as the proportion of participants with a best response of complete response (CR) or PR per RECIST Version 1.1 that occurs prior to the initiation of subsequent anti-cancer treatment and prior to progression, with the denominator defined as the number of participants in the Efficacy Evaluable Analysis Set. ORR will be estimated, and 80% CI based on the exact binomial distribution will be presented by cohort.

The best overall response of CR or PR must be confirmed, which means a response of CR/PR is recorded at a visit and confirmed by repeat imaging not less than 28 days (4 weeks) after the visit when the response was first observed, with no evidence of progression between the initial and confirmation visit.

Analyses of other efficacy endpoints will include:

- TTR, defined as the duration of time from first treatment administration (i.e., [^{225}Ac]-FPI-2068) to first date of observed response (CR or PR). Participants that do not achieve response will be censored at last evaluable disease assessment.
- DoR, defined as the duration of time from first date of observed response (CR or PR) to first date of disease progression. Participants that do not experience disease progression will be censored at last evaluable disease assessment. Participants that do not achieve a response will not be included.
- PFS, defined as the duration of time from first treatment administration to first date of disease progression or death. Participants alive at the time of analysis that do not experience disease progression will be censored at last evaluable disease assessment.
- DCR, defined as the proportion of participants who achieve a PR, CR, or stable disease for at least 8 weeks. This parameter will be summarised using the same methods as described above for ORR.
- OS, defined as the duration of time from first treatment administration to date of death. Participants alive at the time of analysis will be censored at date of last contact.

9.4.3 Safety Analyses

Safety and tolerability will be assessed in terms of DLTs, AEs/SAEs, vital signs, clinical chemistry/haematology parameters, physical examination findings, and ECG data. These

variables will be collected for all participants. All safety analyses will be performed on the Safety Analysis Set.

Medical Dictionary for Regulatory Activities (MedDRA; latest version) will be used to code AEs. AEs will be graded according to the National Cancer Institute CTCAE Version 5.0. The number of participants in each dose regimen experiencing each AE will be summarised by MedDRA system organ class and preferred term. The number and percentage of participants with AEs in different categories (e.g., causally related, CTCAE Grade ≥ 3, etc) will be summarised by dose regimen; events in each category will be further summarised by MedDRA system organ class and preferred term. SAEs will be summarised separately, if a sufficient number occurs.

Adverse event summary tables will include only TEAEs. AEs will be defined as treatment-emergent if they have an onset or worsen (by Investigator report of a change in intensity) during the study treatment or the safety follow-up period (defined as 28 or 42 [+ 14] days after last dose of study treatment) but prior to subsequent cancer therapy. AEs occurring outside this period will only be listed.

During the evaluation of the AE data, a Fusion Pharmaceuticals medically qualified expert will review the list of AEs that were not reported as SAEs and AEs leading to discontinuation. Based on the expert's judgement, significant AEs of particular clinical importance may, after consultation with the Global Patient Safety Physician, be considered other significant adverse events (OAEs) and reported as such in the CSR. A similar review of laboratory/vital signs (pulse and blood pressure)/ECG data will be performed for identification of OAEs. Examples of these could be marked haematological and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious), dose reduction, or significant additional treatment.

Duration of exposure will be summarised.

All safety data including safety laboratory values, vital signs, and ECG data will be listed individually by subject and appropriately summarised. For all laboratory variables that are included in the current version of CTCAE, the CTCAE grade will be calculated. Details of any deaths will be listed for all participants. Graphical presentations of safety data will be presented as appropriate. DLTs will be displayed in a listing.

9.4.4 Other Analyses

9.4.4.1 Pharmacokinetics

PK analysis of [^{225}Ac]-FPI-2068 and [^{111}In]-FPI-2107, with and without preadministration of FPI-2053, will be performed on whole blood radioanalysis and serum antibody (total/conjugated) concentrations collected at time points specified in the SoAs.

Where data allow, PK parameters (including but not limited to clearance, AUC, C_{max}, t_{max}, and half-life) will be calculated using non-compartmental analysis using actual sampling times and

standard non-compartmental methods.

All PK concentrations and any derived PK parameters will be listed and summarised. The PK concentrations and parameters listings will be presented for the Safety Analysis Set. PK concentrations and parameters will be summarised using appropriate descriptive statistics for the PK Analysis Set.

Exploratory analyses including potential population PK and/or PK/pharmacodynamics may be described in a separate analysis plan. Where relevant, data collected from this study may be combined with other data from other studies for modelling purposes in the future. All analysis results may be reported separately from the CSR.

9.4.4.2 Biomarkers

Descriptive statistics of actual and change from baseline will be provided by dose level for exploratory biomarker measurement based on the PK Analysis Set.

9.4.4.3 Immunogenicity

Immunogenicity results will be analysed descriptively by summarising the number and percentage of participants who develop detectable ADAs. The immunogenicity titre may be reported for samples confirmed positive for the presence of ADAs. The potential impact of ADAs on PK, pharmacodynamics, and safety will be assessed if data allow. Samples confirmed positive for ADAs may also be evaluated for neutralising antibody activity.

