STUDY PROTOCOL

AN INTERNATIONAL MULTICENTRE, OPEN-LABEL FIRST IN HUMAN PHASE I/II STUDY TO EVALUATE THE SAFETY, TOLERABILITY, BIODISTRIBUTION AND ANTITUMOUR ACTIVITY OF ^{177}LU-3BP-227 FOR THE TREATMENT OF SUBJECTS WITH SOLID TUMOURS EXPRESSING NEUROTENSIN RECEPTOR 1

Study Number D-FR-01087-001
Protocol Version 8.0, dated 12 June 2020

EUDRACT Number 2017-001263-20
IND # Not Applicable

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AGREEMENT – SIGNATURE PAGE

Protocol Title:

AN INTERNATIONAL MULTICENTRE, OPEN-LABEL FIRST IN HUMAN PHASE I/II STUDY TO EVALUATE THE SAFETY, TOLERABILITY, BIODISTRIBUTION AND ANTITUMOUR ACTIVITY OF ^{177}LU-3BP-227 FOR THE TREATMENT OF SUBJECTS WITH SOLID TUMOURS EXPRESSING NEUROTENSIN RECEPTOR 1

Protocol Version 8.0, dated 12 June 2020

By signing below, I hereby confirm that I have read, discussed and understood the above mentioned version of the protocol and the background information concerning the study drug. I attest that I will carry out the study according to this protocol.

I also agree that the work will be performed according to Good Clinical Practice (GCP) guidelines, the ethical principles, as referenced in Section 13, and all currently applicable laws and regulations of the country(ies) where the study will be conducted.

Coordinating Investigator

Name	PPD
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Date:	
Signature:	

Sponsor

Name	PPD
Title:	PPD
Date:	
Signature:	

SYNOPSIS

Sponsor name	Ipsen Pharma SAS
Name of finished product	^{177}Lu-3BP-227
Name of active ingredient	^{177}Lu-3BP-227
Title of the study	AN INTERNATIONAL MULTICENTRE, OPEN-LABEL FIRST IN HUMAN PHASE I/II STUDY TO EVALUATE THE SAFETY, TOLERABILITY, BIODISTRIBUTION AND ANTITUMOUR ACTIVITY OF ^{177}LU-3BP-227 FOR THE TREATMENT OF SUBJECTS WITH SOLID TUMOURS EXPRESSING NEUROTENSIN RECEPTOR 1
Sponsor study number	D-FR-01087-001
EUDRACT number	2017-001263-20
IND Reference	Not applicable
Type of study/ Phase of development	Phase I / phase II
Number of planned centres	Approximately eight centres in Europe and three centres in the United States of America for the phase I (dose escalation) and additional centres in Europe and the United States of America for the potential phase I dose expansion and phase II.
Study hypothesis and objectives	**STUDY HYPOTHESIS** The present study consists of two parts that aim to test the following hypotheses: **Phase I** ^{177}Lu-3BP-227 is sufficiently well-tolerated to permit clinical investigation in phase II. **Phase II** ^{177}Lu-3BP-227 yields higher objective response rates in subjects who have Neurotensin Receptor 1 (NTSR1) expressing cancers that are unresectable, locally advanced or metastatic, based on Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 by central review and as compared with the historical objective response rate (ORR) obtained with current standard-of-care treatment for each tumour type. **STUDY OBJECTIVES** *Primary objectives* **Phase I** To establish the safety and tolerability of fractionated intravenous (i.v.) administrations of ^{177}Lu-3BP-227 in subjects with unresectable, locally advanced or metastatic cancers expressing NTSR1. **Phase II** To estimate ORR of fractionated i.v. administrations of ^{177}Lu-3BP-227 in subjects with unresectable, locally advanced or metastatic cancers expressing NTSR1. *Secondary objectives* **Phase I** a) To determine the whole-body distribution of ^{177}Lu-3BP-227 and pharmacokinetics (PK) of both ^{177}Lu-3BP-227 and 3BP-227. b) To determine the radiation dosimetry of ^{177}Lu-3BP-227 (organ exposure to radiation). c) To describe the preliminary antitumour activity of ^{177}Lu-3BP-227. **Phase II** a) To further evaluate the safety profile of ^{177}Lu-3BP-227 at the radioactivity recommended by the phase I results. b) To further assess the response to treatment with ^{177}Lu-3BP-227 using RECIST version 1.1 and/or positron emission tomography (PET) Response Criteria in Solid Tumours (PERCIST) version 1.0 criteria. c) To further characterise the whole-body distribution and dosimetry of ^{177}Lu-3BP-227 and PK of both ^{177}Lu-3BP-227 and 3BP-227. d) To describe the influence of ^{177}Lu-3BP-227 on the health-related quality of life of treated subjects.

	Exploratory objectives **Phase I/II** a) To explore the correlation between the tumour uptake of ^{177}Lu-3BP-227 and the NTSR1 expression on tumours. b) To explore renal safety by measuring urinary specific biomarkers. c) To evaluate the tumour microenvironment, transcriptomics, and other markers of interest for the disease through assessment of tumour biopsies. d) To explore genomic alterations in circulating cell-free DNA (cfDNA) and in germline DNA. e) To collect gene mutation status for correlation with clinical outcome. f) To collect biobank samples for future analysis of circulating markers (optional, additional informed consent required). g) To generate a model integrating PK, dosimetry, antitumour activity and safety data.
Study design	This is a multicentre, open-label phase I/II study of ^{177}Lu-3BP-227 in subjects with unresectable, locally advanced or metastatic solid tumours expressing NTSR1 who have exhausted their available standard-of-care treatment options and/or are deemed suitable for treatment with ^{177}Lu-3BP-227 as per the investigator's clinical assessment and/or their individual disease state. The study consists of a phase I with a dose escalation part (and potential expansion cohorts) and a phase II either in selected or over multiple indications in a basket approach. **Phase I** During phase I, it is planned to enrol subjects with unresectable, locally advanced or metastatic tumours expressing NTSR1 originating from either the: • Pancreas (pancreatic ductal adenocarcinoma, PDAC) • Colon and rectum (colorectal cancer, CRC) • Stomach (gastric cancer, GC) • Gastrointestinal stromal tumours (GIST) • Head and neck region (squamous-cell carcinoma of head and neck, SCCHN) • Bone (Ewing Sarcoma, ES) For the dose escalation part, CCI [redacted] Following eligibility confirmation, it is anticipated that a maximum of 30 subjects will receive the ^{177}Lu-3BP-227 therapeutic dose in up to six cohorts with four escalation steps. Three to five subjects will be treated per cohort in order to yield a minimum of three evaluable subjects per radioactivity level, treated at the full planned radioactivity amount fractionated into two administrations. Once five subjects are enrolled in a cohort, the enrolment will be stopped in that cohort. Once the dose escalation part has been completed, the maximum tolerated cumulative activity (MTCA) level may be repeated in an additional cohort. The cumulative starting activity will be 5 GBq fractionated into two administrations (2×2.5 GBq). The cumulative maximum activity will be 15 GBq activity (2×7.5 GBq). However, if the MTCA is not reached and if limiting organ dose levels are not exceeded, an additional cohort with three administrations at 7.5 GBq may be added, leading to a cumulative activity of 22.5 GBq. Of note, for each cohort in the dose escalation part, if a subject has clinical benefit and an acceptable tolerability profile, and if the organ dose limits are not exceeded, up to four additional cycles of ^{177}Lu-3BP-227 can be administered every 4 weeks after the end of the core trial (EOCT). The safety data evaluation will be conducted by the sponsor. The decision to administer additional cycles is based on the investigator's judgement and subject's discretion and must be discussed with and agreed upon by the sponsor.

	The MTCA is defined as the maximum tolerated cumulative activity that may be administered following fractionated i.v. administrations of at least 4 weeks apart, so that: • No more than 33% of the subjects experience a dose limiting toxicity (DLT) during Cycles 1 and/or 2 and • The cumulative radiation in each target organ does not exceed the acceptability limits. The DLTs are defined for any of the following IMP-related AEs according to National Cancer Institute - Common Terminology Criteria for Adverse Events (NCI-CTCAE) scale version 5.0, that occur during the defined DLT assessment period (from the first administration of ^{177}Lu-3BP-227 to EOCT/ED): • Grade 4 neutropenia for seven or more consecutive days; • Febrile neutropenia or neutropenic infection (defined as a documented infection with neutrophil count decreased Grade 3 or 4); • Grade 3 or 4 thrombocytopenia (platelet count decreased) with clinically meaningful bleeding (i.e. requiring urgent hospitalisation or transfusion to manage the bleeding); • Grade 4 thrombocytopenia for seven or more consecutive days; • Any Grade 3 anaemia (Hb<8.0 g/dL; transfusion indicated) or Grade 4 anaemia (life-threatening consequences; urgent intervention indicated); • Any Grade 3 or higher laboratory abnormalities in aspartate aminotransferase/alanine aminotransferase (AST/ALT) with accompanying Grade 2 or higher bilirubin (Hy's law); • Any Grade 3 or higher renal injury/toxicity (estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2); • Any Grade 3 or higher GI AE, not resolved to Grade ≤2 within 48 hours despite optimal adequate medical management, with the following specifications: - Grade 3 nausea, vomiting (inadequate oral caloric or fluid intake; tube feeding, total parenteral nutrition or hospitalisation indicated) - Grade 3 diarrhoea (increase of ≥7 stools per day over baseline; hospitalisation indicated; severe increase in ostomy output compared to baseline; limiting self-care activities of daily living (ADL)) or Grade 4 diarrhoea (life-threatening consequences; urgent intervention indicated) - Grade 3 constipation (obstipation with manual evacuation indicated; limiting self-care ADL) or Grade 4 constipation (life-threatening consequences; urgent intervention indicated); • Any toxicity related to ^{177}Lu-3BP-227 resulting in a treatment delay of more than four weeks due to either delayed recovery to baseline or resolution of any AE to Grade ≤2 (with the exception of alopecia and lymphopenia). • Grade 5 toxicity (death) **Study design following phase I dose escalation results** Upon completion of the phase I dose escalation or upon reaching the MTCA and confirmed jointly by the safety review committee (SRC) and the sponsor, and in consideration of the accumulated subject data, cohorts of subjects will be studied to further characterise the safety and efficacy of ^{177}Lu-3BP-227. In the case of acceptable tolerability and evident antitumour activity across all enrolled subjects in phase I, a phase II basket trial design will be utilised to study the antitumour activity of ^{177}Lu-3BP-227 in subjects with NTSR1 expressing tumours. Sample size estimations for this design will be provided as part of a protocol amendment. However, if the antitumour activity is driven by a type of tumour, tumour-specific phase II cohort(s) will be initiated utilising an Optimal Simon's Two Stage design (see Phase II). If safety evaluation and dose schedules of ^{177}Lu-3BP-227 cannot be fully explored during the phase I dose escalation part, the expansion part will serve to accomplish this objective including, but not limited to, schedules of high loading

	doses followed by fractionated lower doses or evaluation of ^{177}Lu-3BP-227 in combination with other antitumoral treatments (to be defined). The expansion part will also serve to clarify any uncertainties of antitumour responses. The number of cohorts and subjects will be determined based on emerging data from the dose escalation part and the modelling and simulation approach. **Phase II** Phase II study will be conducted either with a basket design trial or indication-specific cohorts with an Optimal Simon's Two Stage design, according to the scenarios described above. CCI [redacted] One or two further cohorts may be opened (subject to results emerging from ongoing preclinical studies and antitumour efficacy seen during dose escalation and amending the current protocol) likely to enrol subjects with GC and/or SCCHN. • The PDAC cohort will enrol approximately 55 subjects and will investigate whether ^{177}Lu-3BP-227 attains an ORR superior to a clinically accepted historical threshold of current standard-of-care treatment for subjects with unresectable, locally advanced or metastatic disease. • The CRC cohort will enrol approximately 70 subjects and will investigate whether ^{177}Lu-3BP-227 attains an ORR superior to a clinically accepted historical threshold of current standard-of-care for subjects with unresectable, locally advanced or metastatic disease. The current protocol will be amended at the end of the phase I to document the rationale of the phase II design. In any case, the cumulative activity administered during phase II will not exceed the MTCA determined during phase I.
Number of subjects	During the phase I escalation part, CCI [redacted] up to 30 subjects will receive the ^{177}Lu-3BP-227 therapeutic dose. For the phase II, approximately 125 subjects (55 PDAC and 70 CRC subjects) are planned to be enrolled for Optimal Simon's Two Stage design. In case of the implementation of phase I expansion cohorts, up to 45 additional subjects will be enrolled. Similarly, if additional cohorts of subjects with GC, ES or SCCHN in the phase II are to be studied, approximately 120 additional subjects will be enrolled. In total, the phase I/II study would therefore enrol up to 320 subjects evaluable for safety and/or efficacy. For a single-arm basket trial approach, sample size justification will be provided as part of a protocol amendment.
Main eligibility criteria	**Inclusion criteria:** Eligible subjects must fulfil all the following inclusion criteria: **Phase I** (1) Signed informed consent form prior to all study procedures. (2) Aged 18 years or older. (3) Histologically or cytologically confirmed unresectable, locally advanced or metastatic disease and has received prior lines of standard-of-care chemotherapy/treatment and has no further suitable treatment options and a documented decision by a multidisciplinary oncology board including a specialist of the concerned pathology. (4) Subjects have: (a) PDAC, or (b) CRC (colorectal adenocarcinoma), or (c) GC (gastric adenocarcinoma), or (d) Gastrointestinal Stromal Tumours (GIST), or (e) SCCHN, or (f) ES. (5) Tumours showing: (a) uptake of ^{177}Lu-3BP-227 (screening formulation) in known primary or metastatic sites as judged by the investigator to be greater than background; or

	(b) uptake of ^{111}In-3BP-227 in known primary or metastatic sites (for subjects who participated in Study D-FR-01087-002) as judged by the investigator to be greater than background. (6) Measurable disease (based on RECIST version 1.1). (7) Criterion 7 is removed by protocol amendment. (8) Documentation of progressive disease in the 6 months prior to study start (treatment). (9) Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (unless if disability is related to surgery in ES and agreed with the sponsor). (10) Adequate organ function as evidenced by: (a) Leukocytes ≥ 3000/µL (b) Absolute neutrophil count ≥1500/µL (c) Platelets ≥75,000/µL (d) Hb >9g/dL or >10 g/dL (if history of cardiac disease) (e) Total serum bilirubin ≤2×upper normal institutional limits (ULN) (f) Aspartate aminotransferase/alanine aminotransferase ≤2.5×ULN (≤5×ULN if subject has liver metastases) (g) Estimated glomerular filtration rate ≥55mL/min. (11) Estimated life expectancy of >3 months. (12) Female subjects must not be pregnant or lactating at study entry and during the course of the study and must not become pregnant for at least 6 months following the last study treatment. Women of childbearing potential must agree to use a highly effective method of contraception (see note below). (13) Male subjects must not father children during the study and for at least 6 months after the last study treatment and in addition must agree to use a condom for this period to protect his partner from contamination with the IMP. For males with partners who are of child bearing potential, effective contraception is a combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods), but these are not considered to be highly effective. A man is considered to be infertile if he has had bilateral orchidectomy or successful vasectomy. Effective contraception includes a female partner of childbearing potential if she is using highly efficacious contraception (see note below), but the male subject must agree to use a condom to protect his partner as described above. (14) Must be willing and able to comply with study restrictions and to remain at the clinic for the required time during the study period and willing to return to the clinic for the follow-up evaluation, as specified in the protocol. *Note: Highly effective methods of contraception that result in a low failure rate (i.e., <1% per year) when used consistently and correctly include combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal), progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, or implantable), intrauterine device, intrauterine hormone-releasing system, bilateral tubal occlusion, vasectomised partner (the vasectomised partner has received medical assessment of the surgical success at least 6 months prior to the first study treatment and provided that partner is the sole sexual partner of the female subject of childbearing potential trial participant), or sexual abstinence;* *True abstinence, when in line with the preferred and usual lifestyle of the subject, is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of study treatment and for 6 months after the last dose of ^{177}Lu-3BP-227. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the subject. Periodic abstinence (e.g. calendar,*

	ovulation, symptothermal, and post-ovulation method) and withdrawal are not acceptable methods of contraception; *Female subject is considered of childbearing potential i.e. fertile, following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.* *For male subjects, acceptable methods of effective contraception include sexual abstinence, successful vasectomy, bilateral orchidectomy and barrier methods (i.e. condom). In addition, male subjects should not donate sperm and female subjects should not donate eggs for at least 2 years after the last study treatment.* **Phase II** The inclusion criteria for phase II will be revised based on the scenario adopted and indication(s) selected for investigation based on the results from phase I and will be documented as part of a protocol amendment. **Exclusion criteria:** Eligible subjects must not have any of the following: **Phase I/II** (1) Prior treatment received (a) Any antitumour treatment since last documented disease progression (b) Any chemotherapy within 3 weeks or nitrosourea within 6 weeks prior to first treatment investigational medicinal product (IMP) administration (c) Any curative radiotherapy within 4 weeks or palliative radiotherapy within 7 days prior to first treatment IMP administration (d) Any, monoclonal antibodies within 4 weeks or tyrosine kinases inhibitors within 2 weeks prior to the first treatment IMP administration (e) Any other IMP within 2 weeks prior to first treatment IMP administration, if the previous compound is a mechanism-based molecularly targeted agent whose half-life ($t_{1/2}$) is not well-characterised. (2) Brain metastases. (3) Nephrectomy, renal transplant or concomitant nephrotoxic therapy putting the subject at high risk of renal toxicity during the study. (4) Only nonmeasurable metastatic bone lesions. (5) Existing or planned colostomy during study participation. (6) Any history of inflammatory bowel disease. (7) Any uncontrolled significant medical, psychiatric or surgical condition or laboratory finding, that would pose a risk to subject safety or interfere with study participation or interpretation of individual subject results. (8) Clinically significant abnormalities on electrocardiogram (ECG) at screening including corrected QT interval (Fridericia's formula) >450 msec for males or 470 msec for females at screening. (9) Previously received external beam irradiation to a field that includes more than 30% of the bone marrow or kidneys. (10) Criterion 10 is removed by protocol amendment. (11) Any unresolved NCI-CTCAE Grade 2 or higher (except alopecia) from previous antitumour treatment and/or medical/surgical procedures/interventions. (12) Known allergy to IMP or its excipients administered in this study, including imaging contrast media. (13) Positive pregnancy test (female subjects).

	(14) Likely to be uncompliant or uncooperative during the study, in the judgment of the investigator. (15) Unable to understand the nature, scope and possible consequences of the study, in the judgment of the investigator. (16) Sponsor employees or investigator site personnel directly affiliated with this study, and their immediate families. Immediate family is defined as a spouse, parent, child or sibling, whether biological or legally adopted.
Treatment: route, strength, regimen	For both screening and treatment formulations, the specific activity of the IMP is 25 µg 3BP-227 per 1 GBq of ^{177}Lu. The screening IMP formulation consists of 1 GBq in a total volume of 10 mL. The treatment IMP formulation consists of 2.5 to 7.5 GBq of ^{177}Lu-3BP-227 in a total volume of 20 mL. The total radioactivity of the treatment IMP formulation will be fractionated and administered in two i.v. infusions separated by at least 4 weeks (28 days). A 100 mL saline solution will be administered intravenously over a period of 30 minutes concomitantly with every IMP administration. The subject will be instructed to drink water (at least 1.5 L/24 hours) on the days following each IMP administration.
Reference treatment: route, strength, regimen	Not applicable
Criteria for evaluation (endpoints)	**STUDY ENDPOINTS** *Primary endpoints* **Phase I** For the dose escalation, the primary endpoint is MTCA or the maximum administered cumulative activity (MACA), if the MTCA is not identified during the dose escalation part. The primary variables used for the MTCA determination will be the incidence of DLTs (as defined above) and the organ exposure to radiation during two cycles of treatment. The DLT period for the determination of the primary endpoint starts at the first administration of ^{177}Lu-3BP-227 to EOCT/ED. Safety evaluation will encompass DLTs, frequency and nature of adverse events (AEs), abnormal findings from physical examination, vital signs, 12-lead ECG and 24-hour 3-lead ECG Holter, ECOG performance status treatment related deterioration and clinical laboratory tests abnormalities (including haematology, blood biochemistry, hormone analysis, urinalysis and pregnancy test). In case the phase I dose expansion cohorts are implemented, the primary endpoint will be safety and tolerability measured by the type, severity, expectedness and frequency of AEs. **Phase II** The primary endpoint is ORR measured by CT or MRI using RECIST version 1.1. Tumour response assessments are performed every 8 weeks or at the time of occurrence of first clinical signs of disease progression as determined by the investigator. *Secondary endpoints* **Phase I** Pharmacokinetics, biodistribution and dosimetry For biodistribution and dosimetry of ^{177}Lu-3BP-227, the secondary endpoints are: a) Maximal uptake (%); maximal concentration achieved (C_{max}); time post injection to achieve maximal concentration (T_{max}); area under the curve (AUC) at the target lesions, discernible organs and blood; terminal $t_{1/2}$ of activity concentrations in blood. b) Highest absorbed dose, specific absorbed dose to the target lesions (Gy/GBq), specific absorbed dose per organ (Gy/GBq) and cumulative absorbed organ doses (Gy). For PK of 3BP-227, the secondary endpoints are: c) Pharmacokinetic parameters including, but not limited to, C_{max}, AUC, $t_{1/2}$, clearance (CL), volume of distribution (V_d), cumulative amount of

	unchanged drug excreted into the urine (Ae), renal clearance of the drug from plasma (CL_R), as measured in plasma and urine at defined timepoints. Pharmacodynamic/efficacy a) Objective response rate and disease control rate (DCR), as determined by RECIST version 1.1 in subjects who received IMP. b) Progression-free survival (PFS) and overall survival (OS) rates as determined from start of study treatment until occurrence of event and/or end of observation period. c) Evaluation of metabolic tumour response using PERCIST (version 1.0) or practical PERCIST. d) Changes in serum tumour markers relevant and specific to the underlying tumour disease from Day of the first treatment administration to EOCT, which is planned 6 weeks after the second ^{177}Lu-3BP-227 dose administration. **Phase II** Efficacy a) Disease control rate, time to progression, time to response, duration of response as per RECIST version 1.1. b) Qualitative and quantitative changes in tumour-to-background uptake using PERCIST version 1.0. c) Progression-free survival (PFS) and OS as determined from start of study treatment until occurrence of event and/or 6 and 12 months after start of study treatment. d) Changes in serum tumour markers relevant and specific to the underlying tumour disease from baseline to EOCT. Subject Reported Outcomes a) Changes in health-related quality of life scores from baseline to EOCT measured by validated questionnaires. Safety a) Safety and tolerability measured by the type, severity, expectedness and frequency of AEs. Pharmacokinetics, biodistribution and dosimetry a) For PK, biodistribution and dosimetry, the endpoints will be similar as for phase I. *Exploratory endpoints* **Phase I/II** a) Tumour uptake of ^{177}Lu-3BP-227 and the correlation with NTSR1 expression on tumour biopsies. b) If applicable, tumour microenvironment and other markers of interest (such as NTSR1 expression, Ki67, gene expression and DNA damage) in tumour biopsies taken at baseline, at EOCT visit or at disease progression, whichever occurs earlier. c) Genomic profiling in circulating cfDNA and in germline DNA. d) Gene mutation status in correlation with clinical outcome. e) Specific renal safety biomarkers specific for proximal tubulus toxicity. *Biobanking (optional):* Serum and whole blood ribonucleic acid samples will be stored for further biomarker analysis after the end of the study. Analysis of additional biomarkers from the biobank samples will be performed outside the scope of the main study and reported separately.
Statistical methodology	**Statistical methodology in phase I** Safety Continued monitoring of DLTs and toxicities will be performed during dose escalation. At the time of the SRC, an interim analysis of the DLTs, toxicities

	and selected organ absorbed doses (kidney, liver and bone marrow) will be performed to guide the dose selection during the dose escalation part. Biodistribution, radiation dosimetry, PK of ^{177}Lu-3BP-227 Descriptive summaries of PK and biodistribution parameters will be presented for each cohort over the treatment period. Pharmacokinetics of 3BP-227 If 3BP-227 levels are measurable in plasma and urine, PK parameters of 3BP-227 will be derived using a noncompartmental approach. An attempt to build an integrated model taking into account PK, dosimetry, antitumour and safety data will be made. Pharmacodynamics/Efficacy Analysis In order to perform preliminary antitumour activity, ORR and DCR will be tabulated. Tumour response will be evaluated by the site investigator. Independent review of tumour assessment may be requested at the discretion of the sponsor. In both cases, response and progression will be evaluated using the revised RECIST guideline (version 1.1). Only subjects with measurable disease at baseline, who have received at least two administrations of ^{177}Lu-3BP-227 and reached the end of Cycle 2 or EOCT visit will be considered evaluable for response. **Statistical methodology in phase II** Efficacy Analysis For phase II cohorts, tumour response will be assessed in imaging modalities of CT or MRI scans after Cycle 2 and subsequently every 8 weeks for the first 6 months and every 12 weeks thereafter. Images will be reviewed by an independent central review core laboratory. ORR, best overall response (BOR) and other efficacy parameters will be tabulated. Objective response rate will be calculated combining the number of subjects with a BOR of confirmed complete response (CR) or partial response (PR) per RECIST version 1.1. For the Simon Two-Stage design, the hypotheses that will be tested for each cohort are: H_0: ORR$\leq$ORR$_0$ versus the alternative H1: ORR>ORR$_0$ where ORR is the true objective response rate following ^{177}Lu-3BP-227 treatment that warrants further clinical development, and ORR$_0$ is the minimum objective response rate to be excluded from further clinical development. The thresholds for ORR and ORR$_0$ may be updated based on results from phase I and the evolving scientific knowledge. Objective response rate will be analysed at the end of Stage 1 (and no later than after the 16-week visit of the last evaluable subject of the Stage 1 cohort for each PDAC and CRC cohort). If the observed number of responders is below a predefined threshold, the respective study cohort will be stopped for futility. Otherwise, additional subjects will be treated to complete the planned enrolment. At the end of Stage 2, the null hypothesis will be rejected depending on the total observed number of responders based on a predefined threshold. At the end of phase II, descriptive summaries will be provided for all primary and secondary efficacy endpoints. For the primary endpoint, final analysis will take into account the sequential sampling procedure of the design and the underlying binomial distribution assumed by the Simon Two-Stage design. Safety Descriptive statistics will be calculated on the safety parameters. No formal statistical analyses of safety data are planned. Biodistribution, radiation dosimetry, PK of ^{177}Lu-3BP-227 and 3BP-227 Analysis will be performed as for phase I.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

RATIONALE FOR PROTOCOL AMENDMENT #7

The protocol was amended to update the following:

- Clarification of the inclusion criteria for subject selection as follows:
  - to clearly state nonresectable locally advanced disease
  - to clearly state that no further suitable treatment options are available for subjects eligible for the study
- Allow subjects screened and found positive for NTSR1 in the ^{111}In-IPN01087 phase I diagnostic study to take part in this study without having the diagnostic dose of ^{177}Lu-IPN01087 during the screening phase
- Extend the long-term follow-up period from 2 years to a maximum of 5 years or until lost to follow-up, withdrawal of consent or death, whichever occurs first.
- Revision of the DLT criteria (Section 4.7.1.1) to adequately describe the grading as stated in the CTCAE 5.0 dictionary
- Revision of the subject discontinuation rules so if there are life threatening toxicities outside of the DLT period, treatment is discontinued
- Optimise the dosimetry evaluation through adaptation of the imaging schedule
- Clarification of biopsy collection
- Clarification about COVID-19 added following the recent pandemic
- CCI [redacted]
- Make various clarifications and minor corrections for consistency

All modifications (except minor changes) are presented in Attachment 19.7.

PROTOCOL HISTORY

Protocol version	Rationale for amendment
V1.0, 02AUG2017	NA – initial version
V2.0, 16OCT2017, Amendment #1	To update tumour biopsy inclusion criteria as per Ethical Committee review.
V3.0, 09NOV17, Amendment #2	To incorporate changes to inclusion criteria, dose escalation part, physical examination and ECG assessments as per review by the Health Authorities in France.
V4.0, 6DEC2017 Amendment #3	To include Ewing Sarcoma as an additional indication in the phase I/II study and to provide updated information regarding the IMP. In addition, some inconsistencies in the protocol have been corrected.
V5.0, 02MAR2018 Amendment #4	To give precision on the calculation of the TGR, information about drug-drug interactions, clarification of discontinuation process, information about infusion rate in response to adverse events and increase time for use of contraception for females in the inclusion criteria from 30 days to 6 months, as well as information about spillages. In addition, some administration changes and minor inconsistencies in the protocol have been corrected.
V6.0, 17 July 2018 Amendment #5	The protocol has been amended to improve the determination of the biokinetics of ^{177}Lu-3BP-227 and perform an absolute quantification of radioactivity in target organs. Whole body scans (planar

Protocol version	Rationale for amendment
	scintigraphy) have been added to single photon emission computed tomography (SPECT /CT) during treatment period. Whole body scans will allow the calculation of whole body time-integrated activity coefficient ("residence time") that is needed for dosimetry analysis as it accounts for nonspecific activity in the body. Inclusion criteria n°3 has been updated to enable the recruitment of patients who do not have a compelling standard-of-care option. In addition, some administration changes and minor corrections have been added.
V7.0, 20 June 2019 Amendment #6	The protocol was amended to update personnel (the sponsor authorised protocol approver and sponsor medical monitor), to update the background information, especially new nonclinical toxicology data, to update the number of subjects receiving screening and therapeutic dose, CCI and add genomic alterations in circulating cell-free DNA and gene mutation status as exploratory objectives and endpoints, to change pharmacokinetic timepoints to improve the clinical feasibility, to specify the biopsy conditions and put them as optional assessments, to remove tumour markers assessments for gastric cancer (CA72-4) and squamous-cell carcinoma of head and neck (TPA), to refine the exclusion criteria regarding body weight, to clarify discontinuation rules, to clarify the duration of the safety follow-up period after the IMP screening dose administration and the reporting of AE collection after the last IMP administration, to specify that death due to disease progression will be reported as an SAE, to specify details on the preparation of the CSR, to add schedule of assessments for screen failure subjects and to make various clarifications and corrections for consistency. Following local competent authority feedback, the sponsor was requested to provide an updated study protocol including only highly effective methods of contraception for female subjects and female partner of male participants. Additionally, the sponsor was requested to: • Clarify the duration of use of effective contraception for male subjects • Clarify the maximum number of subjects participating in the study • Amend the study protocol so that only subjects who fulfil all of the inclusion criteria are included in the clinical study by clarifying the major protocol deviation definition • Specify in detail under which conditions re-screening of subjects will be possible • Clarify that all AEs during the core trial will be followed up until resolution or stabilisation independent of the level of severity or causality for treated subjects

Protocol version	Rationale for amendment
V7.1 (USA), 20 August 2019, Amendment #6	The protocol was amended to update the following as requested by the FDA: • Clarification of the inclusion criteria for subject selection as follows: - to clearly state nonresectable locally advanced disease - to clearly state that no further suitable treatment options are available for subjects eligible for the study • Revision of the DLT criteria to adequately describe the grading as stated in the CTCAE v5.0 dictionary • Revision of the subject discontinuation rules so if there are life-threatening toxicities outside of the DLT period, treatment will be discontinued

LIST OF DEFINITIONS AND ABBREVIATIONS

TERM	Wording Definition
Audit	A systematic and independent examination of the study-related activities and documents to determine whether the evaluated study-related activities were conducted, and the data were recorded, analysed, and accurately reported according to the protocol, sponsor's standard operating procedures, good clinical practices, and the applicable regulatory requirement(s).
Complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
Compliance	Adherence to all the study-related requirements, good clinical practices requirements and the applicable regulatory requirements.
End of study	End of study (EOS) is the date of the last visit or last scheduled procedure shown in the Study Schedule for the last active subject in the study.
Enrol/Randomise	The act of assigning a subject to a treatment. Subjects who are enrolled in the study are those who have been assigned to a treatment.
Enter/Consent	The act of obtaining informed consent for participation in a clinical study from subjects deemed or potentially eligible to participate in the clinical study. Subjects entered into a study are those who sign the informed consent document directly or through their legally acceptable representatives.
Ethics Committee	A board or committee (institutional, regional, or national) composed of medical professionals and non-medical members whose responsibility is to verify that the safety, welfare and human rights of the subjects participating in a clinical study are protected.
Investigator	A physician responsible for the conduct of a clinical study at a study site. If a study is conducted by a team of individuals at a study site, the investigator is the responsible leader of the team and may be called the principal investigator.
Screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study. In this study, screening involves invasive or diagnostic procedures and/or tests (for example, diagnostic psychological tests, x-rays, blood draws). Informed consent for these screening procedures and/or tests shall be obtained; this consent may be separate from obtaining consent for the study.
Subject	An individual who is or becomes a participant in clinical research, either as a recipient of the test article or as a control. A subject may be either a healthy human or a patient.