9.5 Interim Analyses

No interim analyses are planned for this study.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A Regulatory, Ethical, and Study Oversight Considerations

A 1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the CSP and with the following:
    - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
    - Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
    - Applicable laws and regulations
- The CSP, revised CSP, ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any revised CSPs will require IRB/IEC and applicable Regulatory Authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Fusion Pharmaceuticals will be responsible for obtaining the required authorisations to conduct the study from the concerned Regulatory Authority. This responsibility may be delegated to a CRO but the accountability remains with Fusion Pharmaceuticals.
- The Investigator will be responsible for providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European Regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

Regulatory Reporting Requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and Investigators.
- For all studies except those utilising medical devices, Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

- An Investigator who receives an Investigator safety report describing a SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

Regulatory Reporting Requirements for Serious Breaches

- Prompt notification by the investigator to the Sponsor of any (potential) serious breach of the protocol or regulations is essential so that legal and ethical obligations are met.
    - A 'serious breach' means a breach likely to affect to a significant degree the safety and rights of a participant or the reliability and robustness of the data generated in the clinical study.
- If any (potential) serious breach occurs in the course of the study, investigators or other site personnel will inform the appropriate Sponsor representatives immediately after he or she becomes aware of it.
- In certain regions/countries, the Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about such breaches.
    - Sponsor will comply with country-specific regulatory requirements relating to serious breach reporting to the regulatory authority, IRB/IEC, and investigators. If EU Clinical Trials Regulation 536/2014 applies, Sponsor is required to enter details of serious breaches into the European Medicines Agency CTIS. It is important to note that redacted versions of serious breach reports will be available to the public via CTIS.
- The investigator should have a process in place to ensure that:
    - The site staff or service providers delegated by the investigator/institution are able to identify the occurrence of a (potential) serious breach.
- A (potential) serious breach is promptly reported to Sponsor or delegated party, through the contacts (email address or telephone number) provided by Sponsor.

A 2 Financial Disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

A 3 Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the participant and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary, and they are free to refuse to participate and may withdraw their consent at any time and for any reason during the study. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study centre.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorised person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the participant.

A participant who is rescreened is not required to sign another ICF if the rescreening occurs within 28 days from the previous ICF signature date.

The ICF will contain a separate section that addresses and documents the collection and use of any mandatory and/or optional human biological samples. The Investigator or authorised designee will explain to each participant the objectives of the analysis to be done on the samples and any potential future use. Participants will be told that they are free to refuse to participate in any optional samples or the future use and may withdraw their consent at any time and for any reason during the retention period.

A 4 Data Protection

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure and use of their data must also be explained to the participant in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

A 5 Committees Structure

The safety of all Fusion Pharmaceuticals clinical studies is closely monitored on an on-going basis by Fusion Pharmaceuticals representatives in consultation with Patient Safety. Issues identified will be addressed; for instance, this could involve amendments to the CSP and letters to Investigators.

A 6 Dissemination of Clinical Study Data

A description of this clinical study will be available on http://www.clinicaltrials.gov as will the summary of the main study results when they are available. The clinical study and/or summary of main study results may also be available on other websites according to the regulations of the countries in which the study is conducted.

A 7 Data Quality Assurance

- All participant data relating to the study will be recorded on eCRF unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organisations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorised site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved CSP and any other study agreements, ICH GCP, and all applicable regulatory requirements.

- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 25 years after study archiving or as required by local regulations. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

A 8 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data reported on the eCRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study are defined as source documents. Source data are contained in source documents (original records or certified copies).

A 9 Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first site open.

The Sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The Investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the CSP, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the Investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organisation(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Participants from terminated sites will have the opportunity to be transferred to another site to continue the study.

A 10 Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicentre studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Appendix B Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

B 1 Definition of Adverse Events

An AE is the development of any untoward medical occurrence in a participant or clinical study participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (e.g., an abnormal laboratory finding), symptom (for example nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The term AE is used to include both serious and non-serious AEs and can include a deterioration of a preexisting medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no Study treatment has been administered.

B 2 Definitions of Serious Adverse Event

An SAE is an AE occurring during any study phase (i.e., run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-participant hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect
- Is an important medical event that may jeopardise the participant or may require medical treatment to prevent one of the outcomes listed above.

Adverse Events (AEs) for **malignant tumours** reported during a study should generally be assessed as **Serious** AEs. If no other seriousness criteria apply, the 'Important Medical Event' criterion should be used. In certain situations, however, medical judgement on an individual event basis should be applied to clarify that the malignant tumour event should be assessed and reported as a **non-serious** AE. For example, if the tumour is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumour, the AE may not fulfil the attributes for being assessed as serious, although reporting of the progression of the malignant tumour as an AE is valid and should occur. Also, some types of malignant tumours, which do not spread remotely after a routine treatment that does not require hospitalisation, may be assessed as non-serious; examples in adults include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

The above instruction applies only when the malignant tumour event in question is a new

malignant tumour (i.e., it is *not* the tumour for which entry into the study is a criterion and that is being treated by the investigational product under study and is not the development of new or progression of existing metastasis to the tumour under study). Malignant tumours that – as part of normal, if rare, progression – undergo transformation (e.g., Richter's transformation of B-cell chronic lymphocytic leukaemia into diffuse large B-cell lymphoma) should not be considered a new malignant tumour.

Life-threatening

'Life-threatening' means that the participant was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the participant's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (e.g., hepatitis that resolved without hepatic failure).

Hospitalisation

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (e.g., bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the participant was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important Medical Event or Medical Treatment

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life-threatening or result in death, hospitalisation, disability or incapacity but may jeopardise the participant or may require medical treatment to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

- Angioedema not severe enough to require intubation but requiring IV hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (e.g., neutropenia or anaemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalisation
- Development of drug dependency or drug abuse

Intensity Rating Scale:

The grading scales found in the revised National Cancer Institute CTCAE Version 5.0 will be

utilised for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades, the recommendation in the CTCAE criteria that converts mild, moderate and severe events into CTCAE grades should be used. A copy of the CTCAE can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov).

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Appendix B 2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE unless it meets the criteria shown in Appendix B 2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Appendix B 2.