ABBREVIATION	Wording Definition
%	Percent
βHCG	Beta human chorionic gonadotrophin
µL	Microlitre
ACE	Angiotensin-converting enzyme
ADL	Activity of daily living
Ae	Cumulative amount of unchanged drug excreted into the urine
AE	Adverse event
AKI	Acute kidney injury
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the (plasma concentration versus time) curve
AUC_{inf}	Area under the curve from time zero to infinity
BOR	Best overall response
ceCT/MRI	Contrast enhanced computed tomography/magnetic resonance imaging
cfDNA	Cell-free deoxyribonucleic acid
CL	Clearance
CL_R	Renal clearance of the drug from plasma
C_{max}	Observed maximal (peak) concentration
CR	Complete responder
CRC	Colorectal cancer
CRO	Contract research organisation
CSR	Clinical study report
CT	Computed tomography
CYP	Cytochrome P
DCR	Disease control rate
DLT	Dose limiting toxicity
DNA	Deoxyribonucleic acid
DOM	Dosimetry operational manual
DOR	Duration of response
EC	Ethics committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form

ABBREVIATION	Wording Definition
ED	Early discontinuation
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
EGFR	Epidermal growth factor receptor
EOAC	End of additional cycles
EOCT	End of core trial
EOS	End of study
ES	Ewing Sarcoma
FDA	Food and Drug Administration
FIH	First in human
FSH	Follicle stimulating hormone
GBq	Gigabecquerel
GC	Gastric cancer
GCP	Good clinical practice
GI	Gastrointestinal
GIST	Gastrointestinal Stromal Tumours
GPS	Global Patient Safety
Gy	Gray
hERG	Human ether- à-go-go-related gene
HPLC	High performance liquid chromatography
IB	Investigator's brochure
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational medicinal product
IRB	Institutional review board
IU/L	International unit per litre
i.v.	Intravenous
kg	Kilogram
MACA	Maximum administered cumulative activity
MAD	Maximum absorbed dose
mCRC	Metastatic colorectal cancer
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mL	Millilitre

ABBREVIATION	Wording Definition
mL/min	Millilitre per minute
MS	Mass spectrometer
MTCA	Maximum tolerated cumulative activity
MTD	Maximum tolerated dose
MTSA	Maximum tolerated single activity
NCI-CTCAE	National Cancer Institute - Common Terminology Criteria for Adverse Events
NOAEL	No-observed-adverse-effect level
NSAID	Nonsteroidal anti-inflammatory drugs
NTSR1	Neurotensin receptor 1
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease/progression of disease
PDAC	Pancreatic ductal adenocarcinoma
PERCIST	PET Response Criteria in Solid Tumours
PET	Positron emission tomography
PFS	Progression-free survival
PK	Pharmacokinetic
PR	Partial responder
QTcF	QT interval Fridericia's correction
RECIST	Response Evaluation Criteria in Solid Tumours
RL	Radioactivity level
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical analysis plan
SCCHN	Squamous-cell carcinoma of head and neck
SOP	Standard operating procedure
SPECT	Single photon emission computed tomography
SRC	Safety review committee
SUSAR	Suspected unexpected serious adverse reaction
$t_{1/2}$	Half-life
TEAE	Treatment emergent adverse event
T_{max}	Time to maximum observed plasma concentration
TTP	Time to progression

ABBREVIATION	Wording Definition
TTR	Time to response
ULN	Upper limit of normal
Vd	Volume of distribution
WHO	World Health Organization

1 BACKGROUND INFORMATION

1.1 Introduction

This phase I/II study will be the first administration of ^{177}Lu-3BP-227 in humans under controlled study conditions. The study will generate safety and antitumour activity data and is expected to provide a better understanding of the mechanism of action of ^{177}Lu-3BP-227.

The results observed in terms of antitumour activity during dose escalation, will determine whether phase I expansion cohorts will be conducted to further investigate the safety of other activity levels and/or other administration schedule (e. g. hyperfractionation) or the investigation of efficacy of ^{177}Lu-3BP-227 in the context of indication-specific cohorts or over multiple indications.

1.2 Name and Description of the Investigational Medicinal Product

^{177}Lu-3BP-227 is a drug substance consisting of a peptidomimetic neurotensin receptor 1 (NTSR1) targeting moiety, linked to a chelating DOTA moiety (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA), which chelates the radioactive Lutetium (^{177}Lu); it is applied in a theranostic approach.

1.3 Nonclinical Data

1.3.1 In Vitro Studies

^{nat}Lu-3BP-227 has been extensively tested in vitro. ^{nat}Lu-3BP-227 showed specific and high binding affinity (IC_{50} of 2.05 nM) to NTSR1, ^{nat}Lu-3BP-227 has no agonistic activity in a Ca^{2+} mobilisation assay and prevents the Ca^{2+} efflux induced by an NTSR1 agonist, therefore, characterising the molecule as an NTSR1 antagonist. In the same calcium mobilisation assay, 3BP-227 displayed weak agonistic activity (EC_{50} of 95 nM) on the neurotensin receptor 2. 3BP-227 at 10 µM and ^{nat}Lu-3BP-227 at 1 µM did not show any other potential binding in a screening panel (Cerep) of G protein-coupled receptor.

1.3.2 Toxicology

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[redacted]

1.3.3 Pharmacokinetic Properties of Unlabelled 3BP-227

In pharmacokinetics (PK) and metabolism studies, 3BP-227 appeared to be highly bound to human plasma proteins (86%), as well as in mouse plasma proteins (95%), with lesser binding to rat and dog plasma proteins (71% and 69%, respectively) (Study N° IPS000354). 3BP-227 was very stable in human and dog plasma in vitro (>24 hours). Metabolic stability assays in human and dog liver microsomes showed a long half-life ($t_{1/2}$>60 minutes) and consequently a low intrinsic clearance at a concentration of 0.1 µM of 3BP-227.

3BP-227 had a poor inhibitory potential towards cytochrome P (CYP) 1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4 with a maximum inhibition of 33% towards CYP3A4 (midazolam

substrate) at 10 µM. Thus, it is unlikely that these CYPs will be inhibited by 3BP-227 in clinical settings.

The PK of unlabelled 3BP-227 administered as a single i.v. dose has been evaluated in mice. Rat and dog toxicokinetics were performed as part of extended single i.v. dose toxicity studies in rats and dogs and of a 13-week repeated dose study in rats with the unlabelled 3BP-227. After a single i.v. dose in mice, 3BP-227 showed a low plasma clearance (CL of 64.5 mL/hour/kg) and a moderate terminal elimination $t_{1/2}$ (1.63 hours).

After single i.v. administration in rats, the exposure (area under the curve from time zero to infinity (AUC_{inf})) was comparable for males and females. The terminal $t_{1/2}$ was short and approximately two times longer in males than females (0.45 hour and 0.26 hour, respectively). The apparent volume of distribution (V_d) was small and approximately two times higher in males (402 mL/kg) than in females (221 mL/kg). The systemic CL was low and similar for both genders, representing approximately 15% of the hepatic blood flow of in rats. During the 13-week repeated-dose TK study in rats, a rapid elimination phase was observed. The exposure was dose-proportional and no or weak accumulation occurred between Day 1 and Day 85 (accumulation ratios ranged from 0.9 to 1.7).

In dogs, the single i.v. bolus PK data indicate that the plasma concentrations of 3BP-227 decreased in a biphasic manner, with a short elimination $t_{1/2}$ of 2.15±0.257 hours for the second elimination phase and no gender-dependent differences. The apparent Vd was small (107±9.8 mL/kg) and the CL very low, representing 2.2% of the dog hepatic blood flow.

1.3.4 Biodistribution and Dosimetry of Radiolabelled 3BP-227

The specificity of 3BP-227 accumulation in NTSR1-expressing tumours in vivo was demonstrated in biodistribution studies in mouse xenograft models with both ^{111}In-3BP-227 and ^{177}Lu-3BP-227. Besides NTSR1-expressing tumours, the uptake of radioactivity in the organs was very low, including the kidneys and the liver. It was shown that 3BP-227 did not penetrate the blood brain barrier. ^{177}Lu-3BP-227 showed a favourable biodistribution profile exhibiting a good tumour uptake associated with a low uptake in normal tissue and a persistent tumour uptake leading to favourable tumour-to-kidney activity ratio.

In rats, the biodistribution profiles and the effective radioactive doses of ^{111}In-3BP-227 and ^{177}Lu-3BP-227 were comparable. The radioactivity was rapidly cleared from the bloodstream. Tissue concentrations were low. Elimination of radioactivity was primarily through the urine and to a lesser extent via the faeces.

In a biodistribution and dosimetry study of ^{177}Lu-3BP-227 in Beagle dogs, the radioactivity was rapidly cleared from the blood. ^{177}Lu-3BP-227 was predominantly and rapidly excreted through the urinary tract with a secondary elimination route via the liver into the gastrointestinal (GI) tract. The main uptake of radioactivity in organs was observed at 2 and 6 hours after injection in muscles, intestines, bones and bone marrow, liver, lungs and kidneys. At 72 hours post injection, all tissues exhibited less than 1% of the injected dose. The highest absorbed dose coefficients were observed in the urinary bladder wall, the large intestinal wall and the kidneys.

Table 1 below summarises the extrapolation of the organ exposure results from these two studies to humans. The extrapolation to humans was performed using a mass-based extrapolation in which the concentration in the animal organs was converted to a concentration in human organs by multiplying the animal concentration by a ratio of the total body weight of the animals and humans [1]. The dosimetry studies in rats and dogs identified as target organs of special interest: urinary bladder, large intestinal wall, kidneys and osteogenic cells.

From the extrapolation of animal data to human, the expected radiation exposure in human study is acceptable.

Table 1 Radiation Dose Estimates for Adult Humans based on Dosimetry Studies in Rat and Dogs

Compound	^{177}Lu-3BP-227	^{111}In-3BP-227	^{177}Lu-3BP-227
Species	**Rat**	**Rat**	**Dog**
Specific activity	1.2 to 2.4 mCi/nmol	1.2 to 2.4 mCi/nmol	9.9 MBq/µg
Radioactive dose	50 or 100 µCi/rat	50 or 100 µCi/rat	94.6±5.6 MBq
API dose			2.2 µg/kg
Main organs	**M - F (mSv/MBq)**	**M – F (mSv/MBq)**	**M - F (mSv/MBq)**
Kidney	***0.170 - 0.280***	***0.160 - 0.250***	***0.16 - 0.11***
Liver	0.094 - 0.140	0.130 - 0.180	0.03 - 0.02
Brain	0.007 - 0.006	0.033 - 0.040	0.00 - 0.00
Lungs	0.048 - 0.045	0.093 - 0.120	0.02 - 0.01
Osteogenic cells	***0.650 - 0.540***	***0.260 - 0.330***	0.07 - 0.05
LLI wall	***0.450 - 0.530***	***0.190 - 0.230***	***0.30 - 0.16***
ULI wall	***0.290 - 0.290***	***0.150 - 0.190***	***0.27 - 0.15***
Red marrow	***0.160 - 0.110***	***0.110 - 0.120***	0.02 - 0.01
Spleen	0.046 - 0.065	0.110 - 0.150	0.02 - 0.01
Ovaries	0.150	0.180	0.04
Testes	0.200	0.120	0.02
Uterus	0.150	0.190	0.19
Urinary bladder wall	***0.430 - 0.400***	***0.240 - 0.320***	***1.19 - 1.27***
Total body	**0.200 - 0.150**	**0.110 - 0.140**	**0.02 - 0.02**
Effective dose	**0.200 - 0.190**	**0.130 - 0.160**	**0.03 - 0.10**

API=active pharmaceutical ingredient; LLI=lower large intestine; F=female; M=male; mSv=millisievert; ULI=upper large intestine.
In ***bold italic***, organs with the highest absorbed dose coefficients

Currently, no data from human use are available under controlled study conditions. Under full medical responsibility of Professor Baum (see Section 1.4), CCI subjects with either pancreatic adenocarcinoma (n=6), CCI [redacted] have been administered a low dose of ^{177}Lu-3BP-227 (approximately 1 gigabecquerel (GBq)). Among them, five pancreatic ductal adenocarcinoma (PDAC) subjects CCI [redacted] have shown a good tumour uptake after imaging without safety concern. CCI subjects had further administration of 5.1 to 7.5 GBq with therapeutic intention (see Section 1.4).

1.3.5 Pharmacodynamic Effect In Vivo Study

The potential efficacy of ^{177}Lu-3BP-227 has been investigated in an NTSR1-expressing tumour model in mice (HT29 xenograft model in nu/nu mice). ^{177}Lu-3BP-227 was administrated at two different doses (100 and 160 MBq) 7 days after tumour cells inoculation in mice (HT29 human colon carcinoma xenograft implanted in nude mice) and one control mice group received a vehicle. The results showed a dose-dependent tumour growth control for 3 or 5 weeks, without any overt signs of toxic effects [2].

Please see investigator brochure (IB) for more detailed information.

1.4 Clinical Data

In a preliminary salvage therapeutic administration (compassionate use with non-registered medicinal product) , under full medical responsibility of Professor Baum at the Zentralklinik Bad Berka in Germany, hereinafter referred to as "individual clinical treatment use" CCI subjects received ^{177}Lu-3BP-227: Six subjects with PDAC, CCI [redacted] [3].

Out of the six subjects with PDAC who were imaged with ^{177}Lu-3BP-227, five subjects had a good uptake in primary tumours and/or metastases following administration of 1.2 or 1.5 GBq

^{177}Lu-3BP-227 and one subject imaged with 1.5 GBq ^{177}Lu-3BP-227 had no uptake. These results are in line with the 75% of the PDAC expressing NTSR1 as described in the literature [4, 5]. Due to the advanced disease stage, most of the subjects did not have the opportunity to receive further administration in a range of therapeutic activity; three out of the five subjects with NTSR1-expressing tumours had post-imaging administrations.

Dosimetry calculations are available for three subjects. Subjects received diagnostic doses of 1.2 to 1.5 GBq. Only Subject 3 received therapeutic activities (of 6.4 GBq, 7.5 GBq and 5.5 GBq given intra-peritoneally). Kidneys were identified as dose-limiting organs, with absorbed doses ranging from 0.48 Gray (Gy)/GBq to 1.42 Gy/GBq. However, none of the reported subjects received a dose to the kidney that exceeded 23 Gy (highest absorbed renal dose of 22 Gy for a cumulative activity of 20.9 GBq). The specific absorbed doses to the bone marrow was low (0.09 to 0.10 Gy/GBq), as well as the absorbed dose in liver, GI tract, thyroid and urinary bladder, ranging from 0.06 Gy/GBq to 0.09 Gy/GBq. Moreover, the cumulative absorbed doses in these organs were below the organ radiation dose limits of 2 Gy, 35 Gy, 45 Gy, 45 Gy and 60 Gy respectively (ICRP publication 41).

Of interest, following initial administration of 1.5 GBq ^{177}Lu-3BP-227 to assess the tumour uptake and calculate the organ dosimetry, one of the subjects, Subject 3 who received three therapeutic administrations of 6.4, 7.5 and 5.5 GBq of ^{177}Lu-3BP-227 was considered a partial responder (per Response Evaluation Criteria in Solid Tumours (RECIST) and positron emission tomography (PET) Response Criteria in Solid Tumours (PERCIST) criteria). The administered cumulative activity of 20.9 GBq in this subject led to a total organ dose of 22.0 Gy to the kidneys. The haemoglobin of this subject remained low during and after treatment, with a short and reversible episode of Grade 2 anaemia before the last administration.

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Overall, no important safety concern was raised during administration during the individual clinical treatment use.

1.5 Rationale for the Study

The rationale for this phase I/II study is to use the NTSR1 overexpression as target to deliver screening and therapeutic radioactivity to tumour cells. Therefore, tumours with specific overexpression of NTSR1 will constitute the target tumour types for ^{177}Lu-3BP-227.

Previous radiopharmaceutical compounds (e.g. ^{177}Lu-DOTATATE, ^{177}Lu-DOTATOC) have been demonstrated as safe and effective in neuroendocrine tumour subjects [3, 7, 8].This treatment principle can be applied to ^{177}Lu-3BP-227 for the treatment of cancers with increased expression of NTSR1. ^{177}Lu-3BP-227 has been shown to be effective in a NTSR1-expressing xenograft model inhibiting tumour growth. Dosimetry data showed a low accumulation of radioactivity in the organs and an acceptable tumour to tissue radioactivity uptake. Considering the favourable toxicity profile in vitro and in vivo through targeting the NTS/NTSR1 complex and the first clinical evidence from an individual clinical treatment use under full medical responsibility of Professor Baum (see Section 1.4), radiotherapy with ^{177}Lu-3BP-227 may be particularly attractive as it may offer a treatment option, beyond the standard-of-care, for cancers such as PDAC, colorectal cancer (CRC), ES, gastric cancer (GC) and cancers of the head and neck, where there are still high unmet clinical and therapeutic needs.

Even though promising safety data were collected from the individual clinical treatment use (compassionate use with non-registered medicinal product), the safety, tolerability and efficacy of ^{177}Lu-3BP-227 treatment for cancers expressing NTSR1, needs to be assessed in a well-designed prospective clinical study.

The dose escalation part of the study has been designed to primarily investigate the safety, tolerability, dosimetry and preliminary antitumour activity of ^{177}Lu-3BP-227 following fractionated i.v. administrations in subjects with unresectable, locally advanced or metastatic cancers expressing NTSR1. In radiopharmaceutical studies, this safety assessment also includes dosimetry studies to evaluate the radioactive exposure of organs. To optimise the benefit-risk ratio, it is essential to identify the proper target population for therapy. In this study, the target population will be identified by assessing the tumour uptake following the screening administration of ^{177}Lu-3BP-227. Samples will be collected for biomarker exploratory analyses to investigate associations between biological and clinical parameters (e.g. better characterisation of potential responders, response to treatment, tolerability and safety).

For phase I (dose escalation), a statistical Bayesian modelling approach [9] may be implemented to produce a more precise dose-toxicity response curve and predict subsequent activity levels. The objective of the model is to predict activity ranges to be administered that, in combination with the dose escalation rules, remain below the maximum tolerated cumulative activity (MTCA) level in subjects.

Upon termination of dose escalation and/or determination of MTCA by the safety review committee (SRC), and based on the assessment of the preliminary antitumour activity, cohorts of subjects will be studied to further characterise safety and efficacy of ^{177}Lu-3BP-227. Antitumour activity of the ^{177}Lu-3BP-227 is expected to be observed from cohort 2 of the dose escalation part. In case of a weak antitumour activity across all indications and dose cohorts, it is anticipated that further clinical investigations (expansion part) will be needed with optimal radioactivity and small molecule mass determination as well as administration schedule determination in selected indications. The activity levels will be decided based on the safety and preliminary antitumour effect observed in the dose escalation part. The selection of the small-molecule/radionuclide ratio will be driven by data from nonclinical studies that will be conducted in parallel with the dose escalation part. Finally, the targeted populations might be reviewed in light of the tumour uptake, safety, tolerability and preliminary antitumour effects observed during dose escalation.

If a strong antitumour activity signal is observed during phase I, cohorts will be enrolled in the phase II part of the protocol immediately after the end of the dose escalation or dose expansion parts to assess the efficacy of ^{177}Lu-3BP-227.

In case of medium objective response rate (ORR), a substantial clinical benefit would be observed in selected indications. Based on the actual knowledge built from preclinical studies, an individual clinical treatment use (see Section 1.4) and tissue/cancer expression of NTSR1, it is planned to rapidly enrol cohorts in PDAC and CRC in a Simon Two-Stage design. Pancreatic ductal adenocarcinoma is the most common form of pancreatic cancer and constitutes 90% of all cases. It is a highly aggressive tumour with an overall 5-year survival rate of less than 5%, [10] and between 1% to 3% after the second stage [11]. Pancreatic ductal adenocarcinoma, the worst of all malignancies, is predicted to be the second leading cause of cancer-associated mortality within the next 5 to 10 years [12, 13]. This poor overall survival (OS) for subjects with pancreatic cancer is mainly due to a lack of biomarkers to enable early diagnosis and a lack of prognostic markers that can inform decision making and facilitate personalised treatment and an optimal clinical outcome [14]. The overexpression of NTSR1 by PDAC tumoural tissue offer a new promise to demonstrate the safety and efficacy of a NTSRI targeted radiopharmaceutical such as ^{177}Lu-3BP-227. This hypothesis is well supported by the results of

preclinical data (see Section 1.7) as well as by clinical data from an individual clinical treatment use (see Section 1.4).

Metastatic CRC (mCRC) constitutes another pressing unmet need, when current available treatment options are exhausted. Colorectal cancer is currently the second most commonly diagnosed cancer in Europe and the second leading cause of cancer-related death in the United States [15, 16]. Despite significant progress in the treatment of mCRC during the past two decades, the prognosis of subjects with mCRC remains poor, with a 5-year survival rate of approximately 13% [17, 18]. Although a subset of subjects with liver and/or lung isolated disease is potentially curable with surgery, for other subjects with mCRC, treatment is palliative and generally consists of systemic chemotherapy [19, 20]. ^{177}Lu-3BP-227 could be investigated in those subjects who have received prior lines of standard-of-care chemotherapy/treatment and have no further suitable treatment options and their tumour tissue overexpresses NTSR1, knowing that the percentage of CRC tumours expressing NTSR1 is very high, with high degree of expression (see Section 1.7). Moreover, the nonclinical data generated from an NTSR1 expressing tumour model in mice (HT29 xenograft model in nu/nu mice) are supportive of further investigating ^{177}Lu-3BP-227 in mCRC (see Section 1.3.5).

In case of high ORR, it would suggest that the NTSR1 target is the main driver for antitumour activity. In this particular situation, a basket single-arm trial will be conducted to further characterise the efficacy of ^{177}Lu-3BP-227 in the context of the multiple indications. This innovative approach would provide rapid access of the investigational medicinal product (IMP) to subjects with great medical need.

1.6 Selection of Dosage

The radioactivity range (5 to 15 GBq) applied in this study is derived mainly from previous experiences with ^{177}Lu-DOTATATE [21], although some caution should be applied as it refers to other radiolabelled compounds in other indications. In addition, data from an individual clinical treatment use (see Section 1.4) of ^{177}Lu-3BP-227 support the dose range selection and is endorsed by the dosimetry studies performed with the IMP in rats and dogs.

In the phase I dose escalation part of this first in human (FIH) study, 5 GBq fractionated into two administrations (2×2.5 GBq) will be used as starting radioactivity. In radiotherapy, fractionation of the cumulative activity is done for safety and tolerability reasons. Based on the biodistribution data obtained in nontumour bearing rats and dogs and consequent allometric calculation for human exposure and taking the most conservative approach, administration of 5 GBq leads to an organ dose of 0.8 Gy for the bone marrow and 1.4 Gy for the kidneys. These organ doses are more than 50% below the organs dose limits of 2 Gy and 23 Gy, respectively. In an individual clinical treatment use (see Section 1.4), four subjects received single administration of 5 GBq without reporting of adverse events (AEs) >Grade 2.

During dose escalation, it is planned to not exceed the cumulative activity of 15 GBq activity (2×7.5 GBq). However, if the MTCA is not reached and if limiting organ dose levels are not exceeded, an additional cohort with three administrations at 7.5 GBq may be added, leading to a cumulative activity of 22.5 GBq. The dosage used in the dose expansion part will be based on the results obtained from the dose escalation part and from the modelling and simulation approach. Similarly, results generated during the dose expansion part will drive the dosage that will be used in phase II. In any case, subjects will be administered with cumulative activities that may be either the MTCA determined in the escalation part or a lower dose with near optimal activity.

In this study, 25 µg (22.1 nmol) of 3BP-227 per 1 GBq ^{177}Lu will be used. This radioactivity-small-molecule ratio was used in an individual treatment use (see Section 1.4) and yields a specific activity of approximately 45 MBq/nmol, which is routinely achieved with -DOTA-conjugated compounds and is considered clinically acceptable [21, 22].

In Table 2, the safety margins for each species are presented based on the human equivalent dose calculated from body surface area as per Food and Drug Administration (FDA) Guidance for Industry "Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers" [23]. The small-molecule 3BP-227 has been administered within a nonclinical safety program carried out in rats and dogs following a single administration. The NOAELs determined in the rats and dogs were 2 mg/kg and 1 mg/kg, respectively. Compared to the animal studies, a wide safety margin is observed (based on the most sensitive species, a safety factor margin of more than 300 for the starting dose activity and more than 100 for the targeted maximum radioactivity). At the dose range of 3BP-227 used in this study, no pharmacological effect is expected.

Table 2 Estimated Safety Margin in Study/Species based on Human Equivalent Dose Calculated Based on Body Surface Area

Study	Dose/activity	HED of 3BP-227	Estimated safety margin for 3BP-227 [a]
Study phase I/IIa	**Starting dose:** 2.5 GBq of ^{177}Lu-3BP-227 Corresponding to: • A total of 62.5 µg of 3BP-227 (2.5×25µg) per administration • **1 µg/kg** of 3BP-227 per administration **Maximal dose:** 7.5 GBq of ^{177}Lu-3BP-227 Corresponding to: • A total of 187.5 µg of 3BP-227 (7.5×25 µg) per administration • **3.1 µg/kg** of 3BP-227 per administration		
Single dose rat Study 763.321.4274	NOAEL (3BP-227)=**2 mg/kg**	**0.322 mg/kg**	**Starting dose:** 322 times below NOAEL **Maximal dose**: 104 times below NOAEL
Single dose dog Study 763.323.5173	NOAEL (3BP-227)=**1 mg/kg [b]**	**0.556 mg/kg**	**Starting dose:** 556 times below NOAEL **Maximal dose:** 179 times below NOAEL

HED=human equivalent dose; NOAEL=no observed adverse events level.

a based on HED and on body surface area (divided by 1.8 for dogs and 6.2 for rats)
The calculations are based on the following basis: 1 GBq/25 µg 3BP-227 and human body weight of 60 kg

b 2 mg/kg 3BP-227 was tested in study 763.323.5173 and was considered within the Maximum Tolerated Dose due to slight transient increase in QT interval. A safety pharmacology study tested 1mg/kg 3BP-227 did not show any adverse cardiovascular effect. The NOAEL of 1 mg/kg 3BP-227 is derived from the combination of these two studies.

Rationale for use of ^{177}Lu labelling for Screening Purposes and as a Threshold for Radiodiagnosis

^{177}Lu is a beta (β)- and gamma (γ)-emitting radionuclide. It is a medium-energy β emitter with a maximum energy of 0.498 MeV and maximum and mean soft-tissue penetration depths of 1.7 mm and 0.23 mm, respectively. The $t_{1/2}$ is 6.7 days (159.5 hours). ^{177}Lu also emits low-energy γ-rays at 208 and 113 KeV with 11% and 6% relative abundance, respectively, which allows scintigraphy and subsequent dosimetry with the same product. The radiochemical physical characteristics of ^{177}Lu are described in Table 3 [21].

^{177}Lu presents the advantage of emitting just enough γ radiation for quantitative imaging necessary for dosimetry calculation while the β radiation induces the therapeutic effect.

For imaging purposes, the γ emission of ^{177}Lu is accompanied by the additional radiation burden of β emission of ^{177}Lu. Therefore, when radiotherapy is not required, the administration of ^{177}Lu may deliver an undesirable radioactivity to the subject. However, the theranostic potential of ^{177}Lu outweighs the above disadvantage particularly in advanced malignant tumours and avoids the uncertainties that may occur from the use of different isotopes with different kinetics that could result in less accurate dosimetry planning.

Table 3 Radiochemical Physical Characteristics of ^{177}Lutetium

Physical half-life t½	6.65 days
Decay product	^{177}Hf
Maximum β-particle energy	0.498 MeV
Mean β-particle energy	0.133 MeV
Median tissue penetration	0.23 mm
Max. tissue penetration	1.7 mm
Main gamma emission lines	113 keV (6%) 208 keV (11%)

The administration of 1.00±0.1 GBq ^{177}Lu-3BP-227 is considered adequate to ensure a good uptake at tumour level for dosimetry based on a similar application scheme used by Wild et al. [24] for the evaluation of ^{177}Lu-DOTA-JR11 and will thus be used in this study for screening purpose, after all other required screening assessments have been completed.

A lower radioactivity administration would lead to longer acquisition time and a poor diagnostic signal (with an increase in signal noise to background ratio) associated with the risk of missing subjects who would be eligible for participation in the study and could benefit from the treatment.

1.7 Population to be Studied

In this FIH study, the subject population enrolled to receive the IMP will be restricted to PDAC, CRC, GC, GIST, squamous-cell carcinoma of head and neck (SCCHN) and ES, which are unresectable, locally advanced or metastatic and expressing NTSR1. Due to the late metastatic or advanced stage of the disease and progression or failure of response to standard-of-care treatments, this subject population is expected to have a reduced life expectancy.

Tumours/metastases expressing NTSR1 will be identified and documented through the lesion uptake of ^{177}Lu-3BP-227 (at low dose) during the screening period. Subjects who participated in the imaging study, Study D-FR-01087-002, with ^{111}In-3BP-227 (also called ^{111}In-IPN01087) and who have an uptake of ^{111}In-3BP-227 in tumour lesions that is more avid than in the nontumoural surrounding tissue based on whole body imaging (planar scintigraphy), as judged by the investigator, can also be considered for enrolment in this study, provided that they fulfil all other inclusion criteria and do not meet any of the exclusion criteria and were imaged with ^{111}In-3BP-227 before the first treatment administration (therapeutic dose) of ^{177}Lu-3BP-227.

CCI [redacted]

In addition, published data also support these NTSR1 expression profiles in the targeted indications [4, 5, 25, 26, 27]. In the PDAC population, the NTSR1 was found expressed in 73% (8/11) of primary tumours and 63% (14/23) of the metastases. Interestingly, the expression of NTSR1 in the membrane compartment was only observed in tumour tissue (85%; 34/40) and never in normal tissue. In addition, a strong expression of NTSR1 messenger ribonucleic acid (mRNA) was found in 76% (19/25) of the cases of colorectal adenocarcinoma (resection material). Protein overexpression has been documented by immunochemistry in 71% (149/210) of GC samples. For ES, expression of NTSR1 in the membrane compartment has been found in 65% (11/17) of the resection tissue material [6].

The five study populations will be enrolled in the phase I dose escalation part. Based on tumour uptake, safety and preliminary antitumour effect (ORR), the number of study populations might be revised for the potential phase I expansion cohorts and phase II through a protocol amendment.

1.8 Known and Potential Risks to Human Subjects

This is the FIH study conducted with ^{177}Lu-3BP-227 under controlled conditions. The study will primarily evaluate the safety and tolerability of ^{177}Lu-3BP-227 but also its potential antitumour effect in subjects with advanced cancers expressing NTSR1. With the exception of an individual clinical treatment use (see Section 1.4), ^{177}Lu-3BP-227 has never been tested in humans, but has shown no relevant toxicological effects in the animal studies conducted with high safety margins. However, it cannot be ruled out that ^{177}Lu-3BP-227 could have adverse effects in the human population, which have not been detected in animal studies.

As this is the FIH study, the function of organs identified at risk will be checked as part the of exclusion criteria. Based on the current level of knowledge, those organs are bone marrow, kidney, large intestine, liver and urinary bladder. In conventional fractionated external radiotherapy, the experience is that an absorbed dose of 23 Gy to the kidney gives a 5% expected risk of nephrotoxicity within 5 years [28, 29, 30]. For the bone marrow, a maximum absorbed dose (MAD) of 2 Gy gives approximately a 2% risk of developing leukaemia as a long-term toxicity. In this study, the well-established 2 Gy for the bone marrow MAD and the more conservative approach with 23 Gy as MAD for the kidney will be applied.

Safety measures have been taken into consideration to minimise the risk. Each subject recruited across the sites may be hospitalised for 24 hours following administration for observation at the discretion of the investigator. The level of radioactivity will be monitored until it has fallen to safe levels for discharge, to protect medical personnel and relatives. Depending on the local

regulation, the subject will be hospitalised either in the nuclear medicine or regular oncology ward.

The participating subjects will be closely monitored during the study and during the long-term follow-up period until lost to follow-up, withdrawal of consent, death or a maximum of 5 years, whichever occurs first. Subjects may be withdrawn from the study at any time, if judged to be in their best interest by the investigator or upon the subject's wish. The study will be carried out in specialised clinical centres with nuclear medicine and medical oncology specialists.

An SRC will review the safety and dosimetry data on a continuous basis (see Section 4.2.1.4).

Subject-specific dosimetry will be performed on a regular basis for up to 96 hours after each administration to describe the uptake by the tumour and organs identified at risk over the entire course of treatment. The cumulative organ doses of kidney, bone marrow and liver will be monitored on an ongoing basis as for the other organs identified at risk. If a previous cumulative radioactive dose indicates that the organ limit will be exceeded with the next cycle, the activity of the next cycle will be reduced.

Detailed criteria, based on the percentage of subjects experiencing dose limiting toxicities (DLTs), have been carefully defined to provide guidance on the next radioactive dose selection.

The risks associated with this study are considered adequately elucidated and controlled well by planned cautionary measures in the study design and the target population as well as with the potential benefit of the treatment.

2 STUDY HYPOTHESIS

The present study consists of two parts that aim to test the following hypotheses:

2.1 Phase I

^{177}Lu-3BP-227 is sufficiently well-tolerated to permit clinical investigation in phase II.

2.2 Phase II

^{177}Lu-3BP-227 yields higher objective response rates in subjects who have NTSR1 expressing cancers that are unresectable, locally advanced or metastatic based on RECIST version 1.1 by central review and as compared with the historical ORR obtained by current standard-of-care treatment for each tumour type.

3 STUDY OBJECTIVES

3.1 Primary Objectives

3.1.1 Phase I

To establish the safety and tolerability of fractionated i.v. administrations of ^{177}Lu-3BP-227 in subjects with unresectable, locally advanced or metastatic cancers expressing NTSR1.

3.1.2 Phase II

To estimate ORR of fractionated i.v. administrations of ^{177}Lu-3BP-227 in subjects with unresectable, locally advanced or metastatic cancers expressing NTSR1.

3.2 Secondary Objectives

3.2.1 Phase I

(a) To determine the whole-body distribution of ^{177}Lu-3BP-227 and PK of both ^{177}Lu-3BP-227 and 3BP-227.

(b) To determine the radiation dosimetry of ^{177}Lu-3BP-227 (organ exposure to radiation).

(c) To describe the preliminary antitumour activity of ^{177}Lu-3BP-227.

3.2.2 Phase II

(a) To further evaluate the safety profile of ^{177}Lu-3BP-227 at the radioactivity recommended by the phase I results.

(b) To further assess the response to treatment with ^{177}Lu-3BP-227 using RECIST version 1.1 and/or PERCIST version 1.0 criteria.

(c) To further characterise the whole-body distribution and dosimetry of ^{177}Lu-3BP-227 and PK of both ^{177}Lu-3BP-227 and 3BP-227.

(d) To describe the influence of ^{177}Lu-3BP-227 on the health-related quality of life of treated subjects.

3.3 Exploratory Objectives

3.3.1 Phase I/II

(a) To explore the correlation between the tumour uptake of ^{177}Lu-3BP-227 and the NTSR1 expression on tumours.

(b) To explore renal safety by measuring urinary specific biomarkers.

(c) To evaluate the tumour microenvironment, transcriptomics and other markers of interest for the disease through assessment of tumour biopsies.

(d) To explore genomic alterations in circulating cell-free DNA (cfDNA) and in germline DNA.

(e) To collect gene mutation status for correlation with clinical outcome.

(f) To collect biobank samples for future analysis of circulating markers (optional; additional informed consent required).

(g) To generate a model integrating PK, dosimetry, antitumour activity and safety data.

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is a multicentre, open-label phase I/II study of ^{177}Lu-3BP-227 in subjects with unresectable, locally advanced or metastatic solid tumours expressing NTSR1 who have progressed after their available standard-of-care treatment options and/or are deemed suitable for the treatment with ^{177}Lu-3BP-227 as per the investigator's clinical assessment and/or their

individual disease state. The study consists of a phase I dose-escalation (and potential expansion cohorts) and a phase II assessing the efficacy of ^{177}Lu-3BP-227 in subjects with unresectable, locally advanced or metastatic solid tumours expressing NTSR1.

4.2 Phase I

4.2.1 Dose Escalation

Phase I will consist of a radioactivity escalation part with the objective of determining the MTCA. For phase I, subjects enrolled will have unresectable, locally advanced or metastatic tumours expressing NTSR1 originating from either the pancreas (PDAC), colon and rectum (CRC), stomach (GC), gastrointestinal stromal tumours (GIST), head and neck region (SCCHN) or bone (ES).

The study screening period includes a screening administration of ^{177}Lu-3BP-227 to assess the tumour uptake of each subject by whole body scan (planar scintigraphy, 1 or 2 timepoint(s) at the investigator's discretion) and optional single photon emission computed tomography (SPECT)/CT scans (up to 2 at the investigator's discretion). Only subjects with a tumour uptake higher than nontumoural surrounding tissue (based on investigator's decision) will be deemed eligible for treatment. The screening period will last 3 weeks but can be extended by up to 2 weeks if this is required for logistical reasons. Subjects who participated in the imaging study, Study D-FR-01087-002, with ^{111}In-3BP-227 (also called ^{111}In-IPN01087) and who have an uptake of ^{111}In-3BP-227 in tumour lesions that is more avid than in the nontumoural surrounding tissue based on whole body imaging (planar scintigraphy), as judged by the investigator, can also be considered for enrolment in this study, provided that they fulfil all other inclusion criteria and do not meet any of the exclusion criteria and were imaged with ^{111}In-3BP-227 before the first treatment administration (therapeutic dose) of ^{177}Lu-3BP-227.

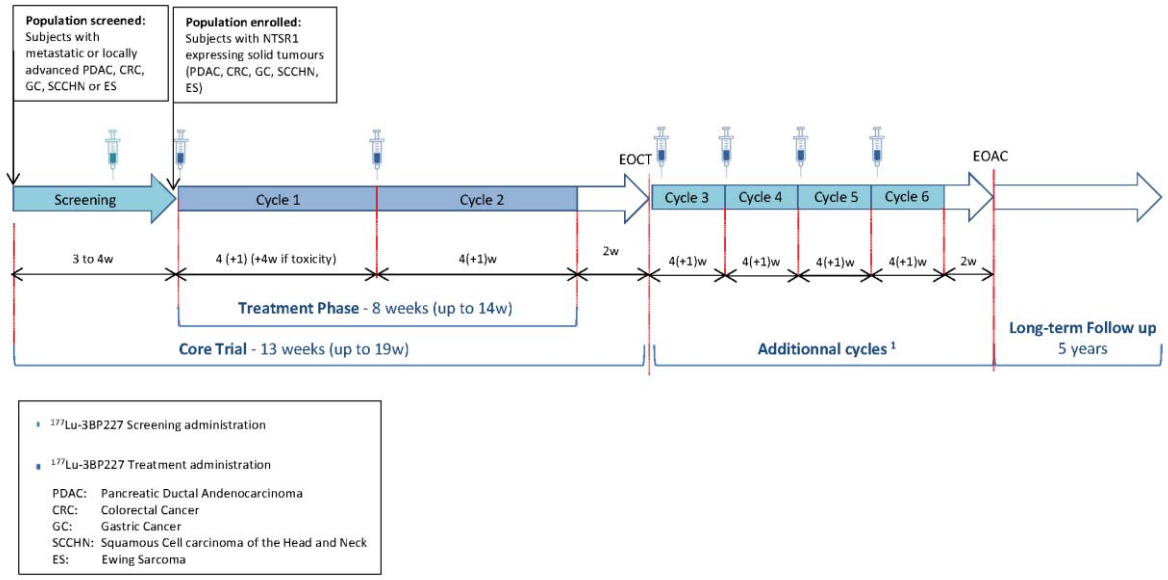
During the treatment phase, it is planned that each subject will receive ^{177}Lu-3BP-227 fractionated into two i.v. administrations separated by 4 to 5 weeks (+4 weeks in case of reversible AEs) (Figure 1). The safety evaluation will be done over 4 weeks between Cycle 1 and Cycle 2 and over 6 weeks between Cycle 2 and end of core trial (EOCT). During this period, subjects will have repeated imaging for the calculation of individual dosimetry data and will be monitored for signs of toxicity.

Tumour response will be assessed on CT or MRI, as well as with ^{18}F-FDG-PET scans at the EOCT visit, (corresponding to 6 weeks after the second administration).

Subjects may receive up to four additional administrations of ^{177}Lu-3BP-227 after the EOCT, if they have clinical benefit and an acceptable tolerability profile and if the organ dose limits are not exceeded. The safety data evaluation will be conducted by the sponsor. The decision to administer additional cycles is based on the investigator's judgement and subject's discretion and must be discussed with and agreed upon by the sponsor. The clinical benefit will be defined as complete responder (CR), partial responder (PR) or stable disease or based on their biochemical response.

A long-term follow-up period will start after the EOCT, early discontinuation (ED) or end of additional cycles (EOAC) visit and subjects will be followed up every 3 months (±2 weeks) until lost to follow-up, withdrawal of consent, death or a maximum of 5 years, whichever occurs first.

Figure 1 Phase I Study Design Scheme



Note: Population screened includes subjects with unresectable disease.
[1]Additional cycles are optional depending on the clinical benefit observed in the subjects during the core trial, as well as on the toxicities and organ absorbed doses.

4.2.1.1 Definition of the MTCA

Several radioactivity amounts of ^{177}Lu-3BP-227 are planned to be tested according to an adaptive radioactivity escalation plan. Each subject will only participate in one part of the protocol. The purpose of the radioactivity escalation part is to determine the MTCA. If not feasible, the maximum tolerated single activity (MTSA) or the maximum administered cumulative activity (MACA) will be determined according to the situation below:

- The MTCA is defined as the maximum tolerated cumulative activity that may be administered following fractionated i.v. administrations of at least 4 weeks apart, so that:
  - No more than 33% of the subjects experience a DLT during Cycles 1 and/or 2 (see DLT definition in Section 4.7.1.1), and
  - The cumulative radiation in each target organ does not exceed the acceptability limits (see Section 4.7.1).
- The MTSA is defined as the highest single radioactivity that can be given so that no more than 33% of the subjects experience a DLT during Cycle 1. The MTSA will be determined in case of unacceptable toxicity seen after Cycle 1.
- The MACA will be determined if the MTCA is not reached during the dose escalation part.

4.2.1.2 Cohorts Description

The dose escalation part will be conducted over five cohorts from a starting cumulative activity of 5 GBq up to a maximum cumulative activity of 15 GBq, fractionated into two administrations of 2.5 GBq and 7.5 GBq respectively.

The size of the cohorts will be three to five treated subjects, to secure a minimum of three evaluable subjects per cohort who completed 2 cycles of treatment. A cohort will be considered as completed once three subjects of the cohort complete Cycle 2 or early discontinue during Cycle 2 (except for cohort 1, see *Proceeding to the Next Cohort* described in Section 4.2.1.4). If a subject replacement is needed to complete the cohort enrolment, see Section 4.7.1.3 for replacement rules.

For safety reasons, the first three subjects of a cohort will be administered sequentially, one week apart to allow a sufficient observation period for any adverse reaction.

4.2.1.3 Dose Escalation Mode

Dose escalation is planned to proceed in two steps, with two different increments for the radioactivity escalation. In the first step, in order to minimise the number of subjects receiving subtherapeutic activity, the inter-cohort radioactivity escalation will be performed by increment of 3 GBq (1.5 GBq per administration), up to the first study drug related treatment-emergent AE (TEAE) (Grade 2 or higher, except hair loss) or until a DLT occurs. Afterwards, the maximum increment will be reduced to 2 GBq (1 GBq per cycle) for all subsequent cohorts if dose escalation is allowed. However, even if no Grade 2 or higher AE are observed up to a cumulative activity of 11 GBq, radioactivity will be increased by 2 GBq (1 GBq per cycle).

Table 5 illustrates the escalation plan based on the escalation scheme defined above. However, if DLTs are reported, a statistical Bayesian modelling approach will be implemented to produce a more precise dose-DLT curve to guide the dose selection (see details in Attachment 5, Section 19.5) and predict an activity not exceeding the MTCA/MTSA that could be tested in the next cohort.

Table 5 Cohorts and Radioactivity Escalation Plan

Planned radioactivity escalation	Cohort 1	Cohort 2	Cohort 3	Cohort 4	Cohort 5
Cumulative	5 GBq	8 GBq	11 GBq	13 GBq	15 GBq
Per cycle	2.5 GBq/C	4 GBq/C	5.5 GBq/C	6.5 GBq/C	7.5 GBq/C

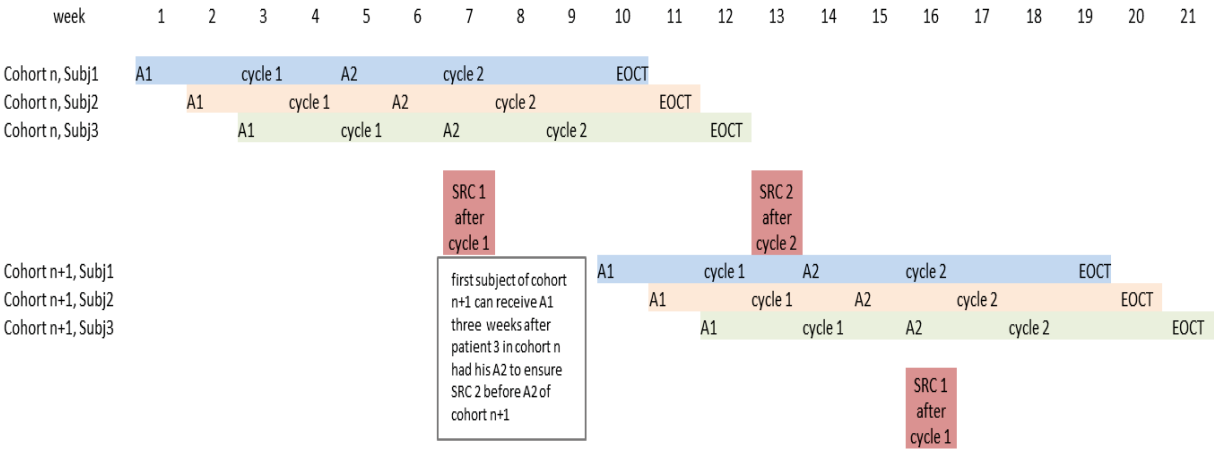
C=cycle; GBq=gigabecquerel.

Once the dose escalation has been completed, the MTCA level may be repeated in a last cohort (see Section 4.2.1.4 for stopping rules and Section 4.2.1.1 for MTCA definition). If the MTCA is not reached and if limiting organ dose levels are not exceeded at the highest planned activity (2×7.5 GBq) and if no individual withdrawal criteria are met, an additional cohort (Cohort 6) with three administrations at the highest single administration level may be added (3×7.5 GBq).

4.2.1.4 Safety Review Committee

The SRC will review the safety and radiation exposure data and jointly decide with the sponsor whether to proceed with the enrolment of the next cohort dose level and the second dosing cycle within a cohort. For this purpose, the SRC will be composed of all phase I investigators, who have treated at least one subject in the study cohort with study medication, one independent expert, a dosimetry expert evaluating the dosimetry data of the study (from a centralised dosimetry centre) and at least one sponsor representative. Regular meetings will be held. A specific charter will be developed to define roles and responsibilities, as well as the dataset to be reviewed by the SRC and the review timepoints.

Figure 2 Flow of Dose Escalation Cohorts and SRC Meetings



A=administration of study compound; EOCT=end of core trial; SRC=Safety Review Committee.
SRC1=Decision on start of next cohort
SRC2=Confirmation or adjustment of A2 in next cohort

Proceeding to the Next Cohort

At the time of radioactivity escalation, the available clinical safety and radiation exposure information will be reviewed and discussed by the SRC to jointly decide with the sponsor if the escalation can proceed as planned.

For each cohort, an SRC meeting will be held after the end of the third subject's Cycle 1. If during that observation period (after the first administration) no DLT occurs and all three subjects can receive the full radioactivity level (RL) as planned for the respective cohort (i.e. all three subjects can receive the second administration), the next cohort can be started with the first administration of the first subject at the earliest 3 weeks after the third subject of the previous cohort has received the second administration. No more than two dose-escalation cohorts will be conducted in parallel (Figure 2). If a DLT occurs after the first administration in cohort n, cohort n+1 will only be started after the second SRC (2nd administration) of the cohort n.

Due to the possible subtherapeutic activity of the lowest dose, the escalation decision to the planned dose of 4 GBq/cycle in Cohort 2 will be taken if only one subject from Cohort 1 has received the second administration without any safety problems at the end of the second cycle (i.e. at Cycle 2 Day 29, see Figure 2).

Proceeding to the Second Administration in a Cohort

For each cohort, a SRC meeting will be held after the end of the third subject's Cycle 2 of the preceding cohort and before the second administration of the first subject in a cohort, (Figure 2) to review all available safety data and radiation exposure from previous cohort(s). The second radioactivity administration will be confirmed based on the rules described in Attachment 5, Section 19.5.

Stopping Rules for Dose Escalation

The MTCA is defined in Section 4.2.1.1.

The radioactivity escalation will be stopped as soon as:

- The MTCA and/or MTSA have been defined with good precision; or
- The maximum planned radioactivity of 15 GBq, fractionated into two administrations separated by 4 weeks, is administered without safety concerns.

Transition from Dose Escalation to Other Study Parts

Upon completion of the phase I dose escalation or upon reaching the MTCA and confirmed jointly by the SRC and the sponsor, and in consideration of the accumulated subject data, cohorts of subjects will be studied to further characterise the safety and efficacy of ^{177}Lu-3BP-227. In the case of acceptable tolerability and evident antitumour activity across all enrolled subjects in phase I, a phase II basket trial design will be utilised to study the antitumour activity of ^{177}Lu-3BP-227 in subjects with NTSR1 expressing tumours. However, if the antitumour activity is driven by a certain type of tumour, tumour-specific phase II cohort(s) will be initiated utilising an Optimal Simon's Two Stage design (see Section 4.3).

4.2.2 Dose Expansion

If safety evaluation and dose schedules of ^{177}Lu-3BP-227 cannot be fully explored during the phase I dose escalation part, a phase I expansion part will serve to accomplish this objective including, but not limited to, schedules of high loading doses followed by fractionated lower doses or evaluation of ^{177}Lu-3BP-227 in combination with other antitumoral treatments (to be defined). The expansion part will also serve to clarify any uncertainties of antitumour responses.

The number of cohorts and subjects will be determined based on emerging data from the dose escalation part and the modelling and simulation approach, and will be documented as part of a protocol amendment.

4.3 Phase II

Phase II study will be conducted either with a basket design trial or indication-specific cohorts with an Optimal Simon's Two Stage design, according to the scenarios described above.

CCI [redacted] One, two or three further cohorts may be initiated (subject to results emerging from ongoing preclinical studies and antitumour efficacy seen during dose escalation and amending the current protocol) likely to enrol subjects with GC, ES and/or SCCHN.

- The PDAC cohort will enrol approximately 55 subjects and will investigate whether ^{177}Lu-3BP-227 attains an ORR superior to a clinically accepted historical threshold of current standard-of-care treatment for subjects with unresectable, locally advanced or metastatic disease.
- The CRC cohort will enrol approximately 70 subjects and will investigate whether ^{177}Lu-3BP-227 attains an ORR superior to a clinically accepted historical threshold of current standard-of-care for subjects with unresectable, locally advanced or metastatic disease.

The current protocol will be amended at the end of the phase I to document the rationale of the phase II design. In any case, the cumulative activity administered during phase II will not exceed the MTCA determined during phase I.

Sample size calculation for cohorts other than PDAC and CRC will be documented as part of a protocol amendment.

4.4 Study Endpoints

4.4.1 Primary Endpoint

4.4.1.1 Phase I

For the dose escalation, the primary endpoint is MTCA or MACA, if the MTCA is not identified during the dose escalation part. The primary variables used for the MTCA determination will be the incidence of DLTs (as defined in Section 4.7.1.1) and the organ exposure to radiation during two cycles of treatment. The DLT period for the determination of the primary endpoint

starts at the first administration of ^{177}Lu-3BP-227 to EOCT/ED. Safety evaluation will encompass DLTs, frequency and nature of AEs, abnormal findings from physical examination, vital signs, 12-lead electrocardiogram (ECG), 3-lead ECG Holter, Eastern Cooperative Oncology Group (ECOG) performance status deterioration, clinical laboratory tests (including haematology, blood biochemistry, hormone analysis, urinalysis and pregnancy test) and changes in specific renal safety biomarkers.

In case the phase I dose expansion cohorts are implemented, the primary endpoint will be safety and tolerability measured by the type, severity, expectedness and frequency of AEs.

4.4.1.2 Phase II

The primary endpoint is ORR measured by CT or MRI using RECIST version 1.1. Tumour response assessments are performed every 8 weeks or at the time of occurrence of first signs of clinical progression as determined by the investigator.

4.4.2 Secondary Endpoints

4.4.2.1 Phase I

For biodistribution and dosimetry of ^{177}Lu-3BP-227, the secondary endpoints are:

- Maximal uptake (%), maximal concentration achieved (C_{max}); time post injection to achieve maximal concentration (T_{max}); AUC at the target lesions, discernible organs and blood; $t_{1/2}$ of activity concentrations in blood;
- Highest absorbed dose, specific absorbed dose to the target lesions (Gy/GBq), specific absorbed dose per organ (Gy/GBq) and cumulative absorbed organ doses (Gy).

For PK of 3BP-227, the secondary endpoints are:

- PK parameters including, but not limited to, C_{max}, AUC, $t_{1/2}$, CL, V_d, cumulative amount of unchanged drug excreted into the urine (Ae), renal clearance of the drug from plasma (CL_R), as measured in plasma and urine at defined timepoints.

For pharmacodynamics, the secondary endpoints are:

- Objective response rate and DCR, as determined by RECIST version 1.1 in subjects who received IMP;
- Progression-free survival (PFS) and OS rates as determined from start of study treatment until occurrence of event and/or end of observation period;
- Evaluation of metabolic tumour response using PERCIST (version 1.0) or practical PERCIST;
- Changes in serum tumour markers relevant and specific to the underlying tumour disease from baseline to EOCT, which is planned 6 weeks after the second ^{177}Lu-3BP-227 dose administration.

4.4.2.2 Phase II

The secondary endpoints are:

- Disease control rate, time to progression (TTP), time to response (TTR), duration of response (DOR) as per RECIST version 1.1;
- Qualitative and quantitative changes in tumour-to-background uptake using PERCIST version 1.0;
- Progression-free survival (PFS) and OS as determined from start of study treatment until occurrence of event and/or 6 and 12 months after start of study treatment;
- Changes in serum tumour markers relevant and specific to the underlying tumour disease from baseline to EOCT;

- Changes in health-related quality of life scores from baseline to EOCT measured by validated and disease-specific questionnaires;
- Safety and tolerability measured by the type, severity, expectedness and frequency of AEs;
- For PK, biodistribution and dosimetry, the endpoints will be similar as for phase I.

4.4.3 Exploratory Endpoints

Exploratory endpoints are the same for phase I and II:

- Tumour uptake of ^{177}Lu-3BP-227 and the correlation with NTSR1 expression on tumour biopsies;
- Tumour microenvironment and other markers of interest (such as NTSR1 expression, Ki67, gene expression and DNA damage) in tumour biopsies taken at baseline, at EOCT visit or at disease progression, whichever occurs earlier;
- Genomic profiling in circulating cfDNA and in germline DNA;
- Gene mutation status in correlation with clinical outcome;
- Specific renal safety biomarkers specific for proximal tubulus toxicity.

4.5 Study Duration

For phase I, the maximum duration of subject participation in the core trial is 21 weeks. However, if, according to the investigator, a subject has clinical benefit, the subject may receive up to four additional cycles after the EOCT, provided they have an acceptable tolerability profile and the organ dose limits are not exceeded. This is at the subject's discretion and must be discussed and agreed upon with the sponsor. The clinical benefit will be defined as CR, PR or stable disease (SD) as per RECIST criteria version 1.1 or based on biochemical responses.

For phase I dose expansion and phase II, the study duration will be refined in light of phase I results and recommended treatment regimen (doses and intervals).

In all cases, a long-term follow-up period will start after the EOCT, ED or EOAC visit and subjects will be followed up every three months (±2 weeks) until lost to follow-up, withdrawal of consent, death or a maximum of 5 years, whichever occurs first.

4.6 Randomisation and Blinding

4.6.1 Method of Randomisation

4.6.1.1 Subject Unique Identifier

At screening, potential subjects will be allocated an 11-digit subject number consisting of:

- The country code (three digits);
- The centre number (three digits);
- The sequential order of entry of the subject at the centre (five digits).

4.6.1.2 Randomisation Number

Not applicable for phase I, as this is not a randomised study.

For the phase II, the protocol could be amended to include randomisation.

4.6.2 Blinding

Not applicable, this is an open-label study.

4.6.3 Code-break

Not applicable, this is not a blinded study.

4.7 Discontinuation Rules

4.7.1 Individual Discontinuation Rules

In accordance with the Declaration of Helsinki and the applicable country's regulations, each subject is free to withdraw from the study at any time and for any reason without prejudice to their future medical care by the investigator at the institution.

The investigator will be responsible for monitoring subject compliance. A subject can be withdrawn from the study at any time if the investigator or the sponsor determines that the subject is not in compliance with the study protocol.

The investigator has the right to withdraw a subject from the study in the event of concurrent illness, AEs, or other reasons concerning the health or well-being of the subject, or in the case of lack of cooperation.

If any of the following occur, no further treatment will be administered:

- life-threatening toxicities outside of the DLT reporting period
- subject withdraws their consent to further treatment;
- cumulative kidney dose exceeds 23 Gy;
- cumulative bone marrow dose exceeds 2 Gy, as determined by dosimetry of peripheral blood samples and imaging;
- cumulative liver dose exceeds 30 Gy;
- occurrence of a DLT for phase I dose escalation only (see Section 4.7.1.1).

All cases of discontinuation will be discussed between the investigator and the sponsor.

4.7.1.1 Definition of Dose Limiting Toxicity (Dose Escalation)

The DLTs are defined for any of the following IMP-related AEs according to National Cancer Institute - Common Terminology Criteria for Adverse Events (NCI-CTCAE) scale version 5.0 [31], that occur during the defined DLT assessment period (from the first administration of ^{177}Lu-3BP-227 to EOCT/ED):

- Grade 4 neutropenia for seven or more consecutive days;
- Febrile neutropenia or neutropenic infection (defined as a documented infection with neutrophil count decreased Grade 3 or 4);
- Grade 3 or 4 thrombocytopenia (platelet count decreased) with clinically meaningful bleeding (i.e. requiring urgent hospitalisation or transfusion to manage the bleeding);
- Grade 4 thrombocytopenia for seven or more consecutive days;
- Any Grade 3 anaemia (Hb<8.0 g/dL; transfusion indicated) or Grade 4 anaemia (life-threatening consequences; urgent intervention indicated);
- Any Grade 3 or higher laboratory abnormalities on aspartate aminotransferase/alanine aminotransferase (AST/ALT) with accompanying Grade 2 or higher bilirubin (Hy's law);
- any Grade 3 or higher renal injury/toxicity (estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2);
- Any Grade 3 or higher GI AE, not resolved to Grade ≤2 within 48 hours despite optimal adequate medical management, with the following specifications:
  - Grade 3 nausea, vomiting (inadequate oral caloric or fluid intake; tube feeding, total parenteral nutrition or hospitalisation indicated)
  - Grade 3 diarrhoea (increase of ≥7 stools per day over baseline; hospitalisation indicated; severe increase in ostomy output compared to baseline; limiting self-care activities of daily living (ADL)) or Grade 4 diarrhoea (life-threatening consequences; urgent intervention indicated)

- Grade 3 constipation (obstipation with manual evacuation indicated; limiting self-care ADL) or Grade 4 constipation (life-threatening consequences; urgent intervention indicated);

- Any toxicity related to ^{177}Lu-3BP-227 resulting in a treatment delay of more than four weeks due to either delayed recovery to baseline or resolution of any AE to Grade ≤2 (with the exception of alopecia and lymphopenia).
- Grade 5 toxicity (death)

4.7.1.2 Procedures for Subject Discontinuation

For subjects who discontinue participation in the study before the planned completion of therapy, it is intended that full end of study (EOS) assessments (see Section) will be performed and the subjects will be followed-up for AEs until the event or its sequelae resolve or stabilise at a level acceptable to the investigator and the sponsor's clinical monitor or his/her designated representative (see Section 8). If a subject drops out or is discontinued from the study after IMP administration and before planned study completion (either during the Core Trial period or if the subject is receiving additional treatment cycles), an ED visit will take place within 14 days after ED. The investigator determines this timepoint taking into account the expected safety profile and the current clinical status of the subject. This visit will correspond to an EOCT visit (or EOAC visit if the subject dropout during additional cycles). Thereafter, follow-up for survival information will take place every three months. For those subjects with ED, every effort should be made to perform a safety follow-up at the latest 5 weeks after the last IMP administration.

The reason for and date of withdrawal from the study must be recorded in the electronic case report form (eCRF).

If the discontinuation is based on subject decision, every attempt will be made to determine:

- The reason for discontinuation;
- Whether the subjects also decided to withdraw consent for the sponsor to collect and use the data collected up to the discontinuation point.

Data collected prior to subject discontinuation may be kept in study records and shared with the sponsor for study analyses (see Section 13), unless a subject formally specifies their decision to withdraw consent for the use of data collected before discontinuation.

Subjects withdrawn from the study for unacceptable AE(s) will be followed until resolution or stabilisation of the AEs.

4.7.1.3 Replacement Rules

In phase I, a cohort will be considered as completed once three subjects of the cohort complete Cycle 2 or discontinue early during Cycle 2 (except for Cohort 1). Except for Cohort 1, if subjects discontinue for any reason other than a DLT (e.g. disease progression) before end of Cycle 2, they may be replaced.

4.7.2 Discontinuation of a Cohort or a Site or Study Termination

A specific site or a given cohort can be discontinued or the complete study terminated prematurely at any time, if the sponsor judges it necessary for any reason. In that case, all scheduled procedures and assessments for subjects who are still in the study will be performed. Some possible reasons for the closure of a study site may include:

- failure of the investigator staff to comply with the protocol or with the GCP guidelines.
- safety concerns
- inadequate subject recruitment.

In case of premature discontinuation of a site or complete study termination, the sponsor will notify the impacted investigator(s) in writing, depending on the reason(s) for discontinuation, whether the ongoing subjects should undergo the remaining IMP dose administration(s).

5 SELECTION OF SUBJECTS

5.1 Inclusion Criteria

5.1.1 Phase I

Eligible subjects must fulfil all the following inclusion criteria:

(1) Signed informed consent form prior to all study procedures.

(2) Aged 18 years or older.

(3) Histologically or cytologically confirmed unresectable, locally advanced or metastatic disease and has received prior lines of standard-of-care chemotherapy/treatment and has no further suitable treatment options and a documented decision by a multidisciplinary oncology board including a specialist of the concerned pathology.

(4) Subjects have:
   (a) PDAC, or
   (b) CRC (colorectal adenocarcinoma), or
   (c) GC (gastric adenocarcinoma), or
   (d) Gastrointestinal stromal tumours (GIST), or
   (e) SCCHN, or
   (f) ES.

(5) Tumours showing:
   (a) uptake of ^{177}Lu-3BP-227 (screening formulation) in known primary or metastatic sites as judged by the investigator to be greater than background; or
   (b) uptake of ^{111}In-3BP-227 in known primary or metastatic sites (for subjects who participated in Study D-FR-01087-002) as judged by the investigator to be greater than background.

(6) Measurable disease (based on RECIST version 1.1).

(7) Criterion 7 is removed by protocol amendment.

(8) Documentation of progressive disease in the 6 months prior to study start (treatment).

(9) Eastern Cooperative Oncology Group performance status of 0 or 1 (unless disability is related to surgery in ES and agreed by the sponsor).

(10) Adequate organ function as evidenced by:
   (a) Leukocytes ≥3000/µL
   (b) Absolute neutrophil count ≥1500/µL
   (c) Platelets ≥75,000/µL
   (d) Hb >9 g/dL or >10 g/dL (if history of cardiac disease)
   (e) Total serum bilirubin ≤2 times upper normal institutional limits (ULN)
   (f) AST/ALT ≤2.5×ULN (or ≤5×ULN, if subject has liver metastases)
   (g) eGFR ≥55 mL/min.

(11) Estimated life expectancy of >3 months.

(12) Female subjects must not be pregnant or lactating at study entry and during the course of the study and must not become pregnant for at least 6 months following the last study treatment. Women of childbearing potential must agree to use a highly effective method of contraception (see note below).

(13) Male subjects must not father children during the study and for at least 6 months after the last study treatment and in addition must agree to use a condom for this period to

protect his partner from contamination with the IMP. For males with partners who are of child bearing potential, effective contraception is a combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods), but these are not considered to be highly effective. A man is considered to be infertile if he has had bilateral orchidectomy or successful vasectomy. Effective contraception includes a female partner of childbearing potential if she is using highly efficacious contraception (see note below), but the male subject must agree to use a condom to protect his partner as described above.

(14) Must be willing and able to comply with study restrictions and to remain at the clinic for the required time during the study period and willing to return to the clinic for the follow-up evaluation, as specified in the protocol.

Note: Highly effective methods of contraception that result in a low failure rate (i.e., <1% per year) when used consistently and correctly include combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal), progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, or implantable), intrauterine device, intrauterine hormone-releasing system, bilateral tubal occlusion, vasectomised partner (the vasectomised partner has received medical assessment of the surgical success at least 6 months prior to the first study treatment and provided that partner is the sole sexual partner of the female subject of childbearing potential trial participant), or sexual abstinence;

True abstinence, when in line with the preferred and usual lifestyle of the subject, is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of study treatment and for 6 months after the last dose of ^{177}Lu-3BP-227. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the subject. Periodic abstinence (e.g. calendar, ovulation, symptothermal, and post-ovulation method) and withdrawal are not acceptable methods of contraception;

Female subject is considered of childbearing potential i.e. fertile, following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

For male subjects, acceptable methods of effective contraception include sexual abstinence, successful vasectomy, bilateral orchidectomy and barrier methods (i.e. condom). In addition, male subjects should not donate sperm and female subjects should not donate eggs for at least 2 years after the last study treatment).

5.1.2 Phase II

The inclusion criteria for phase II will be revised based on the scenario adopted and indication(s) selected for investigation in phase II. This will be documented as part of a protocol amendment.

5.2 Exclusion Criteria (Phase I/II)

Eligible subjects must not have any of the following:

(1) Prior treatment received:

(a) Any antitumour treatment since last documented disease progression

(b) Any chemotherapy within 3 weeks or nitrosourea within 6 weeks prior to first treatment IMP administration

(c) Any curative radiotherapy within 4 weeks, or palliative radiotherapy within 7 days prior to first treatment IMP administration

(d) Any monoclonal antibodies within 4 weeks or tyrosine kinases inhibitors within 2 weeks prior to the first treatment IMP administration

(e) Any other IMP within 2 weeks prior to first treatment IMP administration, if the previous compound is a mechanism-based molecularly targeted agent whose $t_{1/2}$ is not well-characterised.

(2) Brain metastases.

(3) Nephrectomy, renal transplant or concomitant nephrotoxic therapy putting the subject at high risk of renal toxicity during the study.

(4) Only nonmeasurable metastatic bone lesions.

(5) Existing or planned colostomy during study participation.

(6) Any history of inflammatory bowel disease.

(7) Any uncontrolled significant medical, psychiatric or surgical condition or laboratory finding, that would pose a risk to subject safety or interfere with study participation or interpretation of individual subject results.

(8) Clinically significant abnormalities on ECG at screening including corrected QT interval (Fridericia's formula) >450 msec for males or 470 msec for females at screening.

(9) Previously received external beam irradiation to a field that includes more than 30% of the bone marrow or kidneys.

(10) Criterion 10 is removed by protocol amendment.

(11) Any unresolved NCI-CTCAE Grade 2 or higher toxicity (except alopecia) from previous antitumour treatment and/or medical/surgical procedures/interventions.

(12) Known allergy to IMP or its excipients administered in this study, including imaging contrast media.

(13) Positive pregnancy test (female subjects).

(14) Likely to be uncompliant or uncooperative during the study, in the judgment of the investigator.

(15) Unable to understand the nature, scope and possible consequences of the study, in the judgment of the investigator.

(16) Sponsor employees or investigator site personnel directly affiliated with this study, and their immediate families. Immediate family is defined as a spouse, parent, child or sibling, whether biological or legally adopted.