B 3 A Guide to Interpreting the Causality Question

When making an assessment of causality consider the following factors when deciding if there is a 'reasonable possibility' that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the participant actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.
- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? Fusion Pharmaceuticals would not normally recommend or support a re-challenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognised feature of overdose of the drug?
- Is there a known mechanism?

Causality of 'related' is made if following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression

'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgement. With no available facts or arguments to suggest a causal relationship, the event(s) will be assessed as 'not related'.

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

B 4 Medication Error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for a Fusion Pharmaceuticals study drug that either causes harm to the participant or has the potential to cause harm to the participant.

A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study site staff or participant.

Medication error includes situations where an error.

- Occurred
- Was identified and intercepted before the participant received the drug
- Did not occur, but circumstances were recognised that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion
- Dispensing error e.g., medication prepared incorrectly, even if it was not actually given to the participant
- Drug not administered as indicated, for example, wrong route or wrong site of administration
- Drug not taken as indicated e.g., tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed e.g., kept in the fridge when it should be at room temperature
- Wrong participant received the medication (excluding Interactive Response Technology [IRT]/Randomisation and Trial Supply Management [RTSM] errors)
- Wrong drug administered to participant (excluding IRT/RTMS errors)

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Errors related to or resulting from IRT/RTMS - including those which lead to one of the above listed events that would otherwise have been a medication error

- Participant accidentally missed drug dose(s) e.g., forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Participant failed to return unused medication or empty packaging
- Errors related to background and rescue medication, or standard of care medication in open-label studies, even if a Fusion Pharmaceuticals product

Medication errors are not regarded as AEs but AEs may occur as a consequence of the medication error.

Appendix C Contraceptive Guidance and Collection of Pregnancy Information

C 1 Women of Childbearing Potential

Women not of childbearing potential are defined as women who are either permanently sterilised (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy), or who are postmenopausal. Women will be considered postmenopausal if they have been amenorrhoeic for 12 months prior to the planned date of randomisation without an alternative medical cause. The following age-specific requirements apply:

- Women <50 years old would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatment and follicle stimulating hormone levels in the postmenopausal range.
- Women ≥50 years old would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of all exogenous hormonal treatment.

C 2 Contraception Guidance

Women of childbearing potential are allowed to participate in the study if they are using at least 2 forms of contraception, one of which must be a highly effective method, or agree to remain abstinent for the duration of the study. Male participants with female partners of childbearing potential are eligible to participate if they agree to use a male condom and their partner uses a highly effective contraceptive method, are surgically sterile and/or agree to remain abstinent from penile-vaginal intercourse for the duration of study participation and at least 6 months for both women and men following the final dose of both [^{111}In]-FPI-2107 and [^{225}Ac]-FPI-2068. A vasectomised partner is considered a highly effective contraception method provided that the partner is the sole male sexual partner of the female of child-bearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Barrier methods of contraception include male condom, female condom, cervical cap, diaphragm, or contraceptive sponge.

A highly effective method of contraception is defined as one that can achieve a failure rate of < 1% per year when used consistently and correctly. Highly effective methods include:

Non-hormonal Methods

- Copper T intrauterine device
- Levenorgestrel-releasing intrauterine system (e.g., Mirena) [a]
- Tubal occlusion
- Vasectomised sexual partner (with participant assurance that partner received postvasectomy confirmation of azoospermia)

- Total sexual abstinence (evaluate in relation to the duration of the clinical study and the preferred and usual lifestyle choice of the participant)

Hormonal Methods

- Implants [b]
    - Etonorgestrel-releasing implants (e.g., Implanon or Norplan)
- Intravaginal devices [b]
    - Ethinylestradiol/etonorgestrel-releasing intravaginal devices (e.g., NuvaRing)
- Injection [b]
    - Medroxyprogesterone injection (e.g., Depo-Provera)
- Combined pill
    - Normal and low dose combined oral contraceptive pill
- Patch [b]
    - Norelgestromin/ethinylestradiol-releasing transdermal system (e.g., Ortho Evra)
- Minipill [b]
    - Progesterone-based oral contraceptive pill using desogestrel
    - Cerazette is currently the only highly effective progesterone-based pill

[a] This is also considered a hormonal method.
[b] Not approved for use in Japan.
Note: Birth control methods that are NOT highly effective (failure rate of ≥1% per year) include: male or female condom with or without spermicide; cap, diaphragm, or sponge with spermicide; or progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action. A male condom plus cap, diaphragm, or sponge with spermicide (double barrier methods) are not highly effective birth control methods.

C 3 Pregnancy Testing

Women of childbearing potential must have a pregnancy test, which may be either a blood or urine test, performed at the Screening Visit and at time points specified in the SoA. If the results are positive, the participant must be excluded from receiving the IMP.

WCBP must be advised by the Investigator to inform him/her immediately if she suspects she may be pregnant throughout the study or if her menstruation is delayed by more than 7 days. If a menstrual cycle is missed or when pregnancy is suspected in a female participant of child-bearing potential, the participant should return to the site for a pregnancy test as soon as possible.

Male study participants must be advised by the Investigator to inform him/her immediately if they suspect their partner became pregnant after the participant was administered the IMP.

After obtaining the male participant's partner's consent, the Investigator will ask the female partner to have a pregnancy test to confirm the pregnancy.

C 4 Female Participants Who Become Pregnant After Receiving the Investigational Product

The Investigator will collect pregnancy information on any female participant who becomes pregnant after receiving the IMP while participating in this study. Information must be submitted to the Sponsor within 24 hours of learning of the pregnancy. The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant and the neonate, and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of foetal status (presence or absence of anomalies) or indication for the procedure.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication (e.g., spontaneous abortion, foetal death, stillbirth, congenital anomalies, ectopic pregnancy) or elective termination of a pregnancy will be reported as an AE or SAE. Any poststudy pregnancy related SAE considered reasonably related to the study treatment by the Investigator will be reported to the Sponsor as described in Section 8.5 While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting. Any female participant who becomes pregnant while participating in the study will be withdrawn from any further study treatment.

C 5 Male Participants with Partners Who Become Pregnant

After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of foetal status (presence or absence of anomalies) or indication for the procedure.

Appendix D Handling of Human Biological Samples

D 1 Chain of Custody

A full chain of custody is maintained for all samples throughout their lifecycle.

The Investigator at each site keeps full traceability of collected biological samples from the participants while in storage at the centre until shipment or disposal (where appropriate) and records relevant processing information related to the samples whilst at site.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps record of receipt of arrival and onward shipment or disposal.

Fusion Pharmaceuticals or delegated representatives will keep oversight of the entire life cycle through internal procedures, monitoring of study sites, auditing or process checks, and contractual requirements of external laboratory providers.

Samples retained for further use will be stored in the Fusion Pharmaceuticals -assigned biobanks or other sample archive facilities and will be tracked by the appropriate Fusion Pharmaceuticals Team during for the remainder of the sample life cycle.

If required, Fusion Pharmaceuticals will ensure that remaining biological samples are returned to the site according to local regulations or at the end of the retention period, whichever is the sooner.

D 2 Withdrawal of Informed Consent for Donated Biological Samples

Fusion Pharmaceuticals ensures that biological samples are returned to the source or destroyed at the end of a specified period as described in the informed consent.

If a participant withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed/repatriated, and the action documented. If samples are already analysed, Fusion Pharmaceuticals is not obliged to destroy the results of this research.

Following withdrawal of consent for biological samples, further study participation should be considered in relation to the withdrawal processes outlined in the informed consent.

The Investigator:

- Ensures participant’s withdrawal of informed consent to the use of donated samples is highlighted immediately to Fusion Pharmaceuticals or delegate.
- Ensures that relevant human biological samples from that participant, if stored at the study site, are immediately identified, disposed of as appropriate, and the action documented.
- Ensures that the participant and Fusion Pharmaceuticals are informed about the sample disposal.

Fusion Pharmaceuticals ensures the organisation(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of or repatriated as appropriate, and the action documented, and study site notified.

D 3 International Airline Transportation Association 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation Association (IATA) (**https://www.iata.org/whatwedo/cargo/dgr/Pages/download.aspx**) classifies infectious substances into 3 categories: Category A, Category B or Exempt

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals.
Category A pathogens are, e.g., Ebola, Lassa fever virus. Infectious substances meeting these criteria which cause disease in humans or both in humans and animals must be assigned to UN 2814. Infectious substances which cause disease only in animals must be assigned to UN 2900:

Category B Infectious Substances are infectious substances that do not meet the criteria for inclusion in Category A. Category B pathogens are, e.g., Hepatitis A, C, D, and E viruses. They are assigned the following UN number and proper shipping name

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN 3373 and IATA 650

Exempt - Substances which do not contain infectious substances or substances which are unlikely to cause disease in humans or animals are not subject to these Regulations unless they meet the criteria for inclusion in another class.

- Clinical study samples will fall into Category B or exempt under IATA regulations
- Clinical study samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging (https://www.iata.org/whatwedo/cargo/dgr/Documents/DGR-60-EN-PI650.pdf).
- Biological samples transported in dry ice require additional dangerous goods specification for the dry ice content

Appendix E Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

E 1 Introduction

This Appendix describes the process to be followed in order to identify and appropriately report Potential Hy's Law (PHL) cases and Hy's Law (HL) cases. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

Specific guidance on managing liver anomalies can be found in Section 6.7.2 of the CSP; see Table 15 (Toxicity Management Guideline and Retreatment Criteria).

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a participant meets potential PHL criteria at any point during the study.

All sources of laboratory data are appropriate for the determination of PHL and HL events; this includes samples taken at scheduled study visits and other visits including central and all local laboratory evaluations even if collected outside of the study visits; for example, PHL criteria could be met by an elevated ALT from a central laboratory **and/or** elevated TBL from a local laboratory.

The Investigator will also review Adverse Event data (for example, for AEs that may indicate elevations in liver biochemistry) for possible PHL events.

The Investigator participates, together with Fusion Pharmaceuticals clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether HL criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than drug induced liver injury (DILI) caused by the investigational medicinal product (IMP).

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting SAEs and AEs according to the outcome of the review and assessment in line with standard safety reporting processes.

E 2 Definitions

Potential Hy's Law

Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥ 3 × ULN **together with** Total Bilirubin (TBL) ≥ 2 × ULN at any point during the study following the start of study medication irrespective of an increase in Alkaline Phosphatase (ALP).

Hy's Law

AST or ALT ≥ 3 × ULN **together with** TBL ≥ 2 × ULN, where no other reason, other than the IMP, can be found to explain the combination of increases, e.g., elevated ALP indicating cholestasis, viral hepatitis, another drug.

For PHL and HL the elevation in transaminases must precede or be coincident with (i.e., on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

E 3 Identification of Potential Hy's Law Cases

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any participant who meets any of the following identification criteria in isolation or in combination:

- ALT ≥3 × ULN
- AST ≥3 × ULN
- TBL ≥2 × ULN

Local Laboratories Being Used:

The Investigator will without delay review each new laboratory report and if the identification criteria are met will:

- Notify the Fusion Pharmaceuticals representative
- Determine whether the participant meets PHL criteria (see Section E 2 for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory eCRF

E 4 Follow-up

E 4.1 Potential Hy's Law Criteria not met

If the participant does not meet PHL criteria the Investigator will:

- Inform the Fusion Pharmaceuticals representative that the participant has not met PHL criteria.
- Perform follow-up on subsequent laboratory results according to the guidance provided in the CSP.