Eligibility criteria for phase II will be reviewed as soon as phase I results are available.

5.3 Rationale for Specific Inclusion/Exclusion Criteria

Not applicable

6 STUDY CONDUCT

6.1 Study Schedule of Assessments

The schedule of procedures and assessments is summarised and presented in Attachment 1 Section 19.1, related to the dose escalation part of the phase I. The total volume of blood to be drawn for each subject is detailed in Attachment 2, Section 19.2.

In the eventuality of phase I expansion cohorts and for phase II, the schedule of assessment will be adapted based on phase I results and documented through a protocol amendment.

6.2 Study Visits and Procedures

All screened subjects must be identifiable throughout the study. The investigator will maintain a list of all subjects screened, with subject numbers and names, to enable records to be found at a later date, if required. Records should be completed up to the time of premature termination or normal study completion. In the event that a subject is a screen failure or does not receive study treatment, the primary reason will be recorded. Subjects may be re-screened after discussion and agreement with the sponsor. The conditions for re-screening include re-assessment of inclusion criteria (6) and (10) at a later time point.

If the COVID-19 pandemic prevents subjects from coming to the site, subjects can have their study visit assessments performed remotely as judged appropriate by the investigator. This must be discussed with the sponsor before being implemented. In such a case, the investigator will perform a telemedicine visit and will make every effort, where applicable, to contact the subject's general practitioner or specialist physician to ensure all important medical information and safety event(s) occurring since the last visit are collected. Guidance on how to collect protocol-planned assessments will be provided to the investigator in a separate document. This document will be filed in the electronic trial master file. Independent ethics committees (IECs)/institutional review boards (IRBs) will be notified of the changes as applicable locally. Of note, as the adapted visit deviates from the regular protocol plan, the changes will be recorded as protocol deviations related to COVID-19.

6.2.1 Screening

Subjects will attend the clinical unit for an outpatient visit following which they will enter a screening period of 3 weeks prior to the first treatment administration. The screening period can be extended by up to two weeks if this is required for logistical reasons and agreed with the sponsor.

The screening IMP will be administered minimum 1 week prior to Day 1 after all other required screening assessments have been completed.

Subjects may be hospitalised for 24 hours following the screening IMP administration at the discretion of the investigator.

6.2.1.1 Informed Consent

After a subject has received explanations and response(s) to their potential questions about the study by the investigator (or designee) and has been given reasonable time to consider study participation, a signed and dated informed consent form will be obtained prior to any study procedures.

Subjects will be offered to participate to an optional research biobanking program. Subjects who agree to participate will be requested to sign a separate informed consent form.

6.2.1.2 Screening Procedures

After informed consent is obtained, screened subjects will be allocated a study-specific subject number, which must comply with formatting specifications provided by the sponsor (see Section 4.6.1.1).

During this initial screening visit, and subsequent ones, screening tests and assessments will be performed to check compliance with inclusion/exclusion criteria and study requirements in order to confirm subjects' eligibility prior to enrolment.

The screening procedures/evaluations detailed in Attachment 1, Section 19.1 will be performed during one or several outpatient visits.

The baseline assessment is the assessment done closest to Day 1 of the treatment administration (e.g. haematology and biochemistry, see Attachment 1 Section 19.1).

Evaluations obtained as part of routine medical care or previous assessments performed during (or before) the screening period may be used in place of the study specific evaluations. Subjects will acknowledge and agree to the possible use of this information for the study by giving informed consent.

For subjects who received the screening IMP administration and found ineligible to participate in the study, a physical examination, vital sign monitoring and clinical laboratory test assessment (as described in Attachment 3 Section 19.3) will be performed before discharge. Additionally, a safety follow-up visit or contact, whichever is feasible, will be performed within 5 weeks (+2 weeks) after the IMP screening administration to assess the safety (see Table 7). At least, clinical laboratory tests (e.g. haematology and biochemistry, as described in Attachment 3 Section 19.3), AEs and concomitant medication/therapy will be collected. If an on-site visit is not feasible, the visit may be performed by phone call. The clinical laboratory tests may be done locally.

6.2.2 Treatment Period and Additional Cycles for Phase I Dose Escalation

The visit descriptions in this section are relative to the phase I dose escalation part of the study. In case of phase I dose expansion and for phase II, these visits and timepoints will be amended in light of the phase I results.

After each administration of IMP/^{177}Lu-3BP-227, subjects may be hospitalised for at least 24 hours for observation at the investigator's discretion. Afterwards, subjects can be discharged when the radioactivity reaches an acceptable level as per local regulation. The subjects must return to the study centre for further evaluations per the schedule of assessment. All other visits will be outpatient. Subjects are to be observed on study and if the disease comes under control are to be kept on study; if the disease does not appear to come under control, the subject is to be removed from study and treated as clinically indicated.

6.2.2.1 Early Discontinuation or End of Core Trial Visit

Subjects who complete the core trial, i.e. subjects who receive two treatment administrations and who continue the study until 6 weeks after the second dose administration, will be considered as having completed the study.

Subjects who discontinue the study prior to the EOCT visit are considered as early discontinued subjects. The assessments required at the ED visit are the same as the assessments required at the EOCT visit.

Subjects with ongoing AEs or clinically significant laboratory test abnormalities (as determined by the investigator) will be monitored by the investigator as described in Section 4.7.1.

6.2.2.2 End of Additional Cycles

If, according to the investigator, a subject has clinical benefit, the subject may receive up to four additional cycles after the EOCT, provided they have an acceptable tolerability profile and the organ dose limits are not exceeded. This is at the subject's discretion and must be discussed and agreed upon with the sponsor. For these subjects, an EOAC visit will be done 6 weeks after last dose administration.

6.2.2.3 End of Study

End of study (EOS) is defined as the last visit or last scheduled procedure shown in the Schedule of Assessment for the last active subject in the study.

6.2.3 Long-term Follow-up

For both phase I and phase II, a long-term follow-up period will start after the EOCT, ED or EOAC visit and subjects will be followed up every 3 months (±2 weeks) until lost to follow-up, withdrawal of consent, death or a maximum of 5 years, whichever occurs first. During this period, if subjects do not receive any other chemotherapy or radiotherapy, they will be followed for the antitumour effect and long-term safety of the IMP. Otherwise, subjects will be followed for antitumour effect up to the administration of any other chemotherapy or radiotherapy and for the safety aspects (in particular for haematological and renal safety) for the remainder of the long-term follow-up period.

Five Years After the EOCT, ED or EOAC Visit

In the long-term follow-up period, subjects will be followed up every 3 months (±2 weeks) until lost to follow-up, withdrawal of consent, death or a maximum of 5 years, whichever occurs first. The following safety assessments will be performed by the site: these assessments can be performed on-site or by remote visit:

- Survival status
- Haematology and biochemistry tests (haemoglobin, platelet count, white blood cell count (absolute counts), AST, ALT, total bilirubin (with conjugated bilirubin if total bilirubin is abnormal i.e. outside the laboratory normal range), creatinine and urea) performed until the start of new antitumour treatment or up to 2 years after the EOCT, ED or EOAC visit, whichever comes first. Laboratory tests can be performed locally; results should be collected from the local laboratory.
- All AEs and serious adverse events (SAEs) are to be reported up to 6 months after the EOCT, ED or EOAC visit or until new antitumour treatment starts, whichever comes first. Thereafter, only AEs and SAEs related to the IMP or study procedure should be reported for the remainder of the safety follow-up period.
- Subsequent antitumour treatment

All collected data will be recorded in the eCRF.

6.2.4 Unscheduled Visits

Unscheduled visits or assessments may be necessary at any point during the treatment period to assess individual safety or tolerability. For example, laboratory assessments should be performed as clinically indicated during the study, tumour assessment could be performed whenever disease progression is suspected. Should an unscheduled visit or procedure listed in the schedule of assessment be performed during the study, the data will be recorded in the eCRF.

6.3 Study Restrictions

6.3.1 Concomitant Medications

The IMP excretion is partially hepatic; it is at the investigator's discretion to treat subjects with laxatives to accelerate excretion from the intestine.

Any antitumour treatment other than the IMP is prohibited from screening to 6 weeks after the last dose administration. All antitumour treatments given prior the first IMP dosing should be recorded in the eCRF. Dose, trade name, number of cycle and duration of treatment will be recorded as well.

Any prior or concomitant medication or therapy given to a subject either 30 days prior to dosing either within five half-lives of the previous product (if longer than 30 days) and during the study will be indicated in the eCRF. Dose, trade name and duration of treatment will be recorded.

Hormone substitution or therapies impacting one of the respective pituitary axis should be listed in the concomitant medications.

The potential of ^{177}Lu-3BP-227 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 and so medications which might affect renal function should be avoided or used with due 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 underperfusion.
- Angiotensin-converting enzyme (ACE) inhibitors can also cause a deterioration in renal function. However, this is a problem only in patients 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 a number of 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 commonly seen with combination analgesic products that contain aspirin and/or paracetamol.

- Analgesic nephropathy is one of the few preventable causes of chronic kidney disease. Discontinuation of the drugs often results in stabilisation or even improvement in renal function, but continued use leads to further renal damage.

• Lithium: serum levels of lithium consistently above the therapeutic range have been associated with development of nephrogenic diabetes insipidus.

Any further antitumour treatment for the disease under study that may have been taken during the long-term follow-up period should be reported on the prior and concomitant medications page of the eCRF.

7 STUDY TREATMENT

7.1 Investigational Medicinal Product

7.1.1 Dosage Form and Strength

3BP-227 (also called IPN01087) is a DOTA-conjugate of a NTSR1 antagonist, with a CCI [redacted]

The radiolabelled IMP, ^{177}Lu-3BP-227, is intended to be manufactured in two ways either decentralized at local radiopharmacies or centralized by a central manufacturing organisation.

For all screening and treatment formulations of the IMP, the specific activity of ^{177}Lu-3BP-227 stays constant at 25 µg 3BP-227 per 1 GBq ^{177}Lu at time of infusion.

One vial can contain up to 17.5 GBq of ^{177}Lu-3BP-227 at the end of manufacturing, this amount takes into account decay to ensure the administration of the highest planned activity of 7.5 GBq of ^{177}Lu-3BP-227 from the vial.

7.1.1.1 Decentralized Supply Dosage Form and Strength

The 3BP-227 is radiolabelled with ^{177}Lu at a specific ratio, time and temperature. The screening and treatment IMP are in a solution of ethanol and normal saline containing DiethyleneTriaminePentaAcetate (DTPA) and ascorbic acid to complex free ^{177}Lu and to protect the drug product from radiolysis, respectively. The IMP consists of a sterile clear solution, free from visible particles, filled in 27-mL Type I borosilicate glass vials closed with a chlorobutyl rubber stopper and crimped with aluminium seal.

7.1.1.2 Centralized Supply Dosage Form and Strength

The 3BP-227 is radiolabelled with ^{177}Lu at a specific ratio, time and temperature. The screening and treatment IMP are formulated in a solution of sterile water for injection containing DiethyleneTriaminePentaAcetate (DTPA) to complex free ^{177}Lu and ascorbate buffer to protect the drug product from radiolysis and to extend the shelf life. The IMP consists of a sterile clear to slightly yellow solution, free of suspended particles, filled in 25 mL Type I borosilicate glass vials, closed with a chlorobutyl rubber stopper and crimped with aluminium seal.

7.1.2 Supplies, Packaging and Labelling

For some qualified sites, the IMP will be produced and supplied by the local radiopharmacy with a batch number, a date and time of expiry and a certificate of analysis.

For the other sites, the IMP will be produced and supplied by a central manufacturing organisation with batch number, expiry date and time and certificate of analysis.

The IMP will be packaged in a primary Type I borosilicate glass vial and a secondary lead/tungsten containment for shielding, labelled according to applicable regulations, requirements and national laws in force.

7.1.3 Storage

The investigator, or an approved representative (e.g. pharmacist), will ensure that the IMP is maintained all the time in a dedicated, adequate shielding container and stored in a secured area, under recommended temperature monitored storage conditions.

In case of decentralized manufacturing by the local radiopharmacy, the IMP should be stored at ambient temperatures.

In case of manufacturing by the central manufacturing organisation, the IMP should be stored between +2°C and +8°C.

Since the IMP shelf life will vary depending on the mode of manufacturing (decentralised or centralised) and potentially on supporting data generated during the conduct of the study, the exact shelf life is indicated on the IMP label.

7.1.4 Preparation, Dispensing and Administration Procedures

All IMP provided to the site pharmacist will be allocated and dispensed by appropriately trained staff. IMP will be administered under medical supervision.

Specific preparation/reconstitution instructions, if applicable, will be specified in a separate document.

7.1.4.1 Route of Administration

The screening IMP formulation consists of 1 GBq of ^{177}Lu-3BP-227 in a total volume of 10 mL that will be administered by i.v. infusion over 10 minutes.

The treatment IMP formulation consists of a 2.5 to 10 GBq of ^{177}Lu-3BP-227 in a total volume of 20 mL that will be administered by i.v. infusion over 20 minutes.

If infusion reactions are observed, the infusion rate should be slowed to around 30 minutes or stopped if the reaction is severe.

In both cases, a 100 mL saline solution will be administered concomitantly, over a period of 30 minutes and starting at the same time as the IMP administration. The same venous access will be used for IMP and saline solution. Infusion should be done in the contralateral arm of the PK sampling.

7.1.4.2 Dosing Regimen in Phase I

The total radioactivity amount per cohort will be fractionated into two administrations separated by 4 weeks. Each separate dose will be instantly prepared prior to infusion.

The absorbed organ doses, especially the doses to kidney, bone marrow and liver as a limiting organ, will be analysed after each treatment cycle so that the following administrations can be adapted and to not exceed cumulative absorbed organ dose limits.

The subject will be instructed to drink water (at least 1.5 L/24 hours) on the days following each IMP administration.

7.1.4.3 Dosing Regimen in Phase II

The dose regimen in phase II will determined based on the data collected from the dose escalation part and will not exceed the MTCA.

7.1.5 Accountability

The investigator should ensure adequate records (allocation, disposition, shipment, dispensing and returned drugs) are maintained in an IMP accountability log.

Unused IMP will be destroyed on site per local destruction procedure after approval of the sponsor.

7.1.6 Spillage

All due precautions and site procedures should be implemented to prevent spillage or leakage of radiodiagnostics or radiotherapeutics. Infusion bags, i.v. lines and venous access should all be secured, and the connections thoroughly checked. The infusion line should be taped in a loop and taped to the subject to prevent direct tension between the line and the venous access.

Despite precautions, if spillage or leakage should occur, then the site procedures must be implemented to protect the subject, staff and members of the public from radiation exposure. The subject should be moved from the area of the spillage or leakage while the area is decontaminated. Details of the spillage or leakage should be recorded (including how the incident happened, the time of the incident, an estimate (if possible) of the amount of substance lost) and the measures taken. In addition, the incident is to be reported in the same manner as an adverse event using the Medical Dictionary for Drug Regulatory Activities (MedDRA) Preferred Term ‘Product Leakage’ and as appropriate Preferred Term ‘Occupational exposure

to radiation' (if there is exposure to staff) and Preferred Term 'Exposure to radiation' (if there is exposure to the subject or members of the public).

7.2 Product Complaints

The sponsor collects product complaints on study drugs used in clinical trials to ensure the safety of study participants, monitor quality and facilitate process and product improvements.

The investigator is responsible for handling the following aspects of the product complaint process in accordance with the instructions provided for this study:

- Recording a complete description of the product complaint reported and any associated AEs using the study-specific complaint forms provided for this purpose.
- Faxing the completed product complaint form within 24 hours to the sponsor or designee.

If the investigator is asked to return the product for investigation, they should return a copy of the product complaint form with the product.

8 SAFETY ASSESSMENTS

The following safety parameters will be collected and reviewed:

- DLTS (phase I dose escalation only, for definition see Section 4.7.1.1)
- AEs
- physical examination
- vital signs
- 12-lead ECG
- 24-hour 3-lead Holter ECG (phase I dose escalation only)
- ECOG performance status
- clinical laboratory tests including haematology, blood biochemistry, hormone analysis, urinalysis and pregnancy test
- specific renal safety biomarker.

The timepoints referenced in the study schedule of assessments in Attachment 1, Section 19.1 refer to the phase I dose escalation part of the study. In case of dose expansion cohorts and for phase II, these timepoints will be revised based on the dose escalation safety data and documented through a protocol amendment.

Further routine medical assessments or any additional safety procedures may be performed during the study, if warranted and after mutual agreement by the sponsor and the investigator, or when clinically indicated.

Any clinically significant finding that results in a diagnosis should be recorded as an AE from the time informed consent is given.

The investigator will be responsible for a clinical assessment of the study participants during the whole participation of the subjects in the study, from informed consent up to discharge from the study, and for the set-up of a discharge plan if needed.

Every effort should be made to ensure that all safety evaluations are completed by the same individual who made the initial baseline determination.

The sponsor's medical monitor and the Global Patient Safety (GPS) physician will monitor safety data throughout the course of the study.

8.1 Adverse Events

Monitoring of AEs will be done from the time that a subject gives informed consent and throughout the study and will be elicited by direct, nonleading questioning or by spontaneous reports.

8.1.1 Definition of an Adverse Event

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (e.g. nausea, chest pain), signs (e.g. tachycardia, enlarged liver) or the abnormal results of an investigation (e.g. laboratory findings, ECG).

An AE can include an undesirable medical condition occurring at any time, even if no IMP has been administered. All AEs, irrespective of causality, are to be reported to the sponsor up to 6 months after the EOCT, ED or EOAC visit or until new antitumour treatment starts, whichever comes first. After this timepoint, up to the end of the 5-year follow-up period, AEs should only be reported if the event is evaluated as related to the IMP or study procedure by the investigator.

This definition includes events occurring from the time of the subject giving informed consent until the EOS (last visit in the long term follow-up period)/ED.

Natural disease progression or deterioration of the malignancy treated in the study will be recorded as part of the efficacy evaluation. The signs and symptoms of disease progression will be documented as part of the radiological or clinical progression. Events that cannot be differentiated from progressive disease (PD) should be captured as AE/SAEs. Death due to disease progression should be reported as an SAE irrespective of causality if reported during the study period and up to 6 months after the end of the cycle of the last dose of study drug. Serious adverse events including death/fatal outcome will be reported to sponsor if evaluated as related to study treatment or procedure up to the protocol defined follow-up period and EOS.

8.1.2 Adverse Events Categorisation, Recording, and Follow-up

For all AEs, sufficient information should be obtained by the investigator to determine the causality of the AE (i.e. IMP administration, study procedure or other illness). The investigator is required to assess causality and record that assessment in the eCRF.

All AEs, including SAEs, are to be accurately recorded on the AE page of the subject's eCRF. Each event will be graded for severity using the classifications of NCI-CTCAE version 5.0 [31]. For events not addressed in the NCI-CTCAE version 5.0 classifications, the following grading will apply:

- **Mild** (Grade 1): Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- **Moderate** (Grade 2): Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.
- **Severe** (Grade 3): Severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limiting selfcare ADL.
- **Life-threatening** (Grade 4): Life-threatening consequences; urgent intervention indicated.
- **Death** (Grade 5): Death related to AE.

The relationship of an AE to IMP administration will be classified by the investigator according to the following:

- **Related**: Reports including good reasons and sufficient information (e.g. plausible time sequence, dose-response relationship, pharmacology) to assume a causal relationship with IMP administration in the sense that it is plausible, conceivable or likely.
- **Not related**: Reports including good reasons and sufficient information (e.g. implausible time sequence and/or attributable to concurrent disease or other drugs) to rule out a causal relationship with IMP administration.

8.1.2.1 Assessment of Expectedness

The expectedness of an AE shall be determined by the sponsor according to the current approved version of the IB.

8.1.2.2 Follow-up of Adverse Events

Any AEs already recorded and designated as "continuing" should be reviewed at each subsequent assessment.

If an AE is still present at the end of the study, reasonable follow-up clinical monitoring should be managed by the investigator or any appropriate physician until the event or its sequelae resolves or stabilises at an acceptable level, as judged by the investigator and the sponsor's

medical monitor or his/her designated representative. The frequency of follow-up evaluation is left to the investigator's discretion.

8.1.2.3 Reporting of Adverse Events

Any AEs/SAEs, irrespective of causality, are to be reported to the sponsor up to 6 months after the EOCT, ED or EOAC visit or until new antitumour treatment starts, whichever comes first. After this timepoint, up to the end of the 5-year follow-up period, AEs/SAEs should only be reported if the event is evaluated as related to the IMP or study procedure by the investigator.

Any AE considered related to IMP administration that the investigator becomes aware of after completion of the EOS/ED visit must be reported to the sponsor and will be recorded in the eCRF. EOS for AE reporting is defined as the end of the 5-year follow-up or death.

8.1.3 Serious Adverse Event Assessment and Reporting to Sponsor

The investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets criteria for classification as an SAE requiring immediate notification to the GPS department of the sponsor.

An SAE is any AE that:

- Results in death;
- Is life-threatening; that is, any event that places the subject at immediate risk of death from the event as it occurs. It does not include an event that, had it occurred in a more severe form, might have caused death;
- Results in inpatient hospitalisation or prolongation of existing hospitalisation, excluding admission for social or administrative reasons:
    - Hospitalisation is defined as any inpatient admission (even if less than 24 hours). For chronic or long-term inpatients, inpatient admission also includes transfer within the hospital to an acute/intensive care inpatient unit.
    - Prolongation of hospitalisation is defined as any extension of an inpatient hospitalisation beyond the stay anticipated/required in relation to the original reason for the initial admission, as determined by the investigator or treating physician. For protocol-specified hospitalisation in clinical studies, prolongation is defined as any extension beyond the length of stay described in the protocol. Prolongation in the absence of a precipitating, treatment emergent, clinical AE (i.e. not associated with the development of a new AE or worsening of a pre-existing condition) may meet criteria for "seriousness" but is not an adverse experience and thus is not subject to immediate reporting to the sponsor.
    - Preplanned or elective treatments/surgical procedures should be noted in the subject's screening documentation. Hospitalisation for a preplanned or elective treatment/surgical procedure should not be reported as an SAE unless there are complications or sequelae which meet the criteria for seriousness described above.
- Results in a persistent or significant disability/incapacity, where disability is a substantial disruption of a person's ability to conduct normal life functions;
- Results in a congenital anomaly/birth defect in the offspring of a subject who received the IMP;
- Is an important medical event that may not result in death, be life-threatening, or require hospitalisation when, based upon appropriate medical judgement, may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or

convulsions that do not result in inpatient hospitalisation, or the development of drug dependency or drug abuse.

In addition to the above criteria, any additional AE that the sponsor or an investigator considers serious should be immediately reported to the sponsor. This includes any suspected or confirmed coronavirus COVID-19 (SARS-CoV-2) infection (seriousness criteria should be "other medically significant" if no other seriousness criteria are present (e.g. hospitalisation)).

In case of suspected or confirmed COVID-19 infection, the IMP administration may be temporarily discontinued depending on the subject's clinical presentation. In some cases, the investigator may request a subject be retested before the IMP administration is resumed.

All SAEs, regardless of treatment group or suspected relationship to IMP, must be reported immediately (within 24 hours of the investigator's knowledge of the event) to the sponsor's pharmacovigilance contact using the contact details specified on the front page of the current document.

Email is the preferred method of SAE notification. If email is not available, facsimile transmission is the alternative method. In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable. If the immediate report is submitted by telephone, this must be followed by a detailed written report using the SAE report form.

The following information is the minimum that must be provided to the sponsor's pharmacovigilance contact:

- study number
- investigational site identification
- subject number
- AE
- investigator's name and contact details.

The additional information included in the SAE form must be provided to the sponsor or representative as soon as it is available. The investigator should always provide an assessment of causality for each event reported to the sponsor. Upon receipt of the initial report, the sponsor will ask for the investigator's causality assessment, if it was not provided with the initial report.

The investigator should report a diagnosis or a syndrome rather than individual signs or symptoms. The investigator should also try to distinguish a primary AE considered the foremost untoward medical occurrence, from secondary AEs that occurred as complications.

8.1.4 Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the current approved IB and that the investigator identifies as related to the IMP or procedure.

8.1.5 Pregnancy

Information regarding pregnancies occurring during the study must be collected and reported to the sponsor as SAEs. The sponsor will request further information from the investigator regarding the course and outcome of the pregnancy.

The investigator must instruct all female subjects to inform him immediately should they become pregnant. The investigator should counsel the subject, discuss the risks of continuing with the pregnancy and the possible effects on the foetus. Monitoring of the subject should continue until conclusion of the pregnancy.

Investigators must instruct all male subjects to inform them immediately, should their sexual partner become pregnant during the study. The investigator is to report to the sponsor if they become aware of a pregnancy occurring in the partner of a subject participating in the study. If

the female partner gives her consent, the pregnancy outcome should be followed up and reported.

If there is an abnormal pregnancy outcome or an AE reporting in the foetus/neonate/child following exposure to the IMP during an Ipsen-sponsored clinical study, the information will be collected in two clinical study SAE report forms, one for the mother and one for the foetus/neonate/child.

Pregnancies (in female subjects and partners of male subjects) with a conception date within 90 days after subject's dosing must also be reported to the investigator for onward reporting to the sponsor.

8.1.6 Adverse Events of Special Interest

Not applicable.

8.1.7 Deaths

All AEs resulting in death during the study period must be reported as SAEs.

The convention for recording deaths is as follows:

- adverse event term: lead cause of death (e.g. multiple organ failure, pneumonia, myocardial infarction);
- outcome: fatal.

The only exception is if the cause of death is unknown (i.e. sudden or unexplained death), in which case the AE term may be reported as "death" or "sudden death".

8.1.8 Reporting to Competent Authorities, IECs/IRBs and other Investigators

The sponsor will ensure that processes are in place for submission of reports of SUSARs occurring during the study to the competent authorities, IECs/IRBs and other investigators concerned.

Reporting will be done in accordance with the applicable regulatory requirements.

The sponsor must report all SUSARs to the European Medicines Agency's EudraVigilance database within 15 days. Fatal and life-threatening SUSARs should be reported within 7 calendar days, with another 8 days for completion of the report.

The sponsor may prepare additional reports for other authorities (e.g. FDA).

8.2 Specific Safety Assessments

The investigator is responsible for monitoring subjects' safety at all times during the study.

For each assessment performed, the investigator must document their review of the result(s) in the source document(s) and, in case of an abnormal result or value(s) falling outside of predefined normal ranges, he/she should evaluate the finding according to NCI-CTCAE.

An abnormal finding may lead to a retest at the discretion of the investigator.

8.2.1 Physical Examinations

Complete physical examinations will be conducted as timepoints presented in the schedule of assessments in Attachment 1, Section 19.1.

This complete physical examination should include an evaluation of the general health, head, eyes, ears, nose, neck and throat (HEENT), heart, chest, abdomen, extremities, skin, lymph nodes, cardiovascular status and neurological status.

Limited physical examination should be directed at the evaluation of symptoms or specific potential safety issues (in particular in case of haematological or renal toxicity).

Any changes from baseline (prior to the first treatment IMP administration) or new abnormalities in physical examination findings judged to be clinically significant by the

investigator will be recorded as AEs. Any physical examination findings (abnormalities) persisting at the end of the study will be followed by the investigator until resolution or until reaching a clinically stable endpoint.

8.2.2 Vital Signs

Vital signs (systolic and diastolic blood pressure, heart rate and body temperature) will be assessed as presented in the schedule of assessments in Attachment 1, Section 19.1.

Systolic and diastolic blood pressure and heart rate assessments will be performed with an automated device so that measurements are independent of the observer. These parameters will be recorded after at least 5 minutes rest in supine position for supine assessment.

8.2.3 Height and Weight

Height and weight will be assessed as presented in the schedule of assessments in Attachment 1, Section 19.1.

8.2.4 Electrocardiograms

12-lead computerised standard ECGs, with paper printout, will be recorded and assessed locally.

Recordings should be performed in supine position after at least 5 minutes of rest.

During the screening period, a triplicate 12-lead ECG will be recorded to check eligibility criteria by measuring the ECG parameters, in particular the QTc (Fridericia's correction, QTcF) interval in order to exclude subjects with high/abnormal QT values before the screening administration (minus 15 minutes). Afterwards, single 12-lead ECG recordings will be performed at the end of ^{177}Lu-3BP-227 screening infusion (±15 minutes) and 4 hours after the end of ^{177}Lu-3BP-227 infusion (±30 minutes).

At each treatment administration, a triplicate 12-lead ECG will be recorded on Day 1 before the infusion (baseline) (minus 15 minutes).

Afterwards, single 12-lead ECGs, will be recorded on Day 1 just after ^{177}Lu-3BP-227 infusion (±15 minutes), at 4 hours (±30 minutes) after the end of ^{177}Lu-3BP-227 infusion and on Day 2 at 24 hours (±4 hours) after the end of ^{177}Lu-3BP-227 infusion as well as at EOCT and EOAC visits.

The timepoints of postdose assessments and the number of replicates may be modified, or additional timepoints may be added, based on data collected during the study.

Table 7 summarizes the ECG assessments to be performed for QTc monitoring during screening and treatment administration at each cycle.

Table 6 Timepoints and Replicates of 12-lead ECG Recordings

	Timepoint	Replicate
Screening administration	Before infusion (minus 15 minutes)	Triplicate
	End of infusion (±15 minutes)	Single
	4 hours (±30 minutes) after the end of infusion	Single
Treatment administration (at each cycle)	Before infusion (minus 15 minutes)	Triplicate
	End of infusion (±15 minutes)	Single
	4 hours (±30 minutes) after the end of infusion	Single
	24 hours (±4 hours) after the end of infusion	Single

For each timepoint, computerised standard ECGs will be recorded so that the following parameter can be calculated and reported on the ECG paper printout:

- sinus rhythm
- duration of RR interval or heart rate
- duration of PR interval
- duration of QRS interval
- duration of QT interval
- QT interval corrected by the Fridericia's methodology.

Automated ECG interval data will be interpreted by a qualified physician at the site as soon as possible after the time of ECG collection, and ideally while the subject is still present, for immediate subject management. The qualified physician will document their review and interpretation (including evaluation of clinical significance in case of abnormality) on every ECG printout.

The paper printouts will be kept in the source documents at site. The QTcF intervals, ECG interpretation and abnormalities will be reported in the eCRF for integration with other clinical study data.

In the phase I dose escalation part, starting before each administration of the study drug, a 24-hour 3-lead continuous ECG Holter will be recorded to monitor cardiac safety during the treatment. Holter assessments will be reviewed centrally. Results will be provided to the site in a timely manner and retained as source data.

8.2.5 Performance Status

The performance status of the subjects will be defined by the ECOG scoring and assessed as presented in the schedule of assessments in Attachment 1, Section 19.1. For ES subjects, ECOG assessment should take into account disabilities related to surgery (see inclusion criterion 9).

8.2.6 Clinical Laboratory Tests

Blood and urine samples collection will be performed for standard clinical laboratory tests, including biochemistry, haematology, hormone analysis and urinalysis panels, as well as specific tests and pregnancy tests for women of childbearing potential, at timepoints indicated in the schedule of assessments in Attachment 1, Section 19.1.

Clinical laboratory tests will be analysed by local laboratory.

The results of laboratory tests performed during the screening phase must be obtained before dosing on Day 1 (within 48 hours before Cycle 1 Day 1 visit).

The investigator will review each safety laboratory test result, document the review, and if applicable, record any AEs according to NCI-CTCAE.

Abnormalities in laboratory test values should only be reported as AEs if any of the following apply:

- They result in a change in IMP schedule of administration (change in dosage, delay in administration, IMP discontinuation),
- They require intervention or a diagnosis evaluation to assess the risk to the subject,
- They are considered clinically significant by the investigator, or the laboratory test abnormality suggests a disease and/or organ toxicity that is new or has worsened from baseline based on sponsor review.

All clinically significant out of normal range laboratory tests occurring during the study may be repeated at appropriate intervals until they return to baseline or to a level deemed acceptable by the investigator or until the abnormality is explained by an appropriate diagnosis that does not require further follow-up.

NOTE: it is to be borne in mind that all the biological samples will contain the radioactive substance ^{177}Lu-3BP-227 and appropriate measures must be taken during handling, storage and shipment.

8.2.6.1 Blood Analyses

Venous blood samples will be taken at the timepoints described in the schedule of assessment (Attachment 1, Section 19.1). Samples collected at Day 1 are to be taken predose, samples collected at Day 2 are to be collected at 24 hours ±2 hours.

An estimation of the amount of blood required is provided in Attachment 2, Section 19.2.

The parameters to be assessed are listed in Attachment 3, Section 19.3.

For the determination of renal function, eGFR will be calculated by using the MDRD formula preferably; other methods to estimate renal function are acceptable if they are validated measures such as creatinine clearance by Cockcroft & Gault. Hormone analyses will only be performed for subjects who do not have substitution or therapy impacting one of the respective pituitary axis (e.g. no cortisol sampling in subjects who receive corticosteroids, no thyroid-stimulating hormone and free thyroxine sampling in subjects who have thyroxine substitution.

8.2.6.2 Urinalysis

Freshly voided urine samples (at least 10 mL) will be collected at the timepoints described in the schedule of assessment (Attachment 1, Section 19.1).

A dipstick assessment of the parameters listed in Attachment 3, Section 19.3 will be performed. In case of positivity and in the absence of common causes for proteinuria, a proteinuria determination in a 24 hours urine collection sample will be performed, according to the investigator's discretion and within a timeframe compatible with sufficient radioactivity excretion from the subject.

In case of abnormal result on the dipstick, a request for a confirmatory analysis or additional assessments might be sent to the local laboratory, at the discretion of the investigator.

Microscopy will be performed, if indicated, but results will not be collected in the eCRF. If in the opinion of the investigator there are any clinically significant abnormalities in microscopy, they will be recorded as AEs in the eCRF.

8.2.6.3 Pregnancy Test

Serum and urine pregnancy tests will be performed as per the schedule of assessments (Attachment 1, Section 19.1).