E 4.2 Potential Hy's Law Criteria met

If the participant does meet PHL criteria the Investigator will:

- Notify the Fusion Pharmaceuticals representative who will then inform the central Study Team

- Within 1 day of PHL criteria being met, the Investigator will report the case as an SAE of Potential Hy's Law; serious criteria 'Important medical event' and causality assessment 'yes/related' according to CSP process for SAE reporting.
- For participants that met PHL criteria prior to starting IMP, the Investigator is not required to submit a PHL SAE unless there is a significant change# in the participant's condition
- The Study Physician contacts the Investigator, to provide guidance, discuss, and agree an approach for the study participants' follow-up (including any further laboratory testing) and the continuous review of data
- Subsequent to this contact the Investigator will:
    - Monitor the participant until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated. Completes follow-up SAE Form as required.
    - Investigate the aetiology of the event and perform diagnostic investigations as discussed with the Study Physician.
    - Complete the three Liver eCRF Modules as information becomes available.

#A 'significant' change in the participant's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator, this may be in consultation with the Study Physician if there is any uncertainty.

E 5 Review and Assessment of Potential Hy's Law Cases

The instructions in this section should be followed for all cases where PHL criteria are met.

As soon as possible after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP, to ensure timely analysis and reporting to health authorities within 15 calendar days from date PHL criteria was met. The Fusion Pharmaceuticals Global Clinical Lead or equivalent and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

Where there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate eCRF
- If the alternative explanation is an AE/SAE: update the previously submitted Potential Hy's Law SAE and AE eCRFs accordingly with the new information (reassessing event term; causality and seriousness criteria) following the Fusion Pharmaceuticals standard processes.

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the IMP:

- Send updated SAE (report term 'Hy's Law') according to Fusion Pharmaceuticals standard processes.
    - The 'Medically Important' serious criterion should be used if no other serious criteria apply
    - As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If, there is an unavoidable delay, of over 15 calendar days in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Provides any further update to the previously submitted SAE of Potential Hy's Law, (report term now 'Hy's Law case') ensuring causality assessment is related to IMP and seriousness criteria is medically important, according to CSP process for SAE reporting.
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are still met. Update the previously submitted PHL SAE report following CSP process for SAE reporting, according to the outcome of the review and amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

E 6 Laboratory Tests

Hy's Law Lab Kit for Local Laboratories	
Additional standard chemistry and coagulation tests	GGT LDH Prothrombin time INR
Viral hepatitis	IgM anti-HAV

Hy's Law Lab Kit for Local Laboratories	
Additional standard chemistry and coagulation	GGT HBsAg IgM and IgG anti-HBc HBV DNA [a] IgG anti-HCV HCV RNA [b] IgM anti-HEV
	HEV RNA
Other viral infections	IgM & IgG anti-CMV IgM & IgG anti-HSV IgM & IgG anti-EBV
Alcoholic hepatitis	Carbohydrate deficient transferrin (CD-transferrin) [c]
Autoimmune hepatitis	Antinuclear antibody (ANA) Anti-Liver/Kidney Microsomal Ab (Anti-LKM) Anti-Smooth Muscle Ab (ASMA)
Metabolic diseases	alpha-1-antitrypsin Ceruloplasmin Iron Ferritin Transferrin [c] Transferrin saturation

[a] HBV DNA is only recommended when IgG anti-HBc is positive.
[b] HCV RNA is only recommended when IgG anti-HCV is positive or inconclusive.
[c] CD-transferrin and Transferrin are not available in China. Study teams should amend this list accordingly.

Appendix F Changes Related to Mitigation of Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis

Note: Changes below should be implemented only during study disruptions due to any of or a combination of civil crisis, natural disaster, or public health crisis (e.g., during quarantines and resulting site closures, regional travel restrictions and considerations if site personnel or study participants become infected with SARS-CoV-2 or similar pandemic infection) during which participants may not wish to or may be unable to visit the study site for study visits. These changes should only be implemented if allowable by local/regional guidelines and following notification from the Sponsor and instructions on how to perform these procedures will be provided at the time of implementation.

Please note that during civil crisis, natural disaster, or public health crisis, some study assessments and procedures may not be conducted due to international or local policies or guidelines, hospital or clinic restrictions and other measures implemented to ensure the participant's safety. If in doubt, please contact the Study Physician.

F 1 Reconsent of Study Participants During Study Interruptions

During study interruptions, it may not be possible for the participants to complete study visits and assessments on site and alternative means for carrying out the visits and assessments may be necessary, e.g., remote visits. Reconsent should be obtained for the alternative means of carrying out visits and assessments and should be obtained prior to performing the procedures described in Sections F 2 to F 4. Local and regional regulations and/or guidelines regarding reconsent of study participants should be checked and followed. Reconsent may be verbal if allowed by local and regional guidelines (note, in the case of verbal reconsent the ICF should be signed at the participant's next contact with the study site). Visiting the study sites for the sole purpose of obtaining reconsent should be avoided.

F 2 Rescreening of Participants to Reconfirm Study Eligibility

Additional rescreening for screen failure due to study disruption can be performed in previously screened participants. The Investigator should confirm this with the designated study physician.

In addition, during study disruption there may be a delay between confirming eligibility of a participant and either enrolment into the study or commencing of dosing with IMP. If this delay is outside the screening window specified in schedule of assessments the participant will need to be rescreened to reconfirm eligibility before commencing study procedures. This will provide another opportunity to re-screen a participant in addition to that detailed in Section 5.4. The procedures detailed in the SoA must be undertaken to confirm eligibility using the same randomization number as for the participant.

F 3 Telemedicine Visit to Replace On-site Visit (Where Applicable)

In this appendix, the term telemedicine visit refers to remote contact with the participants using telecommunications technology including phone calls, virtual or video visits, and mobile health devices.

During a civil crisis, natural disaster, or public health crisis, on-site visits may be replaced by a telemedicine visit if allowed by local/regional guidelines. Having a telemedicine contact with the participants will allow AEs and concomitant medication, to be reported and documented.

F 4 Data Capture During Telemedicine Visits

Data collected during telemedicine visits will be captured by the qualified Health Care Professional from the study site or Third Party Vendor service.

Appendix G Abbreviations

Abbreviation or special term	Explanation
ADA	anti-drug antibody
ACE	angiotensin converting enzyme
ADC	antibody-drug conjugate
AE	adverse event
AKI	acute kidney injury
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ARPI	androgen receptor pathway inhibitor
AST	aspartate aminotransferase
AUC	area under the curve
bsAb	bispecific monovalent antibody
CA-19-9	carbohydrate antigen-19-9
CEA	carcinoembryonic antigen
CI	confidence interval
C_{max}	maximum concentration after dosing
c-MET	mesenchymal-epithelial transition factor
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CR	complete response
CRC	colorectal cancer
CRO	Contract Research Organisation
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumour DNA
CTIS	Clinical Trial Information System
DCR	disease control rate
DLT	dose limiting toxicity
DNA	deoxyribonucleic acid
DoR	duration of response
DSB	double strand DNA break
EBRT	external beam radiation therapy
ECG	electrocardiogram

Abbreviation or special term	Explanation
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EGFR	epidermal growth factor receptor
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
Gy	gray
HGF	hepatocyte growth factor
HIV	human immunodeficiency virus
HNSCC	head and neck squamous cell carcinoma
HPV	human papilloma virus
HRCT	high resolution computed tomography
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
ICRP	International Commission on Radiological Protection
IEC	Independent Ethics Committee
IHC	immunohistochemistry
ILD	interstitial lung disease
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IRR	infusion-related reaction
IRT/RTSM	Interactive Response Technology System/Randomisation and Trial Supply Management
IV	intravenous(ly)
kBq	kilobecquerel
MBq	megabecquerel
µCi	microcurie
mCi	millicurie
mCRC	metastatic colorectal cancer
mCRPC	metastatic castrate-resistant prostate cancer
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
MTD	maximum tolerated dose

Abbreviation or special term	Explanation
mTPI-2	modified toxicity probability interval-2
NOAEL	no-observed-adverse-effect level
NSAID	nonsteroidal anti-inflammatory drug
NSCLC	non-small cell lung cancer
OAE	other significant adverse event
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PD	progressive disease
PDAC	pancreatic ductal adenocarcinoma
PET	positron emission tomography
PFS	progression free survival
PK	Pharmacokinetic(s)
PR	partial response
PSA	prostate-specific antigen
PSMA	prostate-specific membrane antigen
QTcF	QT interval corrected by Fridericia's formula
RAD	radiation absorbed dose
RECIST	Response Evaluation Criteria in Solid Tumours
RP2D	recommended Phase 2 dose
RT	radiotherapy
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SoA	schedule of activities
SPECT	single-photon emission computed tomography
SRC	Safety Review Committee
SUV_{max}	maximum standardised uptake value
TBR	tumour-to-background-ratio
TCR	T-cell receptor
TEAE	treatment-emergent TEAE
t_{max}	time to reach maximum concentration
TMG	toxicity management guidelines
TTR	time to response
ULN	upper limit of normal
US	United States

Abbreviation or special term	Explanation
USA	United States of America
VAF	variant allelic frequency
WCBP	women of childbearing potential
wt	wild-type

Appendix H Protocol Version History

The Summary of Changes Table for the current revision is located directly before the Table of Contents.

CSP Version 2.0 (18 April 2023)

Overall Rationale for the Modification:

This CSP update has been issued based on USA FDA feedback and includes: updates to the study design to remove Part A [^{225}Ac]-FPI-2068 hot dose escalation with no FPI-2053 pre-dosing, update Part B1 to Part A that includes Cohorts A1 to A3 for FPI-2053 dose exploration with a fixed hot dose of [^{225}Ac]-FPI-2068, and update Part B2 to Part B for [^{225}Ac]-FPI-2068 dose escalation with the optimal dose of FPI-2053; increase of the fixed dose of [^{225}Ac]-FPI-2068 in Part A from 10 kBq/kg to 15 kBq/kg; and updates to the Schedule of Activities to include ophthalmic assessments.

Other minor typographical errors have also been corrected.

Summary of Changes

List of Substantial Modifications		
Section Number and Name	**Description of Change**	**Brief Rationale**
Throughout protocol	Updated the study design to remove Part A [^{225}Ac]-FPI-2068 'hot' dose escalation with no FPI-2053 pre-dosing, changed Part B1 to Part A that includes Cohorts A1 to A3 for FPI-2053 dose exploration with a fixed 'hot' dose of 15 kBq/kg [^{225}Ac]-FPI-2068, and updated Part B2 to Part B for [^{225}Ac]-FPI-2068 dose escalation with the optimised dose of FPI-2053.	In response to FDA feedback to explore cold antibody pre-dosing and optimise the dose prior to dose escalation of 'hot' antibody. Increased Part A fixed dose of [^{225}Ac]-FPI-2068 in response to FDA feedback to minimise risk of treating participants at a sub-therapeutic dose.
Section 1.1 Synopsis, Section 4.1 Overall Design, Section 6.7.4 Starting Dose, Dose Escalation Scheme, and Stopping Criteria	Updated text to specify that Cohorts A1 and A2 will be initiated simultaneously and conducted in parallel, participants will be allocated in an alternating manner to Cohorts A1 or A2, and that the first participant in Cohort A2 will be treated with [^{225}Ac]-FPI-2068 only after the first participant in Cohort A1 has undergone a minimum of one week of safety observation.	In response to FDA feedback regarding the study design.
	Updated details of the SRC review.	
	Removed criteria that Part A may be discontinued due to lack of potential efficacy.	