8.2.7 Specific Renal Safety Biomarkers

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9 PHARMACOKINETIC ASSESSMENTS

The PK of ^{177}Lu-3BP-227 and 3BP-227, as well as the dosimetry assessments and timepoints described below are related to the phase I part of the study. The PK and dosimetry assessments will also be included in phase II. However, the timepoints might be revised based on the phase I results and documented as part of a protocol amendment.

9.1 Pharmacokinetics of ^{177}Lu-3BP-227

9.1.1 Blood Sample Collection

Total activity concentration in whole blood will be determined using a gamma counter calibrated for ^{177}Lu, according to the dosimetry operational manual (DOM).

For each subject, total activity concentration in whole blood will be measured. Each subject will have 18 blood samples (2 mL each) collected at Cycle 1 and Cycle 2 on the following timepoints after the end of ^{177}Lu-3BP-227 infusion:

- Day 1: before the infusion (baseline), at the end of infusion (0), 5 minutes ± 1 minute, 30 minutes ± 5 minutes, 90 minutes ± 15 minutes and 4 hours ± 30 minutes post infusion
- Day 2: 24 hours ± 2 hours
- Day 3: 48 hours ± 2 hours
- Day 4 to Day 5: 72 to 96 hours.

For subjects receiving additional administrations (up to four additional cycles), blood samples will be taken during first and third additional cycles according to the timepoints described above. After the second and fourth additional administrations, a single blood collection will be performed at 24 hours (as close as possible to the SPECT/CT) for the radioactive assessment of ^{177}Lu-3BP-227.

Blood samples should be collected from the arm opposite to that of the study drug infusion, or from another site.

The accurate time of sample collection and the duration for measuring the activity concentration must be recorded. Any issues associated with sample collection or processing should be reported to the sponsor's monitor.

Complete instructions for sample collection, processing and handling will be provided in a DOM.

Note that nominal sample collection times may be changed during the study based on available data. These changes will be decided by the sponsor. In any case, the total number of assessments may be decreased but it will not be increased.

9.1.2 Urine Sample Collection

To determine the renal excretion of ^{177}Lu, total activity concentration in urine will be determined using a gamma counter calibrated for ^{177}Lu, according to the DOM.

The samples for urine total activity concentration analysis will be taken from urine collected during four different periods at Cycle 1 only: from the start of the ^{177}Lu-3BP-227 infusion to 6 hours, 6 to 12 hours, 12 to 24 hours and 24 to 48 hours after the end of infusion (from the start of the ^{177}Lu-3BP-227 infusion to 6 hours after the end of the infusion only for US sites). Subjects should void shortly before the ^{177}Lu-3BP-227 infusion (not to be collected) and shortly before the end of the last collection period.

The accurate time of urine collection and the total urine volume for each collection interval must be recorded. All problems associated with sample collection or processing should be reported to the sponsor's monitor.

Complete instructions for urine collection, processing and handling will be provided in the DOM.

9.2 Nuclear Medicine Imaging for Dosimetry

Imaging of the tumour uptake of ^{177}Lu-3BP-227 will be performed locally by the site investigator. All images will be centralized and analysed by independent readers for dosimetry analysis of the dose limiting organs and tumour lesions. For screening, the uptake of ^{177}Lu-3BP-227 at tumour lesions will be assessed locally and will take precedence to central assessment.

During the treatment period, to improve the determination of the biokinetics of ^{177}Lu-3BP-227 and perform an absolute quantification of radioactivity in target organs, whole body scans (planar scintigraphy) and SPECT/CT will be performed at Cycles 1 and 2 at the following timepoints just after the end of ^{177}Lu-3BP-227 infusion:

- Day 1: 4 (±2) hours
- Day 2: 24 (±6) hours
- Day 3: 48 (±6) hours
- Day 4: 72 to 96 hours
- Days 7 to 8: 138 to 168 hours

Within each cycle, a single SPECT/standard dose CT will be performed. For all other time points, SPECT/low dose CT will be performed. Details of the procedures will be provided in the Image Acquisition Guidelines.

For subjects receiving additional administrations (up to four additional cycles), dosimetry assessments will be performed after the first and third additional administrations with nuclear medicine imaging as described above. After the second and fourth additional administrations, a single whole body scan and SPECT/standard dose CT at 48 (±6) hours will be performed.

Details on the procedures will be given in a separate DOM.

NOTE: The optimal schedule of the whole body scans (planar scintigraphy) and SPECT/CT has not been established. Some adaptations in timepoints or number of assessments might be required during the study and will be decided by the dosimetry expert and the sponsor. In any case, the number of whole-body scans (planar scintigraphy) and SPECT/CT will not increase and corresponds to the maximum number of assessments. The schedule adaptation can only lead to a decreased number of assessments.

9.3 Pharmacokinetics of 3BP-227

9.3.1 Blood Sample Collection

Blood will be sampled for the purpose of determining plasma levels of 3BP-227 using high-performance liquid chromatography (HPLC) with tandem mass spectrometric (MS/MS) detection, according to a separate protocol established with the dedicated analytical laboratory.

For each subject, 3BP-227 plasma concentration will be measured. Each subject will have 10 blood samples (2 mL each) collected at Cycle 1 only at the following time points:

- Day 1: before the infusion (baseline), at the end of infusion of ^{177}Lu-3BP-227 (0), 5 minutes ±1 minute, 30 minutes ±5 minutes, 90 minutes ± 15 minutes and 4 hours ±30 minutes, 6 hours ±30 minutes and 8 hours ±1 hour after the end of infusion.
- Day 2: 24 hours ±2 hours after the end of infusion of ^{177}Lu-3BP-227.
- Day 3: 48 hours ±2 hours after the end of infusion of ^{177}Lu-3BP-227.

Blood samples should be collected from the arm opposite to that of the study drug infusion, or from another site.

The accurate time of sample collection must be recorded. Any issues associated with sample collection or processing should be reported to the sponsor's monitor.

Complete instructions for sample collection, processing, handling and shipment will be provided in the laboratory manual.

Residual plasma used for 3BP-227 PK analysis may also be used for exploratory analysis. This could include using leftover plasma for protein binding analysis, metabolite profiling or analysis of excipients. Plasma samples remaining from the analysis may be retained by the sponsor for additional investigations (i.e. long term stability, reproducibility).

Note that nominal sample collection times may be changed during the study based on available data. These changes will be decided by the sponsor. In any case, the total number of assessments may be decreased but it will not be increased.

9.3.2 Urine Sample Collection

To determine the renal excretion of 3BP-227, the concentration of 3BP-227 in urine will be determined using HPLC with MS/MS detection, according to a separate protocol established with the dedicated analytical laboratory.

The samples for urine 3BP-227 concentration analysis will be taken from urine collected during four different periods at Cycle 1 only: from the start of the infusion to 6 hours, 6 to 12 hours, 12 to 24 hours and 24 to 48 hours after the start of infusion (from the start of the infusion to 6 hours after the end of the infusion only in US sites). Subjects should void shortly before the ^{177}Lu-3BP-227 infusion (not to be collected) and shortly before the end of the last collection.

The accurate time of urine collection and the total urine volume for each collection interval must be recorded. Any issues associated with sample collection or processing should be reported to the sponsor's monitor.

Complete instructions for urine collection, processing, handling and shipment will be provided in the laboratory manual.

10 PHARMACODYNAMIC/EFFICACY ASSESSMENTS

The study schedule of assessments in Attachment 1, Section 19.1 is applicable for the phase I parts of the study. The need and timepoints for phase II will be assessed based on the phase I results. Eventual changes will be described in a protocol amendment.

10.1 Imaging Assessments

Tumour response assessments will be performed by the site investigator (local) for the phase I dose escalation part and by independent reader (central) for the phase II. All contrast enhanced computed tomography/magnetic resonance imaging (ceCT/MRI) scans will be obtained and used for the tumour response assessments as described in RECIST version 1.1 (Attachment 4, Section 19.4) by the investigator and/or independent readers. Either ceCT or MRI images can be used for tumour assessment. However, the same method should be used throughout the study.

All ^{18}F-FDG-PET images will be obtained and used for the metabolic tumour response assessments as described in PERCIST version 1.0 [38,] (see Table 7 in Section 19.6) by the investigator and/or independent readers.

During phase I, even if analysed locally, all images will be transferred to the central imaging laboratory for storage and potential central analysis upon sponsor request, e. g for the analysis of the homogeneity of the tumour uptake by ^{177}Lu-3BP-227, using PERCIST version 1.0 or practical PERCIST. During phase II, the independent panel's assessment will take precedence in case of a discrepancy between the local and central reviews using PERCIST version 1.0.

10.1.1 Screening Imaging Assessments

The screening tumour assessments will be performed within 3 weeks before screening IMP infusion. If a historic ceCT/MRI scan is present that is not older than 1 month at the time of informed consent signature, this scan can be used. However, the site should ensure that all required anatomies (including brain) are covered and perform scanning for missing anatomies. Imaging parameters and approach used at screening should remain consistent throughout the study and follow-up. This examination will serve as inclusion criteria check and baseline assessment for RECIST v1.1 tumour response evaluation.

As bone scan, PET scan, or plain films are not considered adequate imaging techniques to measure bone lesions, these lesions are difficult to assess through RECIST version 1.1. These techniques can be used to confirm the presence or disappearance of bone lesions. Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described in RECIST version 1.1. Blastic bone lesions are nonmeasurable. As a consequence, subjects with only bone lesions are not eligible for the study.

10.1.2 Phase I Imaging Assessments

Radiological assessments for tumour response will be performed as per schedule of assessment (Attachment 1, Section 19.1.) as well as when clinically indicated. Additionally, in the event of biological or clinical signs of disease progression further radiological assessments can be done based upon the investigator's judgment.

For PDAC, CRC, GC and GIST, chest/abdomen/pelvis scans are required and can be performed in two images if required; from chest to abdomen and from abdomen to pelvis. The scans should extend from the lateral ends of the clavicles (to ensure complete coverage of lung apices) down to the lesser trochanters or caudally thereof (to ensure complete coverage of inguinal lymph nodes). For abdominal/pelvic scans, the scan should begin cranially at the right dome of the

diaphragm and extend down to the lesser trochanters or caudally thereof (to ensure complete coverage of inguinal lymph nodes).

For SCCHN, scans from head to pelvis are required and can be performed in three images if required; from head to chest, from chest to abdomen and from abdomen to pelvis).

For ES subject, whole body scans will be performed at screening to assess the localization of the targeted lesions. In case of lesions outside of the usual acquisition areas (chest to pelvis), the number of bed positions will be adapted accordingly for further assessment.

^{18}F-FDG-PET images will be assessed locally and the results for screening and EOCT visit will be collected in the eCRF.

After the EOCT, ED or EOAC visit, subjects will be followed up every 3 months (±2 weeks) to further evaluate the efficacy (by CT or MRI) until disease progression, administration of any other chemotherapy or radiotherapy, lost to follow-up, withdrawal of consent, death or a maximum of 2 years, whichever occurs first (see Section 6.2.3). After disease progression is confirmed, no further CT/MRI scans will be required for tumour/disease assessment. The survival status and safety of the subjects will continue to be monitored as indicated in Section 8.1.2.3 until lost to follow-up, withdrawal of consent, death or a maximum of 5 years, whichever occurs first.

10.1.3 Phase II Imaging Assessments

For phase II, serial radiologic assessments of tumours by CT or MRI will be performed by investigators at Baseline and every 8 weeks (anticipated duration of two cycles), until either disease progression, start of a new antitumour treatment, withdrawal of consent, or maximum cumulative radioactivity is reached. For each subject, the same method of assessment must be used throughout the study.

Tumour assessments should be completed until it has been determined that the subject has progressive disease (in accordance with RECIST version 1.1). In the event of the subject discontinuing study treatment for reasons other than disease progression, a tumour assessment should be completed as soon as possible relative to the date of study termination, to assess overall disease status.

^{18}F-FDG-PET scans images will be assessed to measure metabolic tumour response using PERCIST version 1.0.

Complete instructions from acquisition to central review will be provided by the contract research organisation (CRO) in charge of the central review and assessment.

After the EOCT, ED or EOAC visit, subjects will be followed up every 3 months (±2 weeks) to further evaluate the efficacy (by CT or MRI) until disease progression, administration of any other chemotherapy or radiotherapy, lost to follow-up, withdrawal of consent, death or a maximum of 2 years, whichever occurs first (see Section 6.2.3).

10.2 Quality of Life Questionnaire

Quality of Life questionnaires will be completed by the subjects during phase II. The questionnaire types and the timepoints for assessment will be described as part of a protocol amendment at the end of phase I, based on the selected phase II study design and the selected indications for investigation.

It is important that the quality of life questionnaires are completed prior to the other required assessments and that the investigator does not influence the subject's responses to the questionnaires in any way.

10.3 Tumour Markers

Tumour markers will be measured in serum at specific timepoints as described in the study schedule of assessments in Attachment 1, Section 19.1.

According to the type of tumour, the following tumour markers will be analysed:

- Serum carcinoembryonic antigen (CEA) will be analysed in all subjects.
- Serum cancer antigen 19-9 (CA 19-9) will be analysed in all subjects except in subjects with SCCHN.
- Serum LDH and bone specific alkaline phosphatase will be analysed only in subjects with ES.

All measurements will be done by the local laboratory.

10.4 Genomic Profiling in Circulating Cell-free DNA and Germline DNA

CCI

10.5 Gene Mutation Status

CCI

10.6 Tumour Biopsy

CCI

CCI

11 BIOBANKING

Analysis of biobank samples will be performed outside the scope of the main study and will be reported separately. Therefore, this analysis is optional.

CCI

12 STATISTICAL ANALYSES

An interim analysis of the data will be performed between phase I and phase II.

12.1 Analysis Sets

For dose escalation only, all subjects who complete Cycle 2 or discontinue during Cycle 1 or Cycle 2 due to a DLT will be included in the MTCA and MTSA evaluations.

For the overall study, all subjects who received at least one dose of the IMP will be included in the safety evaluation. All subjects who receive at least one dose of IMP and who have postbaseline efficacy data will be included in the efficacy evaluations. All subjects with evaluable 3BP-227 PK data and no major protocol deviation with an impact on PK analysis will be included in the evaluation of 3BP-227 PK. All subjects with evaluable dosimetry images and no major protocol deviation with an impact on dosimetry analysis will be included in the evaluation of dosimetry. All subjects with evaluable blood or urine dosimetry data and no major protocol deviation with an impact on ^{177}Lu-3BP-227 PK analysis will be included in the evaluation of ^{177}Lu-3BP-227 PK. Major deviations will be described in a specific document.

12.2 Statistical Methodology for Phase I

12.2.1 Sample Size Calculation

12.2.1.1 Dose Escalation

As this is primarily a descriptive safety and tolerability study, the total number of subjects is not based on a formal statistical sample size calculation.

For the dose escalation part, the actual sample size required to adequately determine the MTCA/MTSA during dose escalation depends on the initial dose, rate of dose escalation and the observed dose-toxicity and dose/radiation exposure relationships. Simulation studies have been performed to quantify the operational characteristics (i.e. precision of the MTCA/MTSA, sample size, number of subjects being over/under dosed) of the adaptive dose-escalation design under a number of plausible dose-DLT relationship scenarios. Results are provided in Attachment 5, Section 19.5. Based on experience, the chosen sample size of three to five subjects per cohort is considered sufficient to fulfil the objectives of the study. It is anticipated that approximately 30 subjects will be required to establish the MTCA or MACA.

12.2.1.2 Dose Expansion

If safety evaluation of ^{177}Lu-3BP-227 and dose schedules cannot be fully explored during the phase I dose escalation part, a phase I expansion part enrolling up to 45 subjects will serve to accomplish this objective including, but not limited to, schedules of high loading doses followed by fractionated lower doses or evaluation of ^{177}Lu-3BP-227 in combination with other antitumoral treatments (to be defined). The expansion part will also serve to clarify any uncertainties of antitumour responses. The sample size will be specified in a protocol amendment.

12.2.2 Statistical Methods

Details of the statistical analysis will be specified in the statistical analysis plan (SAP). The statistical analyses will be conducted using Statistical Analysis System. Summary descriptive tables, by RL, will be provided.

Continuous data will be summarised with the following items: frequency, median, range, mean and coefficient of variation (CV) if relevant.

Categorical data will be presented in contingency tables with frequencies and percentages of each modality (including missing data modality). The 95% confidence interval will be calculated following the exact method.

To describe time dependent parameters (PFS, OS), Kaplan-Meier curves and life tables will be provided. The 95% confidence interval of the median will be given.

An overview of the main analysis strategy is provided in the following sections.

12.2.3 Demographic and Other Baseline Characteristics

Summary statistics will be presented for the total study population and by cohort. Frequency tables for qualitative data will be provided. Medical and surgical history findings will be summarised using MedDRA terms.

12.2.4 Maximum Tolerated Single and Cumulative Activity

Individual listings and treatment summaries of DLTs with NCI-CTCAE code and grade will be presented.

The incidence of subjects with DLTs during Cycles 1 or 2 will be summarised by treatment and, if possible, modelled as a function of the fractional doses for Cycles 1 and 2 using Bayesian logistic regression. The moderately-informative independent priors used during the interim analysis (see Attachment 5, Section 19.5 for details) as well as noninformative priors will be used for this analysis in order to assess sensitivity of the estimates. Parameter estimates and model predictions will be reported with 90% credibility sets. The MTCA and MTSA will be computed as a derived function of model parameters.

The posterior distribution of the MTCA and MTSA will be summarised in tabular and graphical formats.

The number of subjects with at least one DLT or NCI-CTCAE Grade ≥2 (excluding hair loss) will be tabulated by RL by cycle and overall. The type of DLT and NCI-CTCAE Grade ≥2 will also be presented.

12.2.5 Safety Evaluation

For the overall study, descriptive statistics will be calculated on the safety parameters. No formal statistical analyses of safety data are planned.

Summaries will be prepared by treatment group and, as needed, by timepoint.

All AEs will be coded according to the latest version of the MedDRA and NCI-CTCAE.

Study drug TEAE summaries will include the overall incidence (by system organ class (SOC) and preferred term (PT)), events by maximum intensity, events by relationship to study drug, events leading to discontinuation of study drug and SAEs.

Physical examination findings, vital signs, ECG 3-lead 24h Holter recordings and clinical laboratory parameters will be summarised descriptively at each timepoint. Actual and change from baseline data will be calculated and summarised where data are available. The investigator's interpretation of 12-lead ECGs will be listed.

Concomitant medications will be coded using the latest version of the World Health Organization (WHO) drug dictionary and will be summarised by treatment group and overall with the number and percentage of subjects receiving concomitant medication by drug class and preferred drug name.

The NCI-CTCAE version 5.0 classification [31] will be used to classify all TEAEs and laboratory abnormalities.

Maximum grade or severity will be tabulated by subject for each MedDRA SOC and PT. Analyses of AEs and SAEs will be performed in two different ways: regardless of the relationship to the study treatment and related to the study treatment. Moreover, all AEs without SAEs and SAEs only will be tabulated.

For haematological and biochemical toxicities, the worst NCI-CTCAE grade by subject and by cycle will be tabulated and listed. For white blood cells, neutrophils, platelets and haemoglobin, with associated Grade 3 or 4 toxicities, nadir and day to nadir will be calculated.

A TEAE is defined as any AE that occurs during the active phase of the study if:

- It was not present prior to receiving the first dose of ^{177}Lu-3B-227; or
- It was present prior to receiving the first dose of ^{177}Lu-3B-227 but the intensity increased during the active phase of the study; or
- It was present prior to receiving the first dose of ^{177}Lu-3B-227, the intensity is the same but the drug relationship became related during the active phase of the study.

12.2.6 Pharmacokinetics, Biodistribution and Dosimetry

12.2.6.1 Biodistribution and Pharmacokinetic Analysis of ^{177}Lu-3BP-227

The biodistribution and PK analyses of the radiopharmaceutical ^{177}Lu-3BP-227 will be performed under the responsibility of the sponsor's Clinical Pharmacokinetics and Pharmacometrics department.

The following biodistribution (i.e. organ PK) parameters will be evaluated:

- maximal uptake (%) at the target lesion
- maximal uptake (%) in discernible organs and blood
- the C_{max} of ^{177}Lu-3BP-227 in discernible thoracic and abdominal organs, target lesion and blood
- the T_{max} of ^{177}Lu-3BP-227 in discernible thoracic and abdominal organs, target lesion and blood
- the AUC of ^{177}Lu-3BP-227 in discernible thoracic and abdominal organs, target lesion and blood
- terminal $t_{1/2}$ of activity concentrations of ^{177}Lu-3BP-227 in blood.

Data analysis and all biodistribution parameters will be further described in a SAP.

Biodistribution data for target lesion and all abdominal and thoracic organs analysed will be listed for each study subject and each sampling timepoint. In addition, arithmetic mean, arithmetic standard deviation, CV and number of data points will be provided per sampling point. The biodistribution parameters will be estimated for each subject. Total radioactivity cumulatively excreted in the urine in the interval 0 to 6 hours, 6 to 12 hours, 12 to 24 hours and 24 to 48 hours postinfusion will be determined for each subject.

Measured total ^{177}Lu-3BP-227 radioactivity concentrations in whole blood and urine will be listed for each study subject and each sampling time point. In addition, means, standard deviation, CV and number of data points will be provided per sampling point. Based on the individual ^{177}Lu-3BP-227 blood time-activity curves, the concentration-time profiles of ^{177}Lu-3BP-227 and the AUC in blood, will be estimated for each subject.

12.2.6.2 Radiation Dosimetry Analysis of ^{177}Lu-3BP-227

The radiation dosimetry analysis of the radiopharmaceutical ^{177}Lu-3BP-227 will be performed by an independent expert under the responsibility of the sponsor's Clinical Pharmacokinetics and Pharmacometrics department.

Further details on dosimetric assessments and on dosimetric parameters will be provided in a Dosimetry Assessment Plan.

The dosimetric assessments will be performed and reported according to the criteria set out by the European Association of Nuclear Medicine Dosimetry Committee guidance document: good practice of clinical dosimetry reporting [32].

Calculations will be conducted for the following parameters (only in organs showing uptake):

- organs receiving the highest absorbed dose
- specific absorbed dose to the target lesion (Gy/GBq)
- specific absorbed dose per organ (Gy/GBq)
- cumulative absorbed organ doses (Gy).

Cumulative absorbed organ doses (Gy) and organs of highest radioactivity uptake will be identified visually. Regions of interest will be placed over these organs to determine the relative activity in the respective organs. Time activity curves (describing % IA/ROI of the activity amount injected versus time, considering renal excretion activity) will be derived. The absorbed doses of the dose-limiting organs (kidney, bone marrow and liver) will be evaluated and reported to the investigator before the next administration of ^{177}Lu-3BP-227 can be initiated to enable activity adaptations in the event the next dose may exceed the organ limits of 23 Gy (kidney), 2 Gy (bone marrow) and 30 Gy (liver). The dosimetry results for all other organs will be finalized for the final study report with the restriction that the dosimetry data must be available for the SRC meeting. These data can be reviewed at any time if a major safety issue occurs.

The proportion of renally excreted radioactivity, whole blood radioactivity, and dosimetric whole body images will be used to calculate the dosimetry of ^{177}Lu-3BP-227.

12.2.6.3 Pharmacokinetic Analysis of 3BP-227

The PK analysis of 3BP-227 will be performed under the responsibility of the sponsor's Clinical Pharmacokinetics and Pharmacometrics department.

Analysis of PK data by a noncompartmental approach will be documented in a separate SAP. Individual plasma and urine concentrations of 3BP-227 will be listed and summarised by time points using descriptive statistics for continuous variables (number of available observations, mean, median, standard deviation, minimum, maximum, geometric mean, and geometric coefficient of variation assuming lognormally distributed data). Linear and semilogarithmic plots of individual and mean plasma concentration-time profiles as well as spaghetti plots will be reported.

Any suspicious concentration will be investigated and kept in the PK analysis if possible. All excluded concentrations will be justified in the report.

If 3BP-227 levels are measurable in plasma and urine, PK parameters of 3BP-227 (including, but not limited to, C_{max}, AUC, $t_{1/2}$, Cl, Vd, Ae, CL_R) will be derived using the noncompartmental approach on the individual plasma concentration-time profiles of 3BP-227 and on the individual urine concentrations.

An attempt to build an integrated model taking into account PK, dosimetry as well as efficacy and safety data will be made if warranted by the data. The exploratory analysis will be captured in a separate data analysis plan and reported in a standalone report.

12.2.7 Pharmacodynamic/Efficacy Evaluation

For phase I, tumour response will be evaluated only by the site investigator, using the revised RECIST guideline version 1.1 (see Attachment 4, Section 19.4). Only subjects with measurable disease at baseline, who have received at least two administrations of ^{177}Lu-3BP-227 and reached the end of Cycle 2 or EOCT visit would be considered evaluable for response.

All measurable lesions up to a maximum of two lesions per organ and five lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs and permit reproducible repeated measurements. On occasion, if the largest lesion does not permit reproducible measurement,

the next largest lesion which can be measured reproducibly will be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are included in the sum, then only the short axis will be added into the sum. The baseline sum of diameters will be used as reference to further characterise any objective tumour regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including any measurable lesions over and above the five target lesions should be identified as nontarget lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or unequivocal progression of each should be noted throughout follow-up.

Subjects will be evaluated as CR, PR, SD, PD, or inevaluable according to RECIST version 1.1. Based on this classification, the following endpoint will be calculated as defined by RECIST version 1.1 and below.

- Objective Response Rates (ORR): proportion of subjects with a best overall response (BOR) characterised as either a Complete Response (CR) or Partial Response (PR) relative to the total number of evaluable subjects
- Disease control rate (DCR): proportion of subjects with a BOR characterised as CR, PR or SD relative to the total number of evaluable subjects

The PFS and OS will also be evaluated as defined per RECIST version 1.1.

Details of the response evaluation will be given in a separate image review charter. Details of the analysis will be specified in the SAP.

Efficacy data will be summarised using descriptive statistics and will be graphically displayed, if appropriate. The correlation between pharmacodynamic parameters and selected safety, efficacy, or PK parameters may be graphically displayed. Further statistical analyses may be conducted. Details of the response evaluation will be given in a separate image review charter. Details of the analysis will be specified in the SAP.

An attempt to build an integrated model taking into account PK, dosimetry as well as efficacy and safety data will be made, if warranted by the data. The exploratory analysis will be captured in a separate data analysis plan and reported in a standalone report.

12.2.8 Interim Analysis/Safety Review Committee

During the dose escalation part and before each decision on further dose escalation, safety and dose limit organ exposure data will be summarised and presented to the SRC. This SRC will be set-up for the dose escalation decisions (after the end of the third subject's Cycle 1) and second dosing cycle (after the end of the third subject's Cycle 2).

At the time of SRC meeting, all cumulative available information will be reviewed.

A continual reassessment method (CRM) in conjunction with a Bayesian approach modelling of DLT rates and radiation exposure to target organs may be performed during the planned review meetings to generate additional relevant information for the adaptive dose selection decisions. PK and pharmacodynamic data may be also incorporated in the model. The SRC will review all available data and make the final decision as to dose escalation, de-escalation, or cohort expansion during the adaptive dose-escalation phase. This group will also determine when to implement predefined stopping rules.

An interim analysis of the escalation cohort data may be done when the MTCA or MACA have been determined.

A specific charter will be developed to define roles and responsibilities, as well as the data set to be reviewed by the SRC.

Full analysis will be performed on the entire dataset at the EOCT and at the end of the long-term follow-up.

12.2.9 Clinical Study Report

A final clinical study report (CSR) will be prepared according to the International Council for Harmonisation (ICH) guideline on structure and contents of CSRs. A final CSR will be prepared where any subject has signed informed consent, regardless of whether the study is completed or prematurely terminated. Where appropriate an abbreviated report may be prepared. The CSR will comply with any applicable regulatory requirements, national laws in force and will be in English.

As indicated in Section 12.2.8, a full analysis based on all data recorded until the last subject completed their EOCT visit will be performed. This analysis will be included in a CSR. An addendum to the report will be prepared, including all data recorded from the follow-up period and additional cycles that occurred after the first data cut-off.

12.3 Statistical Methodology for Phase II

12.3.1 Sample Size Calculation

In case the antitumour activity is driven by a type of tumour, tumour-specific phase II cohort(s) will be initiated utilising an Optimal Simon Two-Stage design [33] to further evaluate the antitumour activity of ^{177}Lu-3BP-227. This approach tends to minimise the average number of subjects exposed to a new drug while addressing the scientific question.

The corresponding hypotheses (H) to be tested are: H_0: ORR $\leq ORR_0$ versus H_1: ORR$>ORR_0$ where ORR is the true objective response rate following ^{177}Lu-3BP-227 treatment and ORR_0 is the minimum objective response rate that would be considered to further clinical development.

For the purpose of the a priori sample size calculation, the following values are used for the PDAC cohort: ORR_0 is 17% and ORR is 35%. These values reflect the results from PDAC therapy [34] currently registered and are considered standard-of-care, and the level of expectation for the IMP prior to phase I.

Similarly, for the CRC cohort (blended population with regard to somatic mutations in BRAF and RAS genes), ORR_0 is 15% and ORR is 30% [35;36]. The value for ORR_0 reflects an estimated average result from different clinical studies that investigated CRC therapies in different populations [35, 36]; it is anticipated that based on lack of available and effective therapies an enrichment of poor-prognosis subjects with metastatic and recurrent CRC and prevalent mutations in BRAF and RAS will occur in the study population, while it is anticipated that it is unlikely for subjects with wild-type disease for which effective therapies exist over multiple lines of treatment to be enrolled. Subjects with somatic BRAF and RAS mutations are anticipated to have less exposure to prior treatment for metastatic disease compared with subjects with prevalent wild type BRAF or RAS tumours.

The assumptions forming the understanding of the expected efficacy of standard-of-care treatment and leading to sample size estimations may be updated based on results emerging from phase I and evolving scientific knowledge.

In the first stage of the design, for the PDAC cohort, 16 subjects will be treated and evaluated for the ORR. If there are three or fewer responders in these 16 subjects, the cohort will be stopped for futility. Otherwise, 28 additional subjects will be treated and evaluated for a total of 44 subjects. The null hypothesis will be rejected if 12 or more responders are observed in the 44 subjects. This design yields a nominal one-sided type I error rate of 5% and a power of 80%, if the true response rate is 35%.

Similarly, in the first stage of the design, for the CRC cohort 19 subjects will be treated and evaluated for the ORR. If there are three or fewer responders in these 19 subjects, the cohort

will be stopped for futility. Otherwise, 36 additional subjects will be treated and evaluated for a total of 55 subjects. The null hypothesis will be rejected if 13 or more responders are observed in the 55 subjects. This design yields a nominal one-sided type I error rate of 5% and a power of 80%, if the true response rate is 30%.

Nonevaluable subjects will be replaced to meet the above numbers of evaluable subjects. A subject will be considered as nonevaluable and therefore replaced, if no evaluation post treatment is available or in case of drop-out before the 4-month visit for PDAC cohort and 8-month visit for CRC cohort with an insufficient follow-up duration (i.e. status being still "Stable Disease" as per RECIST version 1.1). In case of overenrollment, the first 16 evaluable subjects in the PDAC cohort and 19 subjects in the CRC cohort will be analysed at Stage 1 to make the decision about starting Stage 2. Assuming a non-evaluability rate of 20% for the PDAC cohort [34] and the CRC cohort [36], the number of subjects to be enrolled is expected to be approximately 55 and 70, respectively.

One, two or three further cohorts may be initiated (subject to results emerging from ongoing preclinical studies and antitumour efficacy seen during dose escalation and amending the current protocol) likely to enrol approximately 120 subjects with GC, SCCHN and/or ES.

In the case of acceptable tolerability and evident antitumour activity across all enrolled subjects in phase I, a phase II basket trial design will be utilised to study the antitumour activity of ^{177}Lu-3BP-227 in subjects with NTSR1 expressing tumours. The sample size will be described as part of a protocol amendment.

Subjects in each phase of the study will have a 5-year safety follow-up after the EOCT, ED or EOAC visit. The dose, the number and length of cycles in phase II will be refined according to phase I results.

However, if the antitumour activity is driven by a type of tumour, tumour-specific phase II cohort(s) will be initiated utilising an Optimal Simon's Two Stage design (see Phase II).

12.3.2 Analysis Sets

All subjects who receive at least one dose of the study drug will be included in the safety evaluation. All subjects who receive at least one dose of study drug and who have postbaseline efficacy data for the ORR will be included in the efficacy evaluations of the primary endpoint. All subjects who receive at least one dose of study drug and who have any postbaseline secondary efficacy data will be included in the efficacy evaluations of the secondary endpoints.

12.3.3 Demographic and Other Baseline Characteristics

Summary statistics will be presented for all treated subjects. Frequency tables for qualitative data will be provided. Medical and surgical history findings will be summarised using MedDRA terms.

12.3.4 Efficacy Evaluation

Tumour response will be assessed in imaging studies of CT or MRI scans after cycle 2 and subsequently every 8 weeks for the first 6 months and every 12 weeks thereafter.

The primary endpoint is ORR and will be calculated as defined in RECIST version1.1 and in Section 12.2.7. As part of secondary efficacy endpoints, DCR, TTP, Time to response (TTR), DOR, PFS and OS will also be determined as defined by RECIST version 1.1, metabolic response will also be determined as defined by PERCIST version 1.0.

In the particular context of the Simon Two-Stage approach, ORR will be analysed at the end of Stage 1 (and no later than after the 16-week visit of the last evaluable subject of the Stage 1 cohort for each PDAC and CRC cohorts). If the observed number of responders is below a predefined threshold, this part of the study will be stopped for futility. Otherwise, additional subjects will be treated to complete the planned enrolment. At the end of Stage 2, the null

hypothesis will be rejected depending on the total observed number of responders based on a predefined threshold.

At the end of the phase II, descriptive summaries will be provided for all primary and secondary efficacy endpoints. For the primary endpoint, final analysis will take into account the sequential sampling procedure of the design and the underlying binomial distribution assumed by the Simon Two-Stage design.

12.3.5 Safety Evaluation

Safety analyses similar to phase I (see Section 12.2.5) will be performed for phase II, except for DLT assessments and 24-hour 3-lead ECG Holter measurements.

13 DATA HANDLING AND RECORD KEEPING

13.1 Data Collection

In compliance with Good Clinical Practice (GCP), the source data, i.e. medical records/medical notes, etc. should be clearly marked and permit easy identification of a subject's participation in the specified clinical study.

Source data identification and location, whether standalone documents or direct eCRF records, will be specified in a standalone document signed by the investigator(s).

The investigator must record all data relating to protocol procedures, study drug administration, laboratory data, safety, PK and pharmacodynamic data on the source documents and report requested data on eCRFs provided for the study (see Section 13.2).

To ensure accurate, complete and reliable data, the sponsor or its representative will provide instructional material to the study site(s), as appropriate. Training will be given during a start-up/initiation meeting for instructions on the completion/data entry of any source data documents and eCRFs.

The investigators or their designees must verify that all data entries in the eCRF are accurate and consistent with source data records . If certain information is not available for a particular timepoint and/or subject, specific instructions should be followed, e.g. to document that the procedure was either not done or not applicable.

For all subjects who received any administration of ^{177}Lu-3BP-227 the full obtained data set needs to be recorded in the eCRF.

For all screening failures who did not receive the screening IMP administration, a minimum of data including the primary reason for screening failure will be recorded in the eCRF.

13.2 Data Reporting

Electronic data capture (EDC) will be utilised for collecting subject data. The study site is required to have a computer and internet connection available for study site entry of clinical data. All entries in the eCRF will be made under the electronic signature of the person performing the action. This electronic signature consists of an individual and confidential username and password combination. It is declared to be the legally binding equivalent of the handwritten signature. Only sponsor authorised users will have access to the eCRF as appropriate to their study responsibilities. Users must have successfully undergone software application training prior to entering data into the eCRF.

13.3 Data Management

Details of all data management procedures, from the initial planning to the archiving of final data sets/documents following database freeze/lock will be documented in appropriate standalone data management and validation plan(s).

Data management will be conducted by a CRO approved by the sponsor. All data management procedures will be completed in accordance with the contracted CRO's standard operating procedures. Prior to data becoming available for processing at the assigned data management CRO, they will be monitored.

The sponsor will ensure that an appropriate eCRF is developed to capture the data accurately and that suitable queries are raised to resolve any missing or inconsistent data. The investigator will receive the data from the clinical study in an electronic format (PDF files), which will be an exact copy of the eCRF and will include the full audit trail, for archiving purposes and future reference.

Any queries generated during the data management process will also be tracked by the contracted data management CRO. It is the central study monitor's responsibility to ensure that all queries are resolved by the relevant parties.

The CRO will also ensure, via SAE reconciliation, that SAE data collected in the eCRF are consistent with SAE data held in the sponsor's GPS department (and vice versa).

The coding of AE, medical history and prior/concomitant medication/nondrug therapy terms will be performed by the sponsor's Central Group. Prior/Concomitant medications will be coded using the latest version of the WHO drug dictionary and AEs/medical history/nondrug therapy terms will be coded using the latest version of MedDRA.

13.4 Record Keeping

The investigator will keep records of all original source data. This might include laboratory tests, medical records and clinical notes.

During the prestudy and initiation visits, the monitor must ensure the archiving facilities are adequate and archiving/retention responsibilities of the investigator have been discussed.

Study documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or planned marketing applications in an ICH region (that is at least 15 years) or at least 2 years have elapsed since the formal discontinuation of clinical development of the product. However, these documents should be retained for a longer period if required by applicable regulatory requirements or by an agreement with the sponsor. The investigator should take measures to prevent accidental or premature destruction of these documents. The final archiving arrangements will be confirmed by the monitor when closing out the study site. The sponsor will inform the investigator, in writing, as to when these documents no longer need to be retained.

If the principal investigator relocates or retires, or otherwise withdraws responsibility for maintenance and retention of study documents, the sponsor must be notified (preferably in writing) so that adequate provision can be made for their future maintenance and retention.

14 REGULATORY AND ETHICAL CONSIDERATIONS

14.1 Regulatory Considerations

The study will be conducted in compliance with IECs/IRBs, informed consent regulations, the Declaration of Helsinki and ICH Guidelines related to GCP. Any episode of noncompliance will be documented. The EDC system will comply with the FDA, 21 Code of Federal Regulations Part 11, Electronic Records, Electronic Signatures, and FDA, Guidance for Industry: Computerized Systems Used in Clinical Trials.

In addition, the study will adhere to all applicable international and local regulatory requirements.

All or some of the obligations of the sponsor will be assigned to a CRO.

An identification code assigned to each subject will be used in lieu of the subject's name to protect the subject's identity when reporting AEs and/or other trial-related data (see Section 4.6.1.1).

14.2 Ethical Review Considerations

The following documents should be submitted to the relevant ethics committee(s) (EC) for review and approval to conduct the study (this list may not be exhaustive):

- protocol/amendment(s) approved by the sponsor
- currently applicable IB or package labelling
- relevant investigator's curriculum vitae
- subject information and informed consent document(s) and form(s)
- subject emergency study contact cards
- recruitment procedures/materials (advertisements), if any.

The EC(s) will review all submission documents as required, and a written favourable opinion for the conduct of the study should be made available to the investigator before initiating the study. This document must be dated and clearly identify the version number(s) and date(s) of the documents submitted/reviewed and should include a statement from the EC that they comply with GCP requirements.

The study may begin at the investigative site(s) only after receiving this dated and signed documentation of the EC approval or favourable opinion.

During the study, any update to the following documents will be sent to the EC either for information, or for review and approval, depending on how substantial the modifications are: (1) the IB; (2) reports of SAEs; (3) all protocol amendments and revised informed consent(s), if any.

At the end of the study, the EC will be notified about the study completion.

14.3 Subject Information Sheet and Consent

The investigator is responsible for ensuring that the subject understands the potential risks and benefits of participating in the study, including answering, orally and/or in writing, to any questions the subject may have throughout the study and sharing any new information that may be relevant to the subject's willingness to continue his or her participation in the study in a timely manner.

The subject information sheet and consent document will be used to explain the potential risks and benefits of study participation to the subject in simple terms before the subject is entered into the study and to document that the subject is satisfied with his or her understanding of the study and desires to participate.

The investigator is ultimately responsible for ensuring the EC-approved informed consent is appropriately signed and dated by each subject prior to the performance of any study procedures. Informed consent obtained under special circumstances may occur only if allowed by local laws and regulations.

The study has the option for subjects to consent to the collection of serum and whole blood samples for biobanking for future exploratory analysis and storage for up to 15 years (where local regulations allow). A specific informed consent is required for the collection of these samples and will be explained after the subject has given written informed consent for the main study.

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14.4 Final Report Signature

The coordinating investigator or designee will be proposed to review and sign the clinical study report for this study, indicating agreement with the analyses, results, and conclusion of the report.

15 INSURANCE AND FINANCE

15.1 Insurance

The sponsor declares that it has taken out a product liability insurance covering all subjects screened and enrolled in this study in respect to risks involved in the study.

15.2 Financial Agreement

Since this study is to be performed in partnership with a CRO, separate financial agreements between the sponsor and the CRO on one side, and the CRO and the investigator site on the other side, will be signed prior to initiating the study, outlining overall sponsor and investigator responsibilities in relation to the study.

16 QUALITY CONTROL AND QUALITY ASSURANCE

To ensure accurate, complete, and reliable data, the sponsor or its representatives will provide instructional material to the study sites, as appropriate. A startup training session will be done prior to screening start to instruct the investigators and study coordinators. This session will give instruction on the protocol, the completion of the eCRF and all study procedures.

16.1 Protocol Amendments and Protocol Deviations and Exceptions

16.1.1 Protocol Amendments

In the event that an amendment to this protocol is required, it will be classified into one of the following three categories:

- ***nonsubstantial amendments*** are those that are not considered 'substantial' (e.g. administrative changes) and as such only need to be notified to the IECs or regulatory authorities for information purposes;
- ***substantial amendments*** are those considered 'substantial' to the conduct of the clinical study where they are likely to have a significant impact on the:
  - Safety or physical or mental integrity of the subjects;
  - Scientific value of the study;
  - Conduct or management of the study, or
  - Quality or safety of the study drug used in the study.

  Substantial amendments must be submitted to and approved by the IECs and relevant regulatory authorities, according to local regulations, prior to implementing changes.
- ***urgent amendments*** are those that require urgent safety measures to protect the study subjects from immediate hazard and as such may be implemented immediately by the sponsor with subsequent IECs and regulatory authority notification, forthwith.

The principal investigator and the sponsor will sign the protocol amendment.

16.1.2 Protocol Deviations and Exceptions

Protocol deviations are defined and classified as either major or minor for a given study. Major deviations (or a combination of minor becoming major) may or may not impact the analysis population. All minor and major protocol deviations will be identified and recorded by the investigator site personnel and should be traceable.

Major protocol deviation definition:

Any changes in the study design, study conduct and/or procedures that are not in accordance with the protocol and any study materials originally approved by the IEC and which may affect the subject's rights, safety or wellbeing, or the completeness, accuracy and reliability of the study data. A major protocol deviation is any significant divergence from the protocol, i.e. nonadherence on the part of the subject, the investigator, or the sponsor to protocol specific inclusion/exclusion criteria, primary objective evaluation criteria and/or GCP guidelines.

Generally, a protocol deviation qualifies as major if:

(1) The deviation has harmed or posed a significant or substantive risk of harm to the research subject.

(2) The deviation compromises the scientific integrity of the data collected for the study.

(3) The deviation is a wilful or knowing breach of human subject protection regulations, policies, or procedures on the part of the investigator(s).

(4) The deviation involves a serious or continuing noncompliance with any applicable human subject protection regulations, policies, or procedures.

(5) The deviation is inconsistent with Ipsen's research, medical and ethical principles.

Minor protocol deviation definition:

Any changes in the study design, study conduct and/or procedures that are not in accordance with the protocol and any study materials originally approved by the IEC but that do not have an important impact on the subject's rights, safety or well-being, or the completeness, accuracy and reliability of the study data. A minor protocol deviation is any significant divergence from the protocol that does not impact the study results.

As a matter of policy, the sponsor will not grant exceptions to protocol-specific entry criteria to allow subjects to enter a study. If under extraordinary circumstances such action is considered ethically, medically and scientifically justified for a particular subject, prior approval from the sponsor and the responsible IRB/IEC, in accordance with the standard operating procedure (SOP), is required before the subject is allowed to enter the study.

If investigative centre personnel learn that a subject who did not meet the protocol eligibility criteria was entered in a study (a protocol deviation), they must immediately inform the sponsor. Such subjects will be discontinued from the study, except in exceptional instance, following review and written approval by the sponsor and the responsible IRB/IEC, according to the applicable SOP. Retention of these subjects in the study will be discussed between sponsor and investigator, taking into account subject safety and data reliability. The IRB/IEC will be informed if subject safety/protection is ignorantly impacted.

16.1.3 Information to Study Personnel

The investigator is responsible for giving information about the study to all staff members involved in the study or in any element of subject management, both before starting any study procedures and during the course of the study (e.g. when new staff become involved).

The investigator must assure that all study staff members are qualified by education, experience, and training to perform their specific responsibilities. These study staff members must be listed on the clinical unit authorisation form, which includes a clear description of each staff member's responsibilities. This list must be updated throughout the study, as necessary.

The study monitor is responsible for explaining the protocol to all study staff, including the investigator, and for ensuring their compliance with the protocol. Additional information will be made available during the study when new staff become involved in the study and as otherwise agreed upon with either the investigator or the study monitor.

16.2 Monitoring

The investigator is responsible for the validity of all data collected at the site.

The sponsor is responsible for monitoring these data to verify that the rights and wellbeing of subjects are protected, study data are accurate (complete and verifiable to source data), and that the study is conducted in compliance with the protocol, GCP, and regulatory requirements.

Before the study initiation visit, the sponsor-assigned study monitor will write a monitoring plan indicating the monitoring procedures and at which occasions during the study monitoring visits will be performed.

Periodic visits will be made to the study site throughout the study at mutually agreeable times. Any appropriate communication tools will be set-up to ensure the sponsor and/or its representative is/are available for consultation, so they can stay in contact with the study site personnel.

Adequate time and space for monitoring visits should be made available by the investigator.

The investigator will allow direct access to all relevant files (for all subjects) and clinical study supplies (dispensing and storage areas), for the purpose of verifying entries made in the eCRF, and assist with the monitor's activities, if requested.

Quality of the paper-based or electronic data will be reviewed to detect errors in data collection and, if necessary, to verify the quality of the data.

The eCRF is expected to be completed on an ongoing basis to allow regular review by the study monitor, both remotely by the internet and during site visits. The study monitor will use functions of the EDC system to address any queries raised while reviewing the data entered by the study site personnel in a timely manner.

Whenever a subject name is revealed on a document required by the sponsor (e.g. laboratory print outs) the name must be blacked out permanently by the site personnel, leaving the date of birth visible and annotated with the subject number as identification.

16.3 Investigator's Regulatory Obligations

All clinical work under this protocol will be conducted according to GCP rules. This includes that the study may be audited at any time by quality assurance personnel designated by the sponsor, or by regulatory bodies. The investigator must adhere to the GCP principles in addition to any applicable local regulations.

If requested, the investigator will provide the sponsor, applicable regulatory agencies, and applicable EC with direct access to any original source documents.

The investigator(s) should demonstrate due diligence in recruitment and screening of potential study subjects. The enrolment rate should be sufficient to complete the study as agreed with the sponsor. The sponsor should be notified of any projected delays, which may impact the completion of the study.

16.3.1 Audit and Inspection

Authorised personnel from external CAs and the sponsor's authorised quality assurance personnel may carry out inspections and audits.

16.3.2 Data Quality Assurance

Monitored eCRF, transferred from the investigator site to the assigned data management group, will be reviewed (secondary monitoring) for completeness, consistency and protocol compliance.

Reasons should be given in the relevant eCRF for any missing data and other protocol deviations. Any electronic queries and items not adequately explained will require additional electronic manual queries to be raised to the investigator for clarification/correction. The investigator must ensure that queries are dealt with promptly. All data changes and clarifications can be viewed in the audit trail function of the eCRF.

17 PUBLICATION POLICY

The sponsor encourages acknowledgement of all individuals/organisations involved in the funding or conduct of the study, including medical writers or statisticians subject to the consent of each individual and entity concerned, including acknowledgement of the sponsor.

The results of this study may be published or communicated to scientific meetings by the investigators involved in the study. For multicentre studies, a plan for scientific publication and presentation of the results may be agreed and implemented by the study investigators or a steering committee. The sponsor requires that reasonable opportunity be given to review the content and conclusions of any abstract, presentation, or paper before the material is submitted for publication or communicated. This condition also applies to any amendments that are subsequently requested by referees or journal editors. The sponsor will undertake to comment on the draft documents within the time period agreed in the contractual arrangements, including clinical trial agreements, governing the relationship between the sponsor and authors (or the author's institution). Requested amendments will be incorporated by the author, provided they do not alter the scientific value of the material.

If patentability could be adversely affected by publication, this will be delayed until (i) a patent application is filed for the content of the publication in accordance with applicable provisions of the clinical trial agreement concerned, (ii) the sponsor consents to the publication, or (iii) the time period as may be agreed in the contractual arrangements, including clinical trial agreements, governing the relationship between the sponsor and authors (or authors' institution) after receipt of the proposed publication by the sponsor, whichever of (i), (ii) or (iii) occurs first.

The author undertakes to reasonably consider the sponsor's request for delay to the proposed publication should the sponsor reasonably deem premature to publish the results obtained at that particular stage of the study.

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19 ATTACHMENTS

19.1 Attachment 1 – Study Schedule of Assessments for Phase I Dose Escalation

Table 7 Schedule of Assessments for Phase I – For Subjects who are Screen Failures after IMP Screening Administration

Procedures and assessments	IMP Screening Discharge Visit [a]	IMP Screening Follow-up Visit [b]
AEs	x	x
Physical examination	x	x
Vital signs	x	x
Haematology and biochemistry [c]	x	x
Urinalysis	x	x
Prior/concomitant medication/therapy	x	x
^{177}Lu-3BP-227 screening administration	x	

a before site discharge

b 5 weeks after the IMP Screening Discharge Visit +2 weeks. If the subject is not able to come for an onsite visit, the visit may be performed by phone call. The clinical laboratory tests may be done locally. If the subject is not available for a visit or a call, the investigator can contact his oncologist/general practitioner to get the data requested in protocol.

c additional safety assessments including haematology and biochemistry can be done if clinically indicated

Table 8 Schedule of Assessments for Phase I – Dose Escalation

Procedures and assessments	CORE TRIAL [v]																			EOCT or ED [a]	Long-term Follow-up [b]
	Screening	Treatment Period																			
		Cycle 1									Cycle 2										
	D-21 to D-1 [c]	D1 [d]	D2	D3	D4	D5	D7	D 15	D 22	D29	D1 [e]	D2	D3	D4	D5	D7	D15	D22	D29	D43	
	Visit window (days)			+1			+1	±1	±1	+7 (+28) [e]			+1			+1	±1	±1	+7 (+28) [e]	+7	±14
Informed consent	x																				
Inclusion/exclusion criteria	x	x																			
Subject demographics and height	x																				
Medical and disease history	x																				
ECOG performance status	x	x									x									x	
ceCT/MRI	x [f]																			x	x
^{18}F-FDG-PET		x [g]																		x	
^{177}Lu-3BP-227 screening administration [h]	x																				
Tumour biopsy	x [i]																			x	

AE=adverse event; ceCT/MRI=contrast enhanced computed tomography/magnetic resonance imaging; cfDNA=cell-free deoxyribonucleic acid; D=Day; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; ED=early discontinuation; EOCT=end of core trial; IMP=investigational medicinal product; NTSR1=neurotensin receptor 1; PET=positron emission tomography; PK=pharmacokinetic; SPECT=single photon emission computed tomography.

a the ED visit will take place within 14 days after ED from the study and at the latest 5 weeks after the last IMP administration, the visit will correspond to an EOCT visit. For subjects who received the screening IMP administration and found ineligible to participate to the study, an ED visit will be performed within 5 weeks (+ 2 weeks) after the IMP screening administration to assess the safety. At least, clinical laboratory tests (e.g. haematology and biochemistry), AEs and concomitant medication/therapy will be collected. If the subject is not able to come for an on-site visit, the visit may be performed by phone call. The clinical laboratory tests may be done locally.

b follow-up visits will take place every 3 months (±2 weeks) and will start after the EOCT, ED or EOAC visit. Efficacy will be assessed until disease progression, administration of any other chemotherapy or radiotherapy, lost to follow-up, withdrawal of consent, death or a maximum of 2 years, whichever occurs first (see Section 6.2.3). After disease progression is confirmed, no further CT/MRI scans will be required for tumour/disease assessment. The survival status and safety of the subjects will continue to be monitored as indicated in Section 8.1.2.3 until lost to follow-up, withdrawal of consent, death or a maximum of 5 years, whichever occurs first.

c the screening period can be extended by two weeks if this is required for logistical reasons.

d Day 1 of Cycle 1 is the day of the first treatment administration. Day 1 of Cycle 2 and each potential subsequent cycle may coincide with Day 29 of the previous cycle if all safety assessments are performed and allow for the next administration.

e in case of toxicity requiring a delay, the next treatment administration will be delayed by up to 4 weeks.

f whole body ceCT or ceMRI including brain unless a similar exam has already been performed within 1 month prior to Day -21.

g Cycle 1 Day 1 ^{18}FDG-PET between Day -21 and Day 1.

h screening administration will be done after confirmation of eligibility (i.e. after all other screening assessments have been performed), minimum 1 week before the first treatment administration.

Procedures and assessments	CORE TRIAL [v]																			EOCT or ED [a]	Long-term Follow-up [b]
	Screening	Treatment Period																			
		Cycle 1									Cycle 2										
	D-21 to D-1 [c]	D1 [d]	D2	D3	D4	D5	D7	D 15	D 22	D29	D1 [d]	D2	D3	D4	D5	D7	D15	D22	D29	D43	
	Visit window (days)			+1			+1	±1	±1	+7 (+28) [e]			+1			+1	±1	±1	+7 (+28) [e]	+7	±14
^{177}Lu-3BP-227 treatment administration		x									x										
Blood sampling for ^{177}Lu-3BP-227 PK [j]		x	x	x	x						x	x	x	x							
Planar scintigraphy [k]	x	x	x	x	x		x				x	x	x	x		x					
SPECT/CT scan [k]	x	x	x	x	x		x				x	x	x	x		x					
Blood sampling for 3BP-227 PK [l]		x	x	x																	
Urine sampling for ^{177}Lu-3BP-227 PK [m] and 3BP-227 PK [t]		x	x	x																	

i in case subject consents to have a biopsy and in case it can be accomplished with reasonable safety, a tumour biopsy will be taken during screening from the primary or metastatic lesion, whichever is accessible, ideally on lesions which are positive for NTSR1 on ^{177}Lu 3BP-227 SPECT/CT following IMP screening administration, as soon as ^{177}Lu uptake has been confirmed. If not, archival tissue from a previous tumour biopsy can be used for exploratory analysis (tumour microenvironment analysis and transcriptomics).

j eighteen blood samples will be collected during the treatment period. Blood samplings will be performed just before the ^{177}Lu-3BP-227 infusion (baseline), at the end of infusion (0), 5 minutes ±1 minute, 30 minutes ±5 minutes, 90 minutes ±15 minutes and 4 hours ±30 minutes, 24 hours ±2 hours, 48 hours ±2 hours and 72 to 96 hours post infusion.

k eleven whole body scans (planar scintigraphy) and SPECT/CT acquisitions will be performed during the treatment period. Whole body scans (planar scintigraphy) and SPECT/CT scan will be performed at the following timepoints just after the end of ^{177}Lu-3BP-227 infusion: Day 1: 4 (±2) hours, Day 2: 24 (±6) hours, Day 3: 48 (±6) hours, Day 4: 72 to 96 hours, and Days 7 to 8: 138 to 168 hours. Within each cycle, a single SPECT/standard dose CT will be performed. A SPECT/low dose CT will be performed at all other timepoints. Details of the procedures will be provided in the Image Acquisition Guidelines. At screening, planar scintigraphy (1 or 2 timepoint(s) at the investigator's discretion) and optional SPECT/CT scans (up to 2 at the investigator's discretion) will be performed after screening administration of ^{177}Lu-3BP-227.

l ten blood samples will be collected at cycle 1. Blood samplings will be performed just before ^{177}Lu-3BP-227 infusion (baseline), at the end of infusion of ^{177}Lu-3BP-227 (0), 5 minutes ±1 minute, 30 minutes ±5 minutes, 90 minutes ±15 minutes and 4 hours ±30 minutes, 6 hours ±30 minutes, 8 hours ±1 hour, 24 hours ±2 hours and 48 hours ±2 hours after the end of infusion of ^{177}Lu-3BP-227.

m four urine samples will be collected during the treatment period at the following time periods and only for Cycle 1: from the start of the IMP infusion to 6 hours, 6 to 12 hours, 12 to 24 hours, and 24 to 48 hours (from the start of the IMP infusion to 6 hours after the end of the infusion only for US sites) after the end of ^{177}Lu-3BP-227 infusion.

Procedures and assessments	CORE TRIAL [v]																			EOCT or ED [a]	Long-term Follow-up [b]
	Screening	Treatment Period																			
		Cycle 1									Cycle 2										
	D-21 to D-1 [c]	D1 [d]	D2	D3	D4	D5	D7	D 15	D 22	D29	D1[d]	D2	D3	D4	D5	D7	D15	D22	D29	D43	
	Visit window (days)			+1			+1	±1	±1	+7 (+28) [e]			+1			+1	±1	±1	+7 (+28) [e]	+7	±14
AEs	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x [z]
Physical examination	x	x [y]						x		x	x						x		x	x	
Vital signs	x [n]	x [n]	x	x			x	x	x	x	x [n]	x	x			x	x	x	x	x	
Body weight	x	x [y]						x		x	x						x		x	x	
ECG (12-lead) [o]	x	x	x								x	x								x	
24-hour 3-lead Holter ECG [p]		x									x										
Haematology and biochemistry [w]	x	x [y]					x	x	x	x	x					x	x	x	x	x	x
Urinalysis	x	x [y]	x	x						x	x								x	x	
CCI [redacted]																					
Prior/concomitant medication/therapy	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

n prior to and at the end of ^{177}Lu-3BP-227 infusion (0) as well as 30±5 minutes, 90±15 minutes, 4 hours±30 minutes after the end of ^{177}Lu-3BP-227 infusion.

o during the screening period, a triplicate 12-lead ECG will be recorded before the screening administration (minus 15 minutes), and a single 12-lead ECG will be recorded at the end of ^{177}Lu-3BP-227 infusion (±15 minutes) and 4 hours (±30 minutes) after the end of infusion. At each treatment administration, a triplicate 12-lead ECG will be recorded on Day 1 before the infusion (baseline) (minus 15 minutes) and a single 12-lead ECG recordings at the end of ^{177}Lu-3BP-227 infusion (±15 minutes), at 4 hours after the end of ^{177}Lu-3BP-227 infusion (±30 minutes) and on Day 2 at 24 hours after the end of ^{177}Lu-3BP-227 infusion (±4 hours) as well as at EOCT. All 12-lead computerised standard ECGs will be recorded in the supine position after at least 5 minutes of rest.

p starting before ^{177}Lu-3BP-227 infusion, a 24-hour 3-lead continuous ECG Holter will be recorded.

Procedures and assessments	CORE TRIAL [v]																			EOCT or ED [a]	Long-term Follow-up [b]
	Screening	Treatment Period																			
		Cycle 1									Cycle 2										
	D-21 to D-1 [c]	D1 [d]	D2	D3	D4	D5	D7	D 15	D 22	D29	D1[d]	D2	D3	D4	D5	D7	D15	D22	D29	D43	
	Visit window (days)			+1			+1	±1	±1	+7 (+28) [e]			+1			+1	±1	±1	+7 (+28) [e]	+7	±14
Pregnancy test [q]	x	x									x									x	
Hormone analysis [r]	x																			x	
CCI																					
Tumour markers in serum		x									x									x	
CCI																					
Survival status																					x

q serum pregnancy test will be performed at the screening visit. A urine pregnancy test will be performed on Day1 prior to IMP administration and at EOCT/ED.

r sample for hormone analysis (NTSR1 organ expressing) should be taken at the closest to 08:00.

s CCI

t four urine samples will be collected during the treatment period at the following time periods and only for Cycle 1: from the start of the IMP infusion to 6 hours, 6 to 12 hours, 12 to 24 hours, and 24 to 48 hours after the start of ^{177}Lu-3BP-227 infusion (from the start of the infusion to 6 hours after the end of the infusion only for US sites).

u CCI

v if an additional cohort of subjects is recruited to receive 3 cycles of therapy as described in the Study Design (dose escalation part Phase I), the schedule of assessments for the third cycle of therapy is to be the same as the schedule of assessments for Cycle 2.

w additional safety assessments including haematology and biochemistry can be done if clinically indicated.

x urine samples will be collected (and frozen) at the following timepoints: Cycle 1: Day 1: early morning, before the infusion (baseline), Day 3: early morning (48 hours after the end of ^{177}Lu-3BP-227 infusion at the latest) and EOCT/ED: early morning.

y on Day 1, assessments to be done predose and up to 48 hours before IMP infusion.

z Any AEs/SAEs, irrespective of causality, are to be reported to the sponsor up to 6 months after the EOCT, ED or EOAC visit or until new antitumour treatment starts, whichever comes first. After this timepoint, up to the end of the 5-year follow-up period, AEs/SAEs should only be reported if the event is evaluated as related to the IMP or study procedure by the investigator.

Table 9 Schedule of Assessments for Additional Cycles in Case of Clinical Benefit and Good Tolerability

Procedures and assessments	Additional cycles									EOAC or ED [g]
	D1	D2	D3	D4	D5	D7	D15	D22	D29	D43
Visit window (days)			+1			+1	±1	±1	+7 (+28)	+7
ECOG performance status	x									x
ceCT/MRI [a]									x	x
^{18}F-FDG-PET										x
^{177}Lu-3BP-227 treatment administration	x									
Planar scintigraphy [b]	x	x	x	x		x				
SPECT/CT scan [b]	x	x	x	x		x				
Blood sampling for ^{177}Lu 3BP-227 PK [c]	x	x	x	x						
AEs	x	x	x	x	x	x	x	x	x	x
Physical examination	x								x	x
Vital signs	x [d]	x	x			x	x	x	x	x
Body weight	x						x		x	x
ECG (12-lead) [e]	x									x
Haematology and biochemistry	x	x				x	x	x	x	x
Urinalysis	x								x	x
Prior/concomitant medication/therapy	x	x	x	x	x	x	x	x	x	x
Pregnancy test [f]	x									x
Tumour markers in serum	x									x

AE=adverse event; ceCT/MRI=contrast enhanced computed tomography/magnetic resonance imaging; D=Day; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EOAC=end of additional cycles; IMP=investigational medicinal product; PET=positron emission tomography; PK=pharmacokinetic; SPECT=single photon emission computed tomography.

a ceCT/MRI will be done every 2 cycles during additional administrations, to confirm the clinical benefit after 2 additional administrations (i.e. at Cycle 4 and EOAC). In case of early discontinuation, the ceCT/MRI should be performed at the ED visit, to confirm any disease progression.

b full dosimetry assessment will be performed after the first and third additional administrations as described for Cycles 1 and 2. After the second and fourth additional administrations, only a single SPECT/standard dose CT at 48 (±6) hours will be performed

c After the first and the third additional administration, blood samplings will be performed just before ^{177}Lu-3BP-227 infusion (baseline), at the end of infusion of ^{177}Lu-3BP-227 (0), 5 minutes ±1 minute, 30 minutes ±5 minutes, 90 minutes ±15 minutes and 4 hours ±30 minutes, 24 hours ±2 hours and 48 hours ±2 hours, and 72 to 96 hours ±2 hours. After the second and fourth additional administrations a single blood collection will be performed at 24 hours only (as close as possible to the SPECT/CT).

d prior to and at the end of ^{177}Lu-3BP-227 infusion (0) as well as 30±5 minutes, 90±15 minutes, 4 hours±30 minutes after the end of ^{177}Lu-3BP-227 infusion.

e at each cycle, a triplicate 12-lead ECG will be recorded on Day 1 before the infusion (baseline) (minus 15 minutes). A single 12-lead computerised standard ECG, with paper printout, will be recorded in supine position after at least 5 minutes of rest during each cycle on Day 1 at the end of ^{177}Lu-3BP-227 infusion (±15 minutes) and at 4 hours (±30 minutes) after the end of ^{177}Lu-3BP-227 infusion as well as at EOAC.

f a urine pregnancy test will be performed on Day 1 prior to IMP administration.

g the ED visit will take place within 14 days after ED from the study and at the latest 5 weeks after the last IMP administration.

19.2 Attachment 2 – Blood Sampling Summary

This table gives an indication of the number of (veni) punctures and blood volumes for all blood sampling (screening, safety laboratories and bioanalytical assays) during the study. Since this is a multicentre study using local labs, blood volumes for some assessments may vary between labs depending on their internal processes.

Fewer venipunctures and blood draws may actually occur if needed for safety purposes, but this will not require a protocol amendment.

Purpose	Maximum blood volume per sample (mL)	Maximum number of blood samples	Maximum total volume (mL)
Screening			
Clinical laboratory tests [a]	25	1	25
CCI [redacted]			
Core trial			
Clinical laboratory tests [a]	25	10	250
Radiopharmaceutical PK blood	2	18	36
3BP-227 PK	2	11	22
Tumour markers in serum	3	2	6
CCI [redacted]			
EOCT/ED			
Clinical laboratory tests [a]	25	1	25
Tumour markers in serum	2	1	2
CCI [redacted]			
Additional cycles (number per cycle)			
Clinical laboratory tests [a]	25	6	150
Radiopharmaceutical PK blood	2	9	18
Tumour markers in serum	2	1	2
EOAC			
Clinical laboratory tests [a]	25	1	25
Tumour markers in serum	2	1	2
LTFU			
Clinical laboratory tests [a]	25	8	200
Total volume over study period		**Approximately 820 mL**	

βHCG=beta human chorionic gonadotrophin; ED=early discontinuation; EOCT=end of core trial; LTFU=long-term follow-up; PK=pharmacokinetic.

a clinical laboratory tests include blood samples for the analysis of haematology, biochemistry, serum βHCG (pregnancy test) and hormone analysis as applicable according to the schedule of assessments.

b CCI [redacted]

19.3 Attachment 3 – Clinical Laboratory Tests

Haematology	Screening	Core trial	EOCT/ ED	Additional cycles	EOAC	LTFU
RBC count	x	x	x	x	x	
Haematocrit	x	x	x	x	x	
Hb	x	x	x	x	x	x
MCV	x	x	x	x	x	
WBC count	x	x	x	x	x	x
Absolute counts of: • Neutrophils • Lymphocytes • Monocytes • Eosinophils • Basophils	x	x	x	x	x	x
Platelets count	x	x	x	x	x	x

ED=early discontinuation; EOAC=end of additional cycles; EOCT=end of core trial; Hb= haemoglobin; LTFU=long-term follow-up; MCV=mean corpuscular volume; RBC=red blood cell; WBC=white blood cell.