List of Substantial Modifications		
Section Number and Name	**Description of Change**	**Brief Rationale**
	Updated text to specify that Part B of the study will employ a mTPI-2 design to estimate MTD.	
	Updated text to specify that the RP2D will be determined from Part B only.	
Section 1.1 Synopsis, Section 4.1 Overall Design, Section 9.2 Sample Size Determination	The number of participants to be enrolled in Parts A and B updated in-line with revised study design.	Due to revisions in study design of Parts A and B based on FDA feedback.
	Text added to specify that "At least 3 evaluable participants are required at the optimal dose of FPI-2053 to be taken forward to Part B."	
Section 1.1 Synopsis, Section 4.1.4 Study Periods	Updated the footnote of Figures 2 and 4 to state that "The length of each cycle within the treatment period will encompass a minimum of 56 days."	In response to FDA feedback and figure footnotes updated to clarify treatment cycle lengths.
	Updated text to specify that Part B will have escalating doses of [^{225}Ac]-FPI-2068.	
Section 1.1 Synopsis, Section 4.1.5 Dose Levels	Removed table for "Planned Dose Levels (Part A) – [^{225}Ac]-FPI-2068 Dose Escalation".	To reflect updated study design based on FDA feedback. Increased Part A fixed dose of [^{225}Ac]-FPI-2068 in response to FDA feedback to minimise risk of treating participants at a sub-therapeutic dose.
	Updated Table 2 and Table 7 to increase the fixed dose of [^{225}Ac]-FPI-2068 from 10 kBq/kg to 15 kBq/kg, to specify that individual participants will be allocated in an alternating manner to Cohorts A1 and A2, and to specify the details of the SRC reviews for initiation of Cohort A3 and Part B.	
	Updated Table 3 and Table 8 to include Part B Cohort 0 and to increase the [^{225}Ac]-FPI-2068 dose for Cohort B1 to 25 kBq/kg.	
Section 1.2 Schedule of Activities, Section 8.1 Schedule of Activities	Part A SoA tables updated to Part B "Hot-only Dose Escalation".	To reflect updated study design based on FDA feedback. Ophthalmic assessments added due to potential for ocular toxicity with EGFR and c-MET directed bi-specific antibodies.
	Ophthalmologic examinations added to SoA.	
	Footnote (b) added to Table 23 column header "[^{225}Ac]-FPI-2068 Cycle 2 and beyond". Footnote (b) updated for the treatment period tables to state that each cycle must be at least 56 days duration.	
	Footnote (b) of Table 24 updated for timing of Cycle 2 and 3 administrations to 56 + 28 days.	
	Survival follow up added throughout extended safety follow-up (after the last dose) to Table 25.	
Section 4.1 Overall Design	The estimated study treatment duration for participants updated to approximately 12 months.	Due to revisions in study design of Parts A and B.
Section 4.1.1 Backfill	Updated text to remove specification of a	To reflect updated study

List of Substantial Modifications		
Section Number and Name	**Description of Change**	**Brief Rationale**
Cohorts	preliminary signal of activity being observed during the process of dose escalation in Part A or Part B.	design based on FDA feedback.
Section 4.1.6 Study Conduct Mitigation During Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis, Appendix F Changes Related to Mitigation of Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis	Added new section and appendix to describe the study mitigation strategies to be implemented during cases of civil crisis, natural disaster, or public health crisis, such as COVID-19, including for obtaining reconsent, rescreening, telemedicine visits, and data capture during telemedicine visits.	To enable mitigation strategies for clinical studies ongoing during the COVID-19 pandemic, if required.
Section 4.3.2 FPI-2053	Updated text to specify the starting doses of FPI-2053 are 0.3 and 1.0 mg/kg.	Due to revisions in study design of Part A based on FDA feedback.
Section 4.3.3 [^{225}Ac]-FPI-2068	Due to increase of [^{225}Ac]-FPI-2068 dose from 10 kBq/kg to 15 kBq/kg, updated projected radiation absorbed doses to critical organs.	Increased Part A fixed dose of [^{225}Ac]-FPI-2068 in response to FDA feedback to minimise risk of treating participants at a sub-therapeutic dose.
	Updated safety margins according to mass dose range.	
Section 4.3.3 [^{225}Ac]-FPI-2068, Section 6.7.3 [^{225}Ac]-FPI-2068	Updated dosimetry estimates to specify that for Part A only, the participants cumulative radiation absorbed dose will not exceed limits of 2 Gy for red bone marrow.	In response to FDA feedback.
Section 5.2 Exclusion Criteria	Exclusion criterion 7d updated to state that participants with a history of non-infectious ILD were excluded.	Updated to align with the benefit/risk assessment.
Section 6.1.1.2 Dosage	Updated cumulative exposure dosimetry estimates for Part B.	Due to revisions in study design of Parts A and B.
	Updated Table 13 Investigational Products to include proposed doses of 15 and 25 kBq/kg for [^{225}Ac]-FPI-2068.	
	Updated Table 13 footnote (a) with revised details of [^{111}In]-FPI-2107 administration during Part A and Part B.	
Section 6.4 Measures to Minimise Bias: Randomisation and Blinding	Updated text to specify that participants will be allocated to Part A Cohorts 1 and 2 in an alternating manner.	Due to revisions in study design of Parts A and B.