Clinical chemistry	Screening	Core trial	EOCT/ ED	Additional cycles	EOAC	LTFU
ALT	x	x	x	x	x	x
Albumin	x	x	x	x	x	
ALP	x	x	x	x	x	
AST	x	x	x	x	x	x
Calcium	x	x	x	x	x	
Chloride	x	x	x	x	x	
Conjugated bilirubin (direct) [a]	x	x	x	x	x	x
Creatinine	x	x	x	x	x	x
CRP	x	x	x	x	x	
eGFR	x	x	x	x	x	
Glucose	x	x	x	x	x	
Potassium	x	x	x	x	x	
Sodium	x	x	x	x	x	
Total bilirubin	x	x	x	x	x	x
Total cholesterol	x	x	x	x	x	
Total protein	x	x	x	x	x	
TG	x	x	x	x	x	
Urea	x	x	x	x	x	x
Uric acid	x	x	x	x	x	
Serum tumour markers: • CEA - all subjects • CA 19-9 – all subjects except SCCHN • Serum LDH and BSAP for ES		x	x	x	x	

ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BSAP=Bone Specific Alkaline Phosphatase; CA 19-9=cancer antigen 19-9; CEA=carcinoembryonic antigen; eGFR=estimated glomerular filtration rate; ED=early discontinuation; EOAC=end of additional cycles; EOCT=end of core trial; ES=Ewing Sarcoma; LDH=Lactate dehydrogenase; LTFU=long-term follow-up; SCCHN=squamous-cell carcinoma of head and neck; TG=triglycerides.

a only to be performed if the total bilirubin is abnormal i.e. outside the laboratory normal range

Urinalysis	Screening	Core trial	EOCT/ ED	Additional cycles	EOAC	LTFU
Urinalysis (dipstick)						
Bilirubin	x	x	x	x	x	
Blood	x	x	x	x	x	
Glucose	x	x	x	x	x	
Ketones	x	x	x	x	x	
Leucocytes	x	x	x	x	x	
Nitrite	x	x	x	x	x	
pH	x	x	x	x	x	
Protein	x	x	x	x	x	
Proteinuria	x	x	x	x	x	
Specific gravity	x	x	x	x	x	
Urobilinogen	x	x	x	x	x	
Urine collection						
Proteinuria (only in case dipstick is positive, according to investigator's discretion and sufficient radioactivity excretion from the subject)	x	x	x	x	x	

ED=early discontinuation; EOAC=end of additional cycles; EOCT=end of core trial; LTFU=long-term follow-up.

Hormone analysis	Screening	Core trial	EOCT/ ED	Additional cycles	EOAC	LTFU
Cortisol	x		x			
fT4 and TSH	x		x			
IGF-1	x		x			
PTH	x		x			

ED=early discontinuation; EOAC=end of additional cycles; EOCT=end of core trial; fT4=free thyroxine; IGF1=insulin-like growth factor 1; LTFU=long-term follow-up; PTH=parathyroid hormone; TSH=thyroid-stimulating hormone.

Pregnancy test	Screening	Core trial	EOCT/ ED	Additional cycles	EOAC	LTFU
	urine/serum	urine	urine	urine	urine	

ED=early discontinuation; EOAC=end of additional cycles; EOCT=end of core trial; LTFU=long-term follow-up.

19.4 Attachment 4 – RECIST Version 1.1 Guidelines

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New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1)

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ABSTRACT

Background: Assessment of the change in tumour burden is an important feature of the clinical evaluation of cancer therapeutics: both tumour shrinkage (objective response) and disease progression are useful endpoints in clinical trials. Since RECIST was published in 2000, many investigators, cooperative groups, industry and government authorities have adopted these criteria in the assessment of treatment outcomes. However, a number of questions and issues have arisen which have led to the development of a revised RECIST guideline (version 1.1). Evidence for changes, summarised in separate papers in this special issue, has come from assessment of a large data warehouse (>6500 patients), simulation studies and literature reviews.

Highlights of revised RECIST 1.1: Major changes include: *Number of lesions to be assessed:* based on evidence from numerous trial databases merged into a data warehouse for analysis purposes, the number of lesions required to assess tumour burden for response determination has been reduced from a maximum of 10 to a maximum of five total (and from five to two per organ, maximum). *Assessment of pathological lymph* nodes is now incorporated: nodes with a short axis of ⩾15 mm are considered measurable and assessable as target lesions. The short axis measurement should be included in the sum of lesions in calculation of tumour response. Nodes that shrink to <10 mm short axis are considered normal. *Confirmation of response* is required for trials with response primary endpoint but is no longer required in randomised studies since the control arm serves as appropriate means of interpretation of data. *Disease progression* is clarified in several aspects: in addition to the previous definition of progression in target disease of 20% increase in sum, a 5 mm absolute increase is now required as well to guard against over calling PD when the total sum is very

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small. Furthermore, there is guidance offered on what constitutes 'unequivocal progression' of non-measurable/non-target disease, a source of confusion in the original RECIST guideline. Finally, a section on detection of new lesions, including the interpretation of FDG-PET scan assessment is included. *Imaging guidance*: the revised RECIST includes a new imaging appendix with updated recommendations on the optimal anatomical assessment of lesions.

Future work: A key question considered by the RECIST Working Group in developing RECIST 1.1 was whether it was appropriate to move from anatomic unidimensional assessment of tumour burden to either volumetric anatomical assessment or to functional assessment with PET or MRI. It was concluded that, at present, there is not sufficient standardisation or evidence to abandon anatomical assessment of tumour burden. The only exception to this is in the use of FDG-PET imaging as an adjunct to determination of progression. As is detailed in the final paper in this special issue, the use of these promising newer approaches requires appropriate clinical validation studies.

1. Background

1.1. History of RECIST criteria

Assessment of the change in tumour burden is an important feature of the clinical evaluation of cancer therapeutics. Both tumour shrinkage (objective response) and time to the development of disease progression are important endpoints in cancer clinical trials. The use of tumour regression as the endpoint for phase II trials screening new agents for evidence of anti-tumour effect is supported by years of evidence suggesting that, for many solid tumours, agents which produce tumour shrinkage in a proportion of patients have a reasonable (albeit imperfect) chance of subsequently demonstrating an improvement in overall survival or other time to event measures in randomised phase III studies (reviewed in [1–4]). At the current time objective response carries with it a body of evidence greater than for any other biomarker supporting its utility as a measure of promising treatment effect in phase II screening trials. Furthermore, at both the phase II and phase III stage of drug development, clinical trials in advanced disease settings are increasingly utilising time to progression (or progression-free survival) as an endpoint upon which efficacy conclusions are drawn, which is also based on anatomical measurement of tumour size.

However, both of these tumour endpoints, objective response and time to disease progression, are useful only if based on widely accepted and readily applied standard criteria based on anatomical tumour burden. In 1981 the World Health Organisation (WHO) first published tumour response criteria, mainly for use in trials where tumour response was the primary endpoint. The WHO criteria introduced the concept of an overall assessment of tumour burden by summing the products of bidimensional lesion measurements and determined response to therapy by evaluation of change from baseline while on treatment.[5] However, in the decades that followed their publication, cooperative groups and pharmaceutical companies that used the WHO criteria often 'modified' them to accommodate new technologies or to address areas that were unclear in the original document. This led to confusion in interpretation of trial results[6] and in fact, the application of varying response criteria was shown to lead to very different conclusions about the efficacy of the same regimen.[7] In response to these problems, an International Working Party was formed in the mid 1990s to standardise and simplify response criteria. New criteria, known as RECIST (Response Evaluation Criteria in Solid Tumours), were published in 2000.[8] Key features of the original RECIST include definitions of minimum size of measurable lesions, instructions on how many lesions to follow (up to 10; a maximum five per organ site), and the use of unidimensional, rather than bidimensional, measures for overall evaluation of tumour burden. These criteria have subsequently been widely adopted by academic institutions, cooperative groups, and industry for trials where the primary endpoints are objective response or progression. In addition, regulatory authorities accept RECIST as an appropriate guideline for these assessments.

1.2. Why update RECIST?

Since RECIST was published in 2000, many investigators have confirmed in prospective analyses the validity of substituting unidimensional for bidimensional (and even three-dimensional)-based criteria (reviewed in [9]). With rare exceptions (e.g. mesothelioma), the use of unidimensional criteria seems to perform well in solid tumour phase II studies.

However, a number of questions and issues have arisen which merit answers and further clarity. Amongst these are whether fewer than 10 lesions can be assessed without affecting the overall assigned response for patients (or the conclusion about activity in trials); how to apply RECIST in randomised phase III trials where progression, not response, is the primary endpoint particularly if not all patients have measurable disease; whether or how to utilise newer imaging technologies such as FDG-PET and MRI; how to handle assessment of lymph nodes; whether response confirmation is truly needed; and, not least, the applicability of RECIST in trials of targeted non-cytotoxic drugs. This revision of the RECIST guidelines includes updates that touch on all these points.

1.3. *Process of RECIST 1.1 development*

The RECIST Working Group, consisting of clinicians with expertise in early drug development from academic research organisations, government and industry, together with imaging specialists and statisticians, has met regularly to set the agenda for an update to RECIST, determine the evidence needed to justify the various changes made, and to review emerging evidence. A critical aspect of the revision process was to create a database of prospectively documented solid tumour measurement data obtained from industry and academic group trials. This database, assembled at the EORTC Data Centre under the leadership of Jan Bogaerts and Patrick Therasse (co-authors of this guideline), consists of >6500 patients with >18,000 target lesions and was utilised to investigate the impact of a variety of questions (e.g. number of target lesions required, the need for response confirmation, and lymph node measurement rules) on response and progression-free survival outcomes. The results of this work, which after evaluation by the RECIST Working Group led to most of the changes in this revised guideline, are reported in detail in a separate paper in this special issue.[10] Larry Schwartz and Robert Ford (also co-authors of this guideline) also provided key databases from which inferences have been made that inform these revisions.[11]

The publication of this revised guideline is believed to be timely since it incorporates changes to simplify, optimise and standardise the assessment of tumour burden in clinical trials. A summary of key changes is found in Appendix I. Because the fundamental approach to assessment remains grounded in the anatomical, rather than functional, assessment of disease, we have elected to name this version RECIST 1.1, rather than 2.0.

1.4. *What about volumetric or functional assessment?*

This raises the question, frequently posed, about whether it is 'time' to move from anatomic unidimensional assessment of tumour burden to either volumetric anatomical assessment or to functional assessment (e.g. dynamic contrast enhanced MRI or CT or (18)F-fluorodeoxyglucose positron emission tomographic (FDG-PET) techniques assessing tumour metabolism). As can be seen, the Working Group and particularly those involved in imaging research, did not believe that there is at present sufficient standardisation and widespread availability to recommend adoption of these alternative assessment methods. The only exception to this is in the use of FDG-PET imaging as an adjunct to determination of progression, as described later in this guideline. As detailed in paper in this special issue[12], we believe that the use of these promising newer approaches (which could either *add to* or *substitute for* anatomical assessment as described in RECIST) requires appropriate and rigorous clinical validation studies. This paper by Sargent et al. illustrates the type of data that will be needed to be able to define 'endpoints' for these modalities and how to determine where and when such criteria/modalities can be used to improve the reliability with which truly active new agents are identified and truly inactive new agents are discarded in comparison to RECIST criteria in phase II screening trials. The RECIST Working Group looks forward to such data emerging in the next few years to allow the appropriate changes to the next iteration of the RECIST criteria.

2. Purpose of this guideline

This guideline describes a standard approach to solid tumour measurement and definitions for objective assessment of change in tumour size for use in adult and paediatric cancer clinical trials. It is expected these criteria will be useful in all trials where objective response is the primary study endpoint, as well as in trials where assessment of stable disease, tumour progression or time to progression analyses are undertaken, since all of these outcome measures are based on an assessment of anatomical tumour burden and its change on study. There are no assumptions in this paper about the proportion of patients meeting the criteria for any of these endpoints which will signal that an agent or treatment regimen is active: those definitions are dependent on type of cancer in which a trial is being undertaken and the specific agent(s) under study. Protocols must include appropriate statistical sections which define the efficacy parameters upon which the trial sample size and decision criteria are based. In addition to providing definitions and criteria for assessment of tumour response, this guideline also makes recommendations regarding standard reporting of the results of trials that utilise tumour response as an endpoint.

While these guidelines may be applied in malignant brain tumour studies, there are also separate criteria published for response assessment in that setting.[13] This guideline is not intended for use for studies of malignant lymphoma since international guidelines for response assessment in lymphoma are published separately.[14]

Finally, many oncologists in their daily clinical practice follow their patients' malignant disease by means of repeated imaging studies and make decisions about continued therapy on the basis of both objective and symptomatic criteria. It is not intended that these RECIST guidelines play a role in that decision making, except if determined appropriate by the treating oncologist.

3. Measurability of tumour at baseline

3.1. *Definitions*

At baseline, tumour lesions/lymph nodes will be categorised measurable or non-measurable as follows:

3.1.1. *Measurable*

Tumour lesions: Must be accurately measured in at least one dimension (*longest* diameter in the plane of measurement is to be recorded) with a *minimum* size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm; see Appendix II on imaging guidance).
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).
- 20 mm by chest X-ray.

Malignant lymph nodes: To be considered pathologically enlarged *and* measurable, a lymph node must be ⩾15 mm in *short* axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the *short* axis will be measured and followed (see Schwartz et al. in this Special Issue[15]). See also notes below on 'Baseline documentation of target and non-target lesions' for information on lymph node measurement.

3.1.2. *Non-measurable*

All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ⩾10 to <15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

3.1.3. *Special considerations regarding lesion measurability*

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment:

Bone lesions:.

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with *identifiable soft tissue components*, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the *soft tissue component* meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic lesions:.

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumour lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

3.2. Specifications by methods of measurements

3.2.1. *Measurement of lesions*

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

3.2.2. *Method of assessment*

The same method of assessment and the same technique should be used to characterise each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and ⩾10 mm diameter as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by colour photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung. See Appendix II for more details.

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. As is described in Appendix II, when CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans). More details concerning the use of both CT and MRI for assessment of objective tumour response evaluation are provided in Appendix II.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next (described in greater detail in Appendix II). If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, laparoscopy: The utilisation of these techniques for objective tumour evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

Tumour markers: Tumour markers *alone* cannot be used to assess *objective* tumour response. If markers are initially above

the upper normal limit, however, they must normalise for a patient to be considered in complete response. Because tumour markers are disease specific, instructions for their measurement should be incorporated into protocols on a disease specific basis. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer), have been published.[16–18] In addition, the Gynecologic Cancer Intergroup has developed CA125 progression criteria which are to be integrated with objective tumour assessment for use in first-line trials in ovarian cancer.[19]

Cytology, histology: These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumour types such as germ cell tumours, where known residual benign tumours can remain). When effusions are known to be a potential adverse effect of treatment (e.g. with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumour has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

4. Tumour response evaluation

4.1. *Assessment of overall tumour burden and measurable disease*

To assess objective response or future progression, it is necessary to estimate the *overall tumour burden at baseline* and use this as a comparator for subsequent measurements. Only patients with measurable disease at baseline should be included in protocols where objective tumour response is the primary endpoint. Measurable disease is defined by the presence of at least one measurable lesion (as detailed above in Section 3). In studies where the primary endpoint is tumour progression (either time to progression or proportion with progression at a fixed date), the protocol must specify if entry is restricted to those with measurable disease or whether patients having non-measurable disease only are also eligible.

4.2. *Baseline documentation of 'target' and 'non-target' lesions*

When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as *target lesions* and will be recorded and measured at baseline (this means in instances where patients have only one or two organ sites involved a *maximum* of two and four lesions respectively will be recorded). For evidence to support the selection of only five target lesions, see analyses on a large prospective database in the article by Bogaerts et al.[10].

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to *reproducible repeated measurements*. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. To illustrate this point see the example in Fig. 3 of Appendix II.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumour. As noted in Section 3, pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of $\geqslant$15 mm by CT scan. Only the *short* axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumour. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, saggital or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm $\times$ 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement (See also the example in Fig. 4 in Appendix II). All other pathological nodes (those with short axis $\geqslant$10 mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed.

A *sum of the diameters* (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the *baseline sum diameters*. If lymph nodes are to be included in the sum, then as noted above, only the *short* axis is added into the sum. The baseline sum diameters will be used as reference to further characterise any objective tumour regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as *non-target lesions* and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression' (more details to follow). In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g. 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

4.3. *Response criteria*

This section provides the definitions of the criteria used to determine objective tumour response for target lesions.

4.3.1. *Evaluation of target lesions*

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the *smallest sum on study* (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (*Note:* the appearance of one or more new lesions is also considered progression).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

4.3.2. *Special notes on the assessment of target lesions*

Lymph nodes. Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of <10 mm. Case report forms or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis <10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Target lesions that become 'too small to measure'. While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs it is important that a value be recorded on the case report form. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (*Note:* It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

Lesions that split or coalesce on treatment. As noted in Appendix II, when non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

4.3.3. *Evaluation of non-target lesions*

This section provides the definitions of the criteria used to determine the tumour response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only *qualitatively* at the time points specified in the protocol.

Complete Response (CR): Disappearance of all non-target lesions and normalisation of tumour marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumour marker level above the normal limits.

Progressive Disease (PD): *Unequivocal progression* (see comments below) of existing non-target lesions. (*Note:* the appearance of one or more new lesions is also considered progression).

4.3.4. *Special notes on assessment of progression of non-target disease*

The concept of progression of non-target disease requires additional explanation as follows:

When the patient also has measurable disease. In this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumour burden has increased sufficiently to merit discontinuation of therapy (see examples in Appendix II and further details below). A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to quality for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the patient has only non-measurable disease. This circumstance arises in some phase III trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e. an increase in tumour burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic

disease from localised to widespread, or may be described in protocols as 'sufficient to require a change in therapy'. Some illustrative examples are shown in Figs. 5 and 6 in Appendix II. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so, therefore the increase must be substantial.

4.3.5. *New lesions*

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: i.e. not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumour (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was *not* scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The patient's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive[1] FDG-PET at follow-up is a sign of PD based on a new lesion.
b. No FDG-PET at baseline and a positive FDG-PET at follow-up:
   If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.
   If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan).
   If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

[1] A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

4.4. *Evaluation of best overall response*

The best overall response is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation. On occasion a response may not be documented until after the end of therapy so protocols should be clear if post-treatment assessments are to be considered in determination of best overall response. Protocols must specify how any new therapy introduced before progression will affect best response designation. The patient's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the study and the protocol requirements, it may also require confirmatory measurement (see Section 4.6). Specifically, in non-randomised trials where response is the primary endpoint, confirmation of PR or CR is needed to deem either one the 'best overall response'. This is described further below.

4.4.1. *Time point response*

It is assumed that at each protocol specified time point, a response assessment occurs. Table 1 on the next page provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline.

When patients have non-measurable (therefore non-target) disease only, Table 2 is to be used.

4.4.2. *Missing assessments and inevaluable designation*

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and at follow-up only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

4.4.3. *Best overall response: all time points*

The *best overall response* is determined once all the data for the patient is known.

Best response determination in trials where confirmation of complete or partial response IS NOT required: Best response in these trials is defined as the best response across all time points (for example, a patient who has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response of PR). When SD is believed to be best response, it must also meet the protocol specified minimum time from baseline. If the minimum time is not met when SD is otherwise the best time point response, the patient's best response depends on the subsequent assessments. For example, a patient who has SD at first assessment, PD at second and does not meet minimum duration for SD, will have a best response of PD. The same patient lost to follow-up after the first SD assessment would be considered inevaluable.

Table 1 – Time point response: patients with target (+/– non-target) disease.

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.

Table 2 – Time point response: patients with non-target disease only.

Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response, PD = progressive disease, and NE = inevaluable.
a 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

Best response determination in trials where confirmation of complete or partial response IS required: Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point as specified in the protocol (generally 4 weeks later). In this circumstance, the best overall response can be interpreted as in Table 3.

4.4.4. *Special notes on response assessment*

When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (<10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of 'zero' on the case report form (CRF).

In trials where confirmation of response is required, repeated 'NE' time point assessments may complicate best response determination. The analysis plan for the trial must address how missing data/assessments will be addressed in determination of response and progression. For example, in most trials it is reasonable to consider a patient with time point responses of PR-NE-PR as a confirmed response.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration'. Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is *not* a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target disease as shown in Tables 1–3.

Conditions that define 'early progression, early death and inevaluability' are study specific and should be clearly described in each protocol (depending on treatment duration, treatment periodicity).

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine

Table 3 – Best overall response when confirmation of CR and PR required.

Overall response First time point	Overall response Subsequent time point	BEST overall response
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.
a If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

needle aspirate/biopsy) before assigning a status of complete response. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

For equivocal findings of progression (e.g. very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

4.5. *Frequency of tumour re-evaluation*

Frequency of tumour re-evaluation while on treatment should be protocol specific and adapted to the type and schedule of treatment. However, in the context of phase II studies where the beneficial effect of therapy is not known, follow-up every 6–8 weeks (timed to coincide with the end of a cycle) is reasonable. Smaller or greater time intervals than these could be justified in specific regimens or circumstances. The protocol should specify which organ sites are to be evaluated at baseline (usually those most likely to be involved with metastatic disease for the tumour type under study) and how often evaluations are repeated. Normally, all target and non-target sites are evaluated at each assessment. In selected circumstances certain non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when complete response is identified in target disease or when progression in bone is suspected.

After the end of the treatment, the need for repetitive tumour evaluations depends on whether the trial has as a goal the response rate or the time to an event (progression/death). If 'time to an event' (e.g. time to progression, disease-free survival, progression-free survival) is the main endpoint of the study, then routine scheduled re-evaluation of protocol specified sites of disease is warranted. In randomised comparative trials in particular, the scheduled assessments should be performed as identified on a calendar schedule (for example: every 6–8 weeks on treatment or every 3–4 months after treatment) and should not be affected by delays in therapy, drug holidays or any other events that might lead to imbalance in a treatment arm in the timing of disease assessment.

4.6. *Confirmatory measurement/duration of response*

4.6.1. *Confirmation*

In non-randomised trials where response is the primary endpoint, confirmation of PR and CR is required to ensure responses identified are not the result of measurement error. This will also permit appropriate interpretation of results in the context of historical data where response has traditionally required confirmation in such trials (see the paper by Bogaerts et al. in this Special Issue[10]). However, in all other circumstances, i.e. in randomised trials (phase II or III) or studies where stable disease or progression are the primary endpoints, confirmation of response is not required since it will not add value to the interpretation of trial results. However, elimination of the requirement for response confirmation may increase the importance of central review to protect against bias, in particular in studies which are not blinded.

In the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval (in general not less than 6–8 weeks) that is defined in the study protocol.

4.6.2. *Duration of overall response*

The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study).

The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

4.6.3. *Duration of stable disease*

Stable disease is measured from the start of the treatment (in randomised trials, from date of randomisation) until the criteria for progression are met, taking as reference the *smallest sum on study* (if the baseline sum is the smallest, this is the reference for calculation of PD).

The clinical relevance of the duration of stable disease varies in different studies and diseases. If the proportion of patients achieving stable disease for a minimum period of time is an endpoint of importance in a particular trial, the protocol should specify the minimal time interval required between two measurements for determination of stable disease.

Note: The duration of response and stable disease as well as the progression-free survival are influenced by the frequency of follow-up after baseline evaluation. It is not in the scope of this guideline to define a standard follow-up frequency. The frequency should take into account many parameters including disease types and stages, treatment periodicity and standard practice. However, these limitations of the precision of the measured endpoint should be taken into account if comparisons between trials are to be made.

4.7. *Progression-free survival/proportion progression-free*

4.7.1. *Phase II trials*

This guideline is focused primarily on the use of objective response endpoints for phase II trials. In some circumstances, 'response rate' may not be the optimal method to assess the potential anticancer activity of new agents/regimens. In such cases 'progression-free survival' (PFS) or the 'proportion progression-free' at landmark time points, might be considered appropriate alternatives to provide an initial signal of biologic effect of new agents. It is clear, however, that in an uncontrolled trial, these measures are subject to criticism since an apparently promising observation may be related to biological factors such as patient selection and not the impact of the intervention. Thus, phase II screening trials utilising these endpoints are best designed with a randomised control. Exceptions may exist

where the behaviour patterns of certain cancers are so consistent (and usually consistently poor), that a non-randomised trial is justifiable (see for example van Glabbeke et al.[20]). However, in these cases it will be essential to document with care the basis for estimating the expected PFS or proportion progression-free in the absence of a treatment effect.

4.7.2. *Phase III trials*

Phase III trials in advanced cancers are increasingly designed to evaluate progression-free survival or time to progression as the primary outcome of interest. Assessment of progression is relatively straightforward if the protocol requires all patients to have measurable disease. However, restricting entry to this subset of patients is subject to criticism: it may result in a trial where the results are less likely to be generalisable if, in the disease under study, a substantial proportion of patients would be excluded. Moreover, the restriction to entry will slow recruitment to the study. Increasingly, therefore, trials allow entry of both patients with measurable disease as well as those with non-measurable disease only. In this circumstance, care must be taken to explicitly describe the findings which would qualify for progressive disease for those patients *without* measurable lesions. Furthermore, in this setting, protocols must indicate if the maximum number of recorded target lesions for those patients with measurable disease may be relaxed from five to three (based on the data found in Bogaerts et al.[10] and Moskowitz et al.[11]). As found in the 'special notes on assessment of progression', these guidelines offer recommendations for assessment of progression in this setting. Furthermore, if available, validated tumour marker measures of progression (as has been proposed for ovarian cancer) may be useful to integrate into the definition of progression. Centralised blinded review of imaging studies or of source imaging reports to verify 'unequivocal progression' may be needed if important drug development or drug approval decisions are to be based on the study outcome. Finally, as noted earlier, because the date of progression is subject to ascertainment bias, timing of investigations in study arms should be the same. The article by Dancey et al. in this special issue[21] provides a more detailed discussion of the assessment of progression in randomised trials.

4.8. *Independent review of response and progression*

For trials where *objective response* (CR + PR) is the primary endpoint, and in particular where key drug development decisions are based on the observation of a minimum number of responders, it is recommended that all claimed responses be reviewed by an expert(s) independent of the study. If the study is a randomised trial, ideally reviewers should be blinded to treatment assignment. Simultaneous review of the patients' files and radiological images is the best approach.

Independent review of progression presents some more complex issues: for example, there are statistical problems with the use of central-review-based progression time in place of investigator-based progression time due to the potential introduction of informative censoring when the former precedes the latter. An overview of these factors and other lessons learned from independent review is provided in an article by Ford et al. in this special issue.[22]

4.9. *Reporting best response results*

4.9.1. *Phase II trials*

When response is the primary endpoint, and thus all patients must have measurable disease to enter the trial, all patients included in the study must be accounted for in the report of the results, even if there are major protocol treatment deviations or if they are not evaluable. Each patient will be assigned one of the following categories:

1. Complete response
2. Partial response
3. Stable disease
4. Progression
5. Inevaluable for response: specify reasons (for example: early death, malignant disease; early death, toxicity; tumour assessments not repeated/incomplete; other (specify)).

Normally, all *eligible* patients should be included in the denominator for the calculation of the response rate for phase II trials (in some protocols it will be appropriate to include all treated patients). It is generally preferred that 95% two-sided confidence limits are given for the calculated response rate. Trial conclusions should be based on the response rate for all eligible (or all treated) patients and should *not* be based on a selected 'evaluable' subset.

4.9.2. *Phase III trials*

Response evaluation in phase III trials may be an indicator of the relative anti-tumour activity of the treatments evaluated and is almost always a secondary endpoint. Observed differences in response rate may not predict the clinically relevant therapeutic benefit for the population studied. If objective response is selected as a primary endpoint for a phase III study (only in circumstances where a direct relationship between objective tumour response and a clinically relevant therapeutic benefit can be unambiguously demonstrated for the population studied), the same criteria as those applying to phase II trials should be used and all patients entered should have at least one measurable lesion.

In those many cases where response is a secondary endpoint and not all trial patients have measurable disease, the method for reporting overall best response rates must be pre-specified in the protocol. In practice, response rate may be reported using either an 'intent to treat' analysis (all randomised patients in the denominator) or an analysis where only the subset of patients with measurable disease at baseline are included. The protocol should clearly specify how response results will be reported, including any subset analyses that are planned.

The original version of RECIST suggested that in phase III trials one could write protocols using a 'relaxed' interpretation of the RECIST guidelines (for example, reducing the number of lesions measured) but this should no longer be done since these revised guidelines have been amended in such a way that it is clear how these criteria should be applied for all trials in which anatomical assessment of tumour response or progression are endpoints.

Appendix I. Summary of major changes RECIST 1.0 to RECIST 1.1

	RECIST 1.0	RECIST 1.1	Rationale	Reference in special issue (if applicable)
Minimum size measurable lesions	CT: 10 mm spiral 20 mm non-spiral	CT 10 mm; delete reference to spiral scan	Most scans used have 5 mm or less slice thickness Clearer to give instruction based on slice interval if it is greater than 5 mm	
	Clinical: 20 mm	Clinical: 10 mm (must be measurable with calipers)	Caliper measurement will make this reliable	
	Lymph node: not mentioned	CT: ⩾15 mm short axis for target ⩾10–<15 mm for non-target <10 mm is non-pathological	Since nodes are normal structure need to define pathological enlargement. Short axis is most sensitive	Schwartz et al.[15]
Special considerations on lesion measurability	–	Notes included on bone lesions, cystic lesions	Clarify frequently asked questions	
Overall tumour burden	10 lesions (5 per organ)	5 lesions (2 per organ)	Data warehouse analysis shows no loss of information if lesion number reduced from 10 to 5. A maximum of 2 lesions per organ yields sufficient representation per disease site	Bogaerts et al.[10]
Response criteria target disease	CR lymph node not mentioned	CR lymph nodes must be <10 mm short axis	In keeping with normal size of nodes	Schwartz et al.[15]
	PD 20% increase over smallest sum on study or new lesions	PD 20% increase over smallest sum on study (including baseline if that is smallest) and at least 5 mm increase or new lesions	Clarification that if baseline measurement is smaller than any on study measurement, it is reference against which PD is assessed 5 mm absolute increase to guard against over calling PD when total sum is very small and 20% increase is within measurement error	
Response criteria non-target disease	'unequivocal progression' considered as PD	More detailed description of 'unequivocal progression' to indicate that it should not normally trump target disease status. It must be representative of overall disease status change, not a single lesion increase	Confusion with RECIST 1.0 where some were considering PD if 'increase' in any non-target lesion, even when target disease is stable or responding	
New lesions	–	New section on New lesions	To provide guidance on when a lesion is considered new (and thus PD)	
Overall response	Table integrated target and non-target lesions	Two tables: one integrating target and non-target and the other of non-target only	To account for the fact that RECIST criteria are now being used in trials where PFS is the endpoint and not all patients have measurable (target) disease at baseline	Dancey et al.[21]
		Special notes: How to assess and measure lymph nodes CR in face of residual tissue Discussion of 'equivocal' progression	Frequently asked questions on these topics	
Confirmatory measure	For CR and PR: criteria must be met again 4 weeks after initial documentation	Retain this requirement ONLY for non-randomised trials with primary endpoint of response	Data warehouse shows that response rates rise when confirmation is eliminated, but the only circumstance where this is important is in trials where there is no concurrent comparative control and where this measure is the primary endpoint	Bogaerts et al.[10]
Progression-free survival	General comments only	More specific comments on use of PFS (or proportion progression-free) as phase II endpoint Greater detail on PFS assessment in phase III trials	Increasing use of PFS in phase III trials requires guidance on assessment of PD in patients with non-measurable disease	Dancey et al.[21]
Reporting of response results	9 categories suggested for reporting phase II results	Divided into phase II and phase III 9 categories collapsed into 5 In phase III, guidance given about reporting response	Simplifies reporting and clarifies how to report phase II and III data consistently	
Response in phase III trials	More relaxed guidelines possible if protocol specified	This section removed and referenced in section above: no need to have different criteria for phase II and III	Simplification of response assessment by reducing number of lesions and eliminating need for confirmation in randomised studies where response is not the primary endpoint makes separate 'rules' unnecessary	
Imaging appendix	Appendix I	Appendix II: updated with detailed guidance on use of MRI, PET/CT Other practical guidance included	Evolving use of newer modalities addressed. Enhanced guidance in response to frequent questions and from radiology review experience	
New appendices		Appendix I: comparison of RECIST 1.0 and 1.1 Appendix III: frequently asked questions		

Conflict of interest statement

None declared.

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Appendix II. Specifications for standard anatomical radiological imaging

These protocols for image acquisition of computed tomography (CT) and magnetic resonance imaging (MRI) are recommendations intended for patients on clinical trials where RECIST assessment will be performed. Standardisation of imaging requirements and image acquisition parameters is ideal to allow for optimal comparability of subjects within a study and results between studies. These recommendations are designed to balance optimised image acquisition protocols with techniques that should be feasible to perform globally at imaging facilities in all types of radiology practices. These guidelines are not applicable to functional imaging techniques or volumetric assessment of tumour size.

Scanner quality control is highly recommended and should follow standard manufacturer and facility maintenance schedules using commercial phantoms. It is likely that for RECIST unidimensional measurements this will be adequate to produce reproducible measurements. Imaging quality control for CT includes an analysis of image noise and uniformity and CT number as well as spatial resolution. The frequency of quality control analysis is also variable and should focus on clinically relevant scanning parameters. Dose analysis is always important and the use of imaging should follow the ALARA principle, 'As Low As Reasonably Achievable', which refers to making every reasonable effort to maintain radiation exposures as far below the dose limits as possible.

Specific notes

Chest X-ray measurement of lesions surrounded by pulmonary parenchyma is feasible, but not preferable as the measurement represents a summation of densities. Furthermore, there is poor identification of new lesions within the chest on X-ray as compared with CT. Therefore, measurements of pulmonary parenchymal lesions as well as mediastinal disease are optimally performed with CT of the chest. MRI of the chest should only be performed in extenuating circumstances. Even if IV contrast cannot be administered (for example, in the situation of allergy to contrast), a non-contrast CT of the chest is still preferred over MRI or chest X-ray.