List of Substantial Modifications		
Section Number and Name	**Description of Change**	**Brief Rationale**
Section 6.7.4.1 Stopping Criteria	Updated stopping criteria for the study and included that these should be at least potentially related to the investigational products, and not related to disease progression or intercurrent illness.	Clarification of stopping rules following FDA feedback.
Section 6.7.7 Definition of a DLT	Updated text to state that following the DLT observation period, subsequent cycles will be administered every 56 days.	For consistency with other updates.
	Updated text to specify that the cycle length is set at 56 days.	
Section 6.7.7.1 Events considered DLTs	Removed Grade 3 hypertension in the absence of maximal medical therapy as a non-haematological AE that is considered a DLT.	In response to FDA feedback.
Section 6.7.8 Safety Review Committee	Updated the details of the SRC review and the information that will be recorded in the SRC Charter.	Updated SRC review language as recommended for dose escalation studies.
Section 7.1 Discontinuation of Study Intervention	Updated the criteria the participants are to meet to remain on study treatment following confirmed radiological PD.	In response to Health Authority feedback.
Section 8 Study Assessments and Procedures	Updated text to specify that the total volume of blood to be collected will depend on study treatment.	Due to revisions in study design of Parts A and B in response to FDA feedback.
Section 8.2.2 Overall Survival	New section added to include details of efficacy assessments for overall survival.	Omitted in error from previous version.
Section 8.4.6.2 Ophthalmological Examinations	New section added to include details of ophthalmological examinations for the participants at baseline and last visit.	In response to FDA request due to potential for ocular toxicity with EGFR and c-MET directed bi-specific antibodies.
Section 8.5.9 Reporting of SAEs	Updated text regarding the reference documents to refer to for the definition of expectedness.	For clarity.
Section 8.5.13 Medication Error	Updated text to include the definition of a medication error.	Updated to standard CSP text.
Appendix A 1 Regulatory and Ethical Considerations	New text added for regulatory reporting requirements for serious breaches.	Updated to standard CSP text.
Appendix A 7 Data Quality Assurance	Updated time-frame for archiving of study records and documents.	Updated to standard CSP text.

AE, adverse event; COVID-19, coronavirus disease 2019; CSP, Clinical Study Protocol; DLT, dose limiting toxicity; EGFR, epidermal growth factor receptor; FDA, Food and Drug Administration; ILD, interstitial lung disease; MTD, maximum tolerated dose; mTPI-2, modified toxicity probability interval-2; PD, progressive disease; RP2D, recommended Phase 2 dose; SAE, serious adverse event; SoA, schedule of activities; SRC, Safety Review Committee.

List of Non-substantial Modifications		
Section Number and Name	**Description of Change**	**Brief Rationale**
Section 4.2 Scientific Rationale for Study Design	Updated description of "cold" antibody to "unlabelled".	For consistency.
Section 4.3.3 [^{225}Ac]-FPI-2068	Updated units within Table 10, Table 11, and Table 12.	For accuracy.
Section 8.2.1 Tumour Assessments	New subheading added for Section 8.2.1 Tumour Assessments within Section 8.2 Efficacy Assessments.	For clarity, as new subsection added.
Section 8.3 Dosimetry Assessments	Updated details of critical organ radiation dose limits for red bone marrow. Updated text to specify that outcomes of the dosimetry assessments will be shared with the study Investigators prior to the administration of each participants first cycle of treatment.	For clarification and consistency.
Section 8.7.1 Pharmacokinetics	Removed details regarding population PK analyses.	Removed as sufficient details are provided within Section 9.

PK, pharmacokinetics

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Clinical Study Protocol	
Study Intervention	[^{111}In]-FPI-2107, FPI-2053, and [^{225}Ac]-FPI-2068
Study Code	FPI-2068-101
Version	3.0
Date	05 June 2023

A Phase 1, First-in-human, Multicentre, Open-label, Dose-escalation Study of [^{225}Ac]-FPI-2068 in Adult Patients with Advanced Solid Tumours

Approver Name	William Trigg
Approver Role	Senior Director, Clinical Programs, Early Global Development
Signature	
Signature Date (Day Month Year)	8th June 2023

Clinical Study Protocol	
Study Intervention	[^{111}In]-FPI-2107, FPI-2053, and [^{225}Ac]-FPI-2068
Study Code	FPI-2068-101
Version	3.0
Date	05 June 2023

A Phase 1, First-in-human, Multicentre, Open-label, Dose-escalation Study of [^{225}Ac]-FPI-2068 in Adult Patients with Advanced Solid Tumours

Approver Name	Baisong Huang
Approver Role	Statistical Science Director
Signature	Baisong Huang
Signature Date (Day Month Year)	08 Jun 2023

Clinical Study Protocol	
Study Intervention	[^{111}In]-FPI-2107, FPI-2053, and [^{225}Ac]-FPI-2068
Study Code	FPI-2068-101
Version	3.0
Date	05 June 2023

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Approver Name	Moditha Nawinne
Approver Role	Medical Director, Early Global Development
Signature	M Nawinne
Signature Date (Day Month Year)	06-06-2023

SIGNATURE PAGE

Sponsor's Approval

The protocol has been approved by Fusion Pharmaceuticals Inc.

Sponsor's Authorized Officer:

J. Schindler	05-Jun-2023
Joanne Schindler, MD, DVM Executive VP, Clinical Development Fusion Pharmaceuticals, Inc.	Date