CT scans: CT scans of the chest, abdomen, and pelvis should be contiguous throughout all the anatomic region of interest. As a general rule, the minimum size of a measurable lesion at baseline should be no less than double the slice thickness and also have a minimum size of 10 mm (see below for minimum size when scanners have a slice thickness more than 5 mm). While the precise physics of lesion size and partial volume averaging is complex, lesions smaller than 10 mm may be difficult to accurately and reproducibly measure. While this rule is applicable to baseline scans, as lesions potentially decrease in size at follow-up CT studies, they should still be measured. Lesions which are reported as 'too small to measure' should be assigned a default measurement of 5 mm if they are still visible.

The most critical CT image acquisition parameters for optimal tumour evaluation using RECIST are *anatomic coverage, contrast administration, slice thickness, and reconstruction interval.*

a. *Anatomic coverage:* Optimal anatomic coverage for most solid tumours is the chest, abdomen and pelvis. Coverage should encompass all areas of known predilection for metastases in the disease under evaluation and

should additionally investigate areas that may be involved based on signs and symptoms of individual patients. Because a lesion later identified in a body part not scanned at baseline would be considered as a new lesion representing disease progression, careful consideration should be given to the extent of imaging coverage at baseline and at subsequent follow-up time points. This will enable better consistency not only of tumour measurements but also identification of new disease.

b. *IV contrast administration*: Optimal visualisation and measurement of metastases in solid tumours requires consistent administration (dose and rate) of IV contrast as well as timing of scanning. Typically, most abdominal imaging is performed during the portal venous phase and (optimally) about the same time frame after injection on each examination (see Fig. 1 for impact of different phase of IV contrast on lesion measurement). Most solid tumours may be scanned with a single phase after administration of contrast. While triphasic CT scans are sometimes performed on other types of vascular tumours to improve lesion conspicuity, for consistency and uniformity, we would recommend triphasic CT for hepatocellular and neuroendocrine tumours for which this scanning protocol is generally standard of care, and the improved temporal resolution of the triphasic scan will enhance the radiologists' ability to consistently and reproducibly measure these lesions. The precise dose and rate of IV contrast is dependent upon the CT scanning equipment, CT acquisition protocol, the type of contrast used, the available venous access and the medical condition of the patient. Therefore, the method of administration of intravenous contrast agents is variable. Rather than try to institute rigid rules regarding methods for administering contrast agents and the volume injected, it is appropriate to suggest that an adequate volume of a suitable contrast agent should be given so that the metastases are demonstrated to best effect and a *consistent method* is used on subsequent examinations for any given patient (ideally, this would be specified in the protocol or for an institution). It is very important that the same technique be used at baseline and on follow-up examinations for a given patient. This will greatly enhance the reproducibility of the tumour measurements. If prior to enrolment it is known a patient is not able to undergo CT scans with IV contrast due to allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (with or without IV contrast) should be used to evaluate the subject at baseline and follow-up should be guided by the tumour type under investigation and the anatomic location of the disease. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) should be performed should also be based on the tumour type, anatomic location of the disease and should be optimised to allow for comparison to the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, if not, the patient should be considered not evaluable from that point forward. Care must be taken in measurement of target lesions on a different modality and interpretation of non-target disease or new lesions, since the same lesion may appear to have a different size using a new modality (see Fig. 2 for a comparison of CT and MRI of the same lesion). Oral contrast is recommended to help visualise and differentiate structures in the abdomen.

c. *Slice thickness and reconstruction interval*: RECIST measurements may be performed at most clinically obtained slice thicknesses. It is recommended that CT scans be performed at 5 mm contiguous slice thickness or less and indeed this guideline presumes a minimum 5 mm thickness in recommendations for measurable lesion definition. Indeed, variations in slice thickness can have an impact on lesion measurement and on detection of new lesions. However, consideration should also be given for minimising radiation exposure. With these parameters, a minimum 10 mm lesion is considered measurable at baseline. Occasionally, institutions may perform medically acceptable scans at slice thicknesses *greater than* 5 mm. If this occurs, the minimum size of measurable lesions at baseline should be *twice the slice*

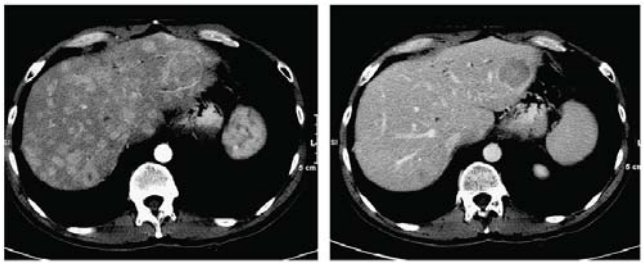

Fig. 1 – Difference in measurement/visualisation with different phases of IV contrast administration. Hypervascular metastases imaged in the arterial phase (left) and the portal venous phase (right). Note that the number of lesions visible differs greatly between the two phases of contrast administration as does any potential lesion measurement. Consistent CT scan acquisition, including phase of contrast administration, is important for optimal and reproducible tumour

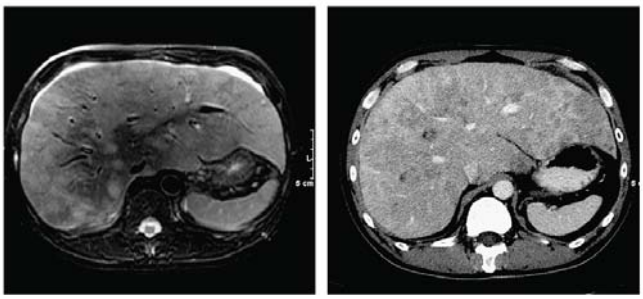

Fig. 2 – CT versus MRI of same lesions showing apparent 'progression' due only to differing method of measurement.

thickness of the baseline scans. Most contemporary CT scanners are multidetector which have many imaging options for these acquisition parameters.[23] The equipment vendor and scanning manual should be reviewed if there are any specific system questions.

d. *Alternative contrast agents*: There are a number of other, new contrast agents, some organ specific.[24] They may be used as part of patient care for instance, in liver lesion assessment, or lymph node characterisation[25], but *should not as yet be used in clinical trials*.

FDG-PET has gained acceptance as a valuable tool for detecting, staging and restaging several malignancies. Criteria for incorporating (or substituting) FDG-PET into anatomical assessment of tumour response in phase II trials are not yet available, though much research is ongoing. Nevertheless, FDG-PET is being used in many drug development trials both as a tool to assess therapeutic efficacy and also in assessment of progression. If FDG-PET scans are included in a protocol, by consensus, an FDG uptake period of 60 min prior to imaging has been decided as the most appropriate for imaging of patients with malignancy.[26] Whole-body acquisition is important since this allows for sampling of all areas of interest and can assess if new lesions have appeared thus determining the possibility of interval progression of disease. Images from the base of the skull to the level of the mid-thigh should be obtained 60 min post injection. PET camera specifications are variable and manufacturer specific, so every attempt should be made to use the same scanner, or the same model scanner, for serial scans on the same patient. Whole-body acquisitions can be performed in either 2- or 3-dimensional mode with attenuation correction, but the method chosen should be consistent across all patients and serial scans in the clinical trial.

PET/CT scans: Combined modality scanning such as with PET–CT is increasingly used in clinical care, and is a modality/technology that is in rapid evolution; therefore, the recommendations in this paper may change rather quickly with time. At present, low dose or attenuation correction CT portions of a combined PET–CT are of limited use in anatomically based efficacy assessments and it is therefore suggested that they should not be substituted for dedicated diagnostic contrast enhanced CT scans for anatomically based RECIST measurements. However, if a site can document that the CT performed as part of a PET–CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast) then the CT portion of the PET–CT can be used for RECIST measurements. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound examinations should not be used in clinical trials to measure tumour regression or progression of lesions because the examination is necessarily subjective and operator dependent. The reasons for this are several: Entire examinations cannot be reproduced for independent review at a later date, and it must be assumed, whether or not it is the case, that the hard-copy films available represent a true and accurate reflection of events. Furthermore, if, for example, the only measurable lesion is in the para-aortic region of the abdomen and if gas in the bowel overlies the lesion, the lesion will not be detected because the ultrasound beam cannot penetrate the gas. Accordingly, the disease staging (or restaging for treatment evaluation) for this patient will not be accurate.

While evaluation of lesions by *physical examination* is also of limited reproducibility, it is permitted when lesions are superficial, at least 10 mm size, and can be assessed using calipers. In general, it is preferred if patients on clinical trials have at least one lesion that is measurable by CT. Other skin or palpable lesions may be measured on physical examination and be considered target lesions.

Use of *MRI* remains a complex issue. MRI has excellent contrast, spatial and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimised for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. Generally, axial imaging of the abdomen and pelvis with T1 and T2 weighted imaging along with gadolinium enhanced imaging should be performed. The field of view, matrix, number of excitations, phase encode steps, use of fat suppression and fast sequences should be optimised for the spe-

cific body part being imaged as well as the scanner utilised. It is beyond the scope of this document or appendix to prescribe specific MRI pulse sequence parameters for all scanners, body parts and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques if possible.

Selection of target lesions: In general, the *largest* lesions representative of involved organs (up to a maximum of two per organ and five total) are selected to follow as target lesions. However, in some cases, the largest lesions may not be easily measured and are not suitable for follow-up because of their configuration. In these cases, identification of the largest *most reproducible* lesions is advised. Fig. 3 provides an illustrative example where the largest lesion is not the most reproducible and another lesion is better to select and follow:

Measurement of lesions

The longest diameter of selected lesions should be measured in the plane in which the images were acquired. For body CT, this is the axial plane. In the event isotropic reconstructions are performed, measurements can be made on these reconstructed images; however, it should be cautioned that not all radiology sites are capable of producing isotropic reconstructions. This could lead to the undesirable situation of measurements in the axial plane at one assessment point and in a different plane at a subsequent assessment. There are some tumours, for instance paraspinal lesions, which are better measured in the coronal or sagittal plane. It would be acceptable to measure these lesions in these planes if the reconstructions in those planes were isotropic or the images were acquired with MRI in those planes. Using the same plane of evaluation, the maximal diameter of each target lesion should always be measured at subsequent follow-up time points even if this results in measuring the lesion at a different slice level or in a different orientation or vector compared with the baseline study. Software tools that calculate the maximal diameter for a perimeter of a tumour may be employed and may even reduce variability.

The only exception to the longest diameter rule is lymph node measurement. Because malignant nodes are identified by the length of their short axis, this is the guide used to determine not only whether they are pathological but is also the dimension measured for adding into the sum of target lesions. Fig. 4 illustrates this point: the large arrow identifies a malignant node: the shorter perpendicular axis is $\geqslant$15 mm and will be recorded. Close by (small arrow) there is a normal node: note here the long axis is greater than 10 mm but the short axis is well below 10 mm. This node should be considered non-pathological.

If a lesion disappears and reappears at a subsequent time point it should continue to be measured. However, the patient's response at the point in time when the lesion reappears will depend upon the status of his/her other lesions. For example, if the patient's tumour had reached a CR status and the lesion reappeared, then the patient would be considered PD at the time of reappearance. In contrast, if the tumour status was a PR or SD and one lesion which had disappeared then reappears, its maximal diameter should be added to the sum of the remaining lesions for a calculated response: in other words, the reappearance of an apparently 'disappeared' single lesion amongst many which remain is not in itself en-

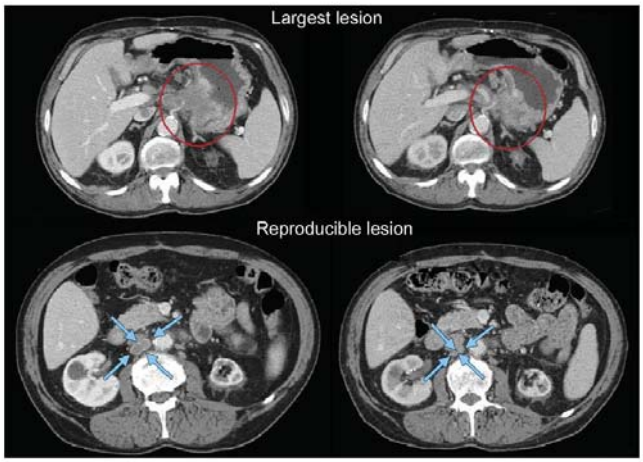

Fig. 3 – Largest lesion may not be most reproducible: most reproducible should be selected as target. In this example, the primary gastric lesion (circled at baseline and at follow-up in the top two images) may be able to be measured with thin section volumetric CT with the same degree of gastric distention at baseline and follow-up. However, this is potentially challenging to reproduce in a multicentre trial and if attempted should be done with careful imaging input and analysis. The most reproducible lesion is a lymph node (circled at baseline and at follow-up in the bottom two images).

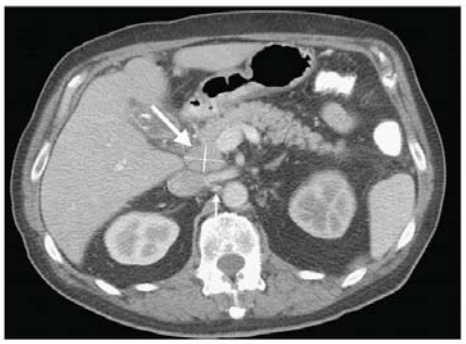

Fig. 4 – Lymph node assessment: large arrow illustrates a pathological node with the short axis shown as a solid line which should be measured and followed. Small arrow illustrates a non-pathological node which has a short axis <10 mm.

ough to qualify for PD: that requires the sum of all lesions to meet the PD criteria. The rationale for such a categorisation is based upon the realisation that most lesions do not actually 'disappear' but are not visualised because they are beyond the resolving power of the imaging modality employed.

The identification of the precise boundary definition of a lesion may be difficult especially when the lesion is embedded in an organ with a similar contrast such as the liver, pancreas, kidney, adrenal or spleen. Additionally, peritumoural oedema may surround a lesion and may be difficult to distinguish on certain modalities between this oedema and actual tumour. In fact, pathologically, the presence of tumour cells within the oedema region is variable. Therefore, it is most critical that the measurements be obtained in a reproducible manner from baseline and all subsequent follow-up timepoints. This is also a strong reason to consistently utilise the same imaging modality.

When lesions 'fragment', the individual lesion diameters should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'merged lesion'.

Progression of non-target lesions

To achieve 'unequivocal progression' there must be an *overall* level of substantial worsening in non-target disease that is of a magnitude that, even in the presence of SD or PR in target disease, the treating physician would feel it important to change therapy. Examples of unequivocal progression are shown in Figs. 5 and 6.

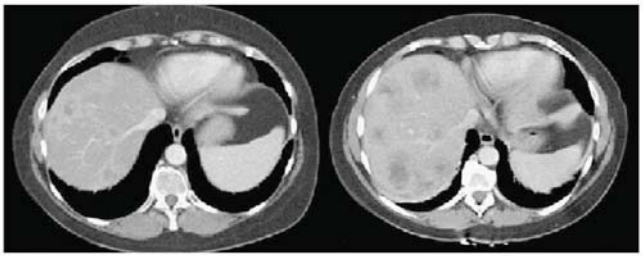

Fig. 5 – Example of unequivocal progression in non-target lesions in liver.

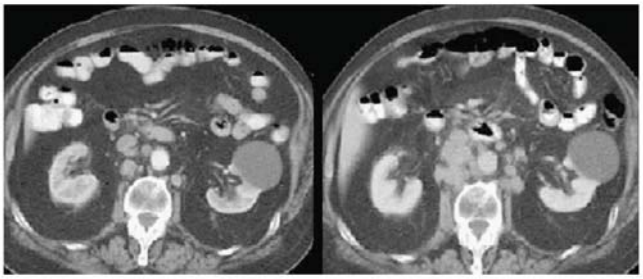

Fig. 6 – Example of unequivocal progression in non-target lesion (nodes).

Appendix III. Frequently asked questions

Question	Answer
What should be done if several unique lesions at baseline become confluent at a follow-up evaluation?	Measure the longest diameter of the confluent mass and record to add into the sum of the longest diameters
How large does a new lesion have to be to count as progression? Does any small subcentimetre lesion qualify, or should the lesion be at least measurable?	New lesions do not need to meet 'measurability criteria' to be considered valid. If it is clear on previous images (with the same technique) that a lesion was absent then its definitive appearance implies progression. If there is any doubt (because of the techniques or conditions) then it is suggested that treatment continue until next scheduled assessment when, generally, all should be clear. Either it gets bigger and the date of progression is the date of the first suspicion, or it disappears and one may then consider it an artefact with the support of the radiologists
How should one lesion be measured if on subsequent exams it is split into two?	Measure the longest diameter of each lesion and add this into the sum
Does the definition of progression depend on the status of all target lesions or only one?	As per the RECIST 1.1 guideline, progression requires a 20% increase in the sum of diameters of all target lesions AND a minimum absolute increase of 5 mm in the sum
Are RECIST criteria accepted by regulatory agencies?	Many cooperative groups and members of pharma were involved in preparing RECIST 1.0 and have adopted them. The FDA was consulted in their development and supports their use, though they don't require it. The European and Canadian regulatory authorities also participated and the RECIST criteria are now integrated in the European note for guidance for the development of anticancer agents. Many pharmaceutical companies are also using them. RECIST 1.1 was similarly widely distributed before publication
What is the criterion for a measurable lesion if the CT slice thickness is >5 mm?	RECIST 1.1 recommends that CT scans have a maximum slice thickness of 5 mm and the minimum size for a measurable lesion is twice that: 10 mm (even if slice thickness is <5 mm). If scanners with slice thickness >5 mm are used, the minimum lesion size must have a longest diameter twice the actual slice thickness
What should we record when target lesions become so small they are below the 10 mm 'measurable' size?	Target lesion measurability is defined at baseline. Thereafter, actual measurements, even if <10 mm, should be recorded. If lesions become very small, some radiologists indicate they are 'too small to measure'. This guideline advises that when this occurs, if the lesion is actually still present, a default measurement of 5 mm should be applied. If in fact the radiologist believes the lesion has gone, a default measurement of 0 mm should be recorded
If a patient has several lesions which have decreased in size to meet PR criteria and one has actually disappeared, does that patient have PD if the 'disappeared' lesion reappears?	Unless the sum meets the PD criteria, the reappearance of a lesion in the setting of PR (or SD) is not PD. The lesion should simply be added into the sum. If the patients had had a CR, clearly reappearance of an absent lesion would qualify for PD
When measuring the longest diameter of target lesions in response to treatment, is the same axis that was used initially used subsequently, even if there is a shape change to the lesion that may have produced a new longest diameter?	The longest diameter of the lesion should always be measured even if the actual axis is different from the one used to measure the lesion initially (or at different time point during follow-up) The only exception to this is lymph nodes: as per RECIST 1.1 the short axis should always be followed and as in the case of target lesions, the vector of the short axis may change on follow-up
Target lesions have been selected at baseline and followed but then one of these target lesions then becomes non-evaluable (i.e. different technique used) What is the effect this has on the other target lesions and the overall response?	What may be done in such cases is one of the following: (a) If the patient is still being treated, call the centre to be sure that future evaluations are done with the baseline technique so at least SOME courses are fully evaluable (b) If that is not possible, check if there IS a baseline exam by the same technique which was used to follow patients...in which case if you retrieve the baseline measures from that technique you retrieve the lesion evaluability (c) If neither (a) nor (b) is possible then it is a judgement call about whether you delete the lesion from all forms or consider the impact of the lesion overall is so important that its being non-evaluable makes the overall response interpretation inevaluable without it. Such a decision should be discussed in a review panel It is NOT recommended that the lesion be included in baseline sums and then excluded from follow-up sums since this biases in favour of a response

(continued on next page)

Appendix III – *continued*

Question	Answer
What if a single non-target lesion cannot be reviewed, for whatever reason; does this negate the overall assessment?	Sometimes the major contribution of a single non-target lesion may be in the setting of CR having otherwise been achieved: failure to examine one non-target in that setting will leave you unable to claim CR. It is also possible that the non-target lesion has undergone such substantial progression that it would override the target disease and render patient PD. However, this is very unlikely, especially if the rest of the measurable disease is stable or responding
A patient has a 32% decrease in sum cycle 2, a 28% decrease cycle 4 and a 33% decrease cycle 6. Does confirmation of PR have to take place in sequential scans or is a case like this confirmed PR?	It is not infrequent that tumour shrinkage hovers around the 30% mark. In this case, most would consider PR to have been confirmed looking at this overall case. Had there been two or three non-PR observations between the two time point PR responses, the most conservative approach would be to consider this case SD
In the setting of a breast cancer neoadjuvant study, would mammography not be used to assess lesions? Is CT preferred in this setting?	Neither CT nor mammography are optimal in this setting. MRI is the preferred modality to follow breast lesions in a neoadjuvant setting
A patient has a lesion measurable by clinical exam and by CT scan. Which should be followed?	CT scan. Always follow by imaging if that option exists since it can be reviewed and verified
A lesion which was solid at baseline has become necrotic in the centre. How should this be measured?	The longest diameter of the entire lesion should be followed. Eventually, necrotic lesions which are responding to treatment decrease in size. In reporting the results of trials, you may wish to report on this phenomenon if it is seen frequently since some agents (e.g. angiogenesis inhibitors) may produce this effect
If I am going to use MRI to follow disease, what is minimum size for measurability?	MRI may be substituted for contrast enhanced CT for some sites, but not lung. The minimum size for measurability is the same as for CT (10 mm) as long as the scans are performed with slice thickness of 5 mm and no gap. In the event the MRI is performed with thicker slices, the size of a measurable lesion at baseline should be two times the slice thickness. In the event there are inter-slice gaps, this also needs to be considered in determining the size of measurable lesions at baseline
Can PET–CT be used with RECIST?	At present, the low dose or attenuation correction CT portion of a combined PET–CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if your site has documented that the CT performed as part of a PET–CT is of the same diagnostic quality as a diagnostic CT (with IV and oral contrast) then the PET–CT can be used for RECIST measurements. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed

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19.5 Attachment 5 – Statistical Details and Simulation Results for Implementation of Adaptive Bayesian Dose Escalation Design

19.5.1 Statistical Model

After study screening procedures, eligible subjects will receive up to 2 i.v. administrations of ^{177}Lu-3BP-227 in two consecutive treatment cycles 4 weeks apart. A range of doses will be tested, including possibly 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7 and 7.5 GBq per cycle. Additional or alternative dose levels may be chosen. These possible dose levels are labelled as d=1, …, N, where N is the maximum number of dose levels for the study.

The analysis is based on a method reported by Guede et al.[9] and Tibaldi et al. [37].

If, during Cycle 1, a subject receives dose d_1 and in Cycle 2 dose d_2, the probability, p, of observing a subject with DLTs up to 4 weeks after the two cycles of dosing is modelled as a function of dose as:

$$\text{logit}\,(p) = \text{logit}\,(p_0) + \frac{\text{logit}(\,33\%) - \text{logit}\,(p_0)}{MTSA} d_1 + \beta * d_2$$

where p_0, MTSA and β are the model parameters having the following interpretation:

- p_0 is the probability of observing DLTs under placebo (d_1=d_2=0),
- MTSA is the maximum tolerated single activity, being defined as the dose d_1 at which the predicted probability of DLTs is 33% for dosing Cycle 1 (single dose), and
- β is a slope coefficient indicating the impact of a second dose d_2 on DLT probability.

The prior distribution on p_0, MTSA and β determine the prior distribution on the probability of DLT as a function of up to two doses. For cycle 1 data analysis, the dose d_2 is set to zero. So, only parameters p_0 and MTSA are involved. β is involved when subjects undergo their second cycle. A positive β indicates an increase in DLT probability with second dose.

The MTCA is defined as the maximum tolerated cumulative activity (d=d_1+d_2, where d_1=d_2) that may be administered following fractionated i.v. administrations of the same dose d_1 at least 4 weeks apart so that no more than 33% of the subjects experience a DLT during Cycles 1 and/or 2.

The MTCA can be presented as a derived parameter from the logistic regression model. It is expressed as:

$$\text{MTCA} = 2^* \text{MTSA} * \frac{\text{logit}\ 33\% - \textit{l}\text{ogit}\, p_0}{\text{logit}\ \ 33\% - \text{logit}\ \ \text{p}_0 + \beta * MTSA}.$$

The MTCA will be equal to twice the MTSA when β equals 0 (i.e. the DLT probability is not changed after a second dose). When the DLT probability is increased (β>0), the MTCA will be decreased (and vice versa).

During the study, the target organ exposure will be monitored after each dose and doses may be adapted if the exposure exceeds organ-specific maximum acceptability limits. As such, if the predicted MTCA exceeds the maximum acceptability limits for target organ exposure, the maximum radioactivity dose will be used instead. This feature was not considered in the simulation study, where it was assumed that a cumulative dose up to 15 GBq would induce an acceptable organ exposure.

Prior distributions were elicited based on historical knowledge about the placebo DLT rate and the MTSA target. The following prior distributions are used in the trial:

$p_0 \sim beta(a = 1, b = 9)$,

MTSA$\sim gamma\ (shape = 4, rate = 0.5)$,

and

$\beta \sim normal\ (\mu = 0, sd = 0.25)$.

Based on these distributions, 20 dose-DLT curves from the prior distribution were simulated after Dose 1 (black) and after Dose 1 and 2 (red) (see Figure 3). The prior probability distributions for the MTSA is summarised in Table 10. The prior probability distributions for the MTCA is summarised in Table 11

Figure 3 40 Random Observations (Curves) from the Prior Distribution

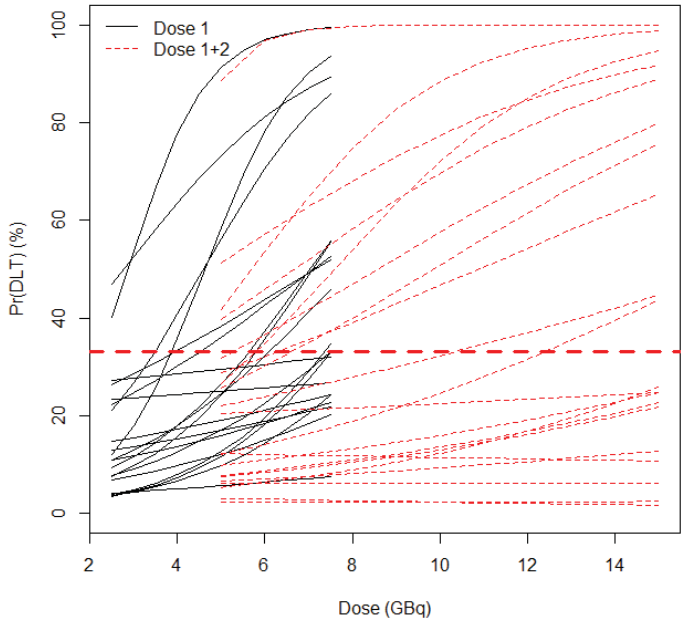


Table 10 Prior Probability Distribution of MTSA

Dose range for Cycle 1	Prior MTSA probability
2.5 GBq	5.2%
2.5 to 5 GBq	20.6%
5 to 7.5 GBq	28.6%
>7.5 GBq	45.6%

MTSA=Maximum tolerated single activity.

Table 11 Prior Probability Distribution of MTCA

Dose range (cumulative)	Prior MTCA probability
≤5 GBq	32.5%
5 to 10 GBq	24.6%
10 to 15 GBq	15.7%
>15 GBq	27.2%

MTCA= Maximum tolerated cumulative activity.

Given any set of data, the prior distribution can be updated, yielding a posterior distribution of the parameters. From this posterior distribution many different quantities of relevance can be calculated:

- $E(p|d_1, d_2)$=Posterior mean probability of DLT for Cycle 1 dose d_1 and Cycle 2 dose d_2.
- TS_d=(tolerable) Probability that the DLT rate is below 0.33, $Pr(p \leq 0.33|\ d,0)$, for a Cycle 1 dose d (d_2=0).
- QS_d=Probability of Cycle 1 dose d being the maximum dose where $E(p|d,0) \leq 0.33$.
- TC_d=(tolerable) Probability that the DLT rate is below 0.33, $Pr(p \leq 0.33|\ d/2,d/2)$, for a cumulative dose d (d_1=d_2=d/2).
- QC_d=Probability of cumulative dose d being the maximum dose where $E(p|d/2,d/2) \leq 0.33$.

Note that, in this model, the MTSA and MTCA are parameters. They have a probability distribution. A consequence of the Bayesian modelling is the probabilities, QS_d, which is the probability that a dose is the MTSA for Cycle 1 and QC_d, which is the probability that a cumulative fractional dose is the MTCA after Cycle 2. This is a powerful question that cannot be answered from a frequentist perspective.

19.5.2 Trial Simulation Details

This section present results of trial simulation study that was performed to determine the operational characteristics of the adaptive dose escalation procedure. The design of that simulation study is very similar to the actual study design, with some changes necessary to enable the automation of trial simulations. The impact of any discrepancy should be negligible.

The trial design involves two sets of rules, namely:

(1) dose-escalation rules for the next cohort when the current cohort completes Cycle 2, and

(2) rules for Cycle 2 dosing after completion of Cycle 1.

A cohort will be considered as ended once three subjects of the cohort complete Cycle 2 or early discontinue during Cycle 2. Subjects with DLTs in Cycle 1 will be discontinued prior to Cycle 2.

Once five subjects are enrolled in a cohort, the cohort will be considered as ended, after all five subjects complete Cycle 2 or discontinue early during Cycle 1 or 2.

For the purpose of simulations, the dose decisions will be made at the following milestones:

- Cycle 2 dosing will be determined only once the full cohort, including any replacement subjects, completes Cycle 1 (as opposed to on an individual basis in the study).
- The dose for the next cohort will be decided once the current cohort has ended.

The timing of these decisions will slightly vary during the study, as it is currently planned to decide the Cycle 2 dose on an individual subject basis and to decide for the next cohort once up to three subjects in the current cohort are 3 weeks into Cycle 2. The impact of these changes should be minimal.

The inter cohort dose escalation will be performed as follows:

(1) The starting dose will be d=5 GBq fractionated into two administrations of $d_1=d_2=2.5$ GBq per cycle and the first cohort will include three subjects.

(2) If there is no DLT during Cycle 1, the radioactivity for the next cohort will be increased by 3 GBq (1.5 GBq/cycle) up to 11 GBq (5.5 GBq/cycle) and then by 2 GBq (1 GBq/cycle) up to the last planned cohort of 15 GBq (7.5 GBq/cycle). Cohort size will be three subjects.

(3) If at least one subject in a cohort reports any DLT, wait for the corresponding cohort (including any replacement) to end the study, then fit the Bayesian model to all available Cycle 1 and Cycle 2 data, and select next dose as the dose d at which QS_d is maximum, or the maximum allowed dose if any of the following constraints are met:

   (a) if there are two DLTs out of three, three DLTs out of five, or three DTLs out of six subjects receiving a single or cumulative dose, d must be lower than or equal to that dose;

   (b) if there are three DLTs out of three, or at least three DLTs out of four, or at least four DLTs out of five, or at least four DLTs out of six subjects receiving a single or cumulative dose, d must be lower than that dose;

   (c) dose d must be at most 1 GBq larger than the maximum Cycle 1 dose tested previously.

Repeat steps 2 and 3 again, assigning the subjects/cohort to this dose. Terminate study enrolment when any of the following stopping rules happen:

A the MTSA is precisely estimated: CV (MTSA) calculated as the inter-quartile range over the median is lower than 30%;

B maximum possible dose (7.5 GBq) is safe: $TS_{7.5}$>80% and d_1=7.5 GBq administered;

C minimum dose tested (2.5 GBq) is toxic: $TS_{2.5}$ <20%;

D total sample size for next dose is already ≥6.

The MTSA will be declared to be found when study stops for criteria A or D.

Individual dosing decision for the second treatment cycle will be done as follows:

- Subject will be eligible for Cycle 2 only if subject had no DLT during Cycle 1. Subjects with DLTs in Cycle 1 will be discontinued and replaced with a maximum of two replacements.
- The same fractional dose as in Cycle 1 will be repeated during Cycle 2 (d_2=d_1), if the dose having the largest probability to be the MTCA is larger than 2 x d_1.
- The fractional dose for Cycle 2 will be decreased to d_2=MTCA-d_1 dose, if the predicted cumulative exposure after Cycle 2 is above the MTCA target. In this situation, the cumulative exposure after two cycles should not exceed the MTCA.

The study will be terminated when all cohorts have ended the study, as defined above.

19.5.3 Simulation Scenarios

Five dose-DLT profiles were considered to evaluate the operational characteristics of the adaptive dose escalation trial (see Figure 4 and Table 12 below). The five scenarios are:

Scenario A – Maximum dose safe: This scenario represents a negative scenario under which all doses are safe for the two dosing occasions. The true MTSA (15 GBq) and true MTCA (30 GBq) are larger than the maximum possible doses in the study.

Scenario B - Late MTCA: This is a scenario is which the MTCA=MTSA=14 GBq. All Cycle 1 doses are safe. After Cycle 2, cumulative doses up to and including 14 GBq are safe. The probability of a DLT is gradually increasing across all dose levels.

Scenario C – Early MTCA: In this scenario, the rate of DLT progression is faster over doses so that the MTSA (7 GBq) during Cycle 1 appears near the end of the dosage range. The MTCA after Cycle 2 is 9 GBq.

Scenario D - Toxic: Under this scenario, all doses are toxic, with a DLT rate of 46% at the lowest single dose of 2.5 GBq or at the repeated cumulative dose of 5 GBq. The MTSA (2 GBq) is below but close to the lowest single dose of 2.5 GBq. The MTCA is also equal to 2 GBq, so that any Cycle 2 dosing is toxic.

Scenario E - Peak: In this scenario, there is a step function in the probability of DLTs occurring in the middle of the dose escalation process during Cycle 1 and early in Cycle 2. The first doses up to and including MTSA=5.5 GBq are very safe (p=5%), and all subsequent single doses are toxic (p=80%). After Cycle 2, the MTCA is 5 GBq and all subsequent doses are toxic.

Figure 4 Dose versus DLT Rates After Cycle 1 and Cycle 2 Simulation Scenarios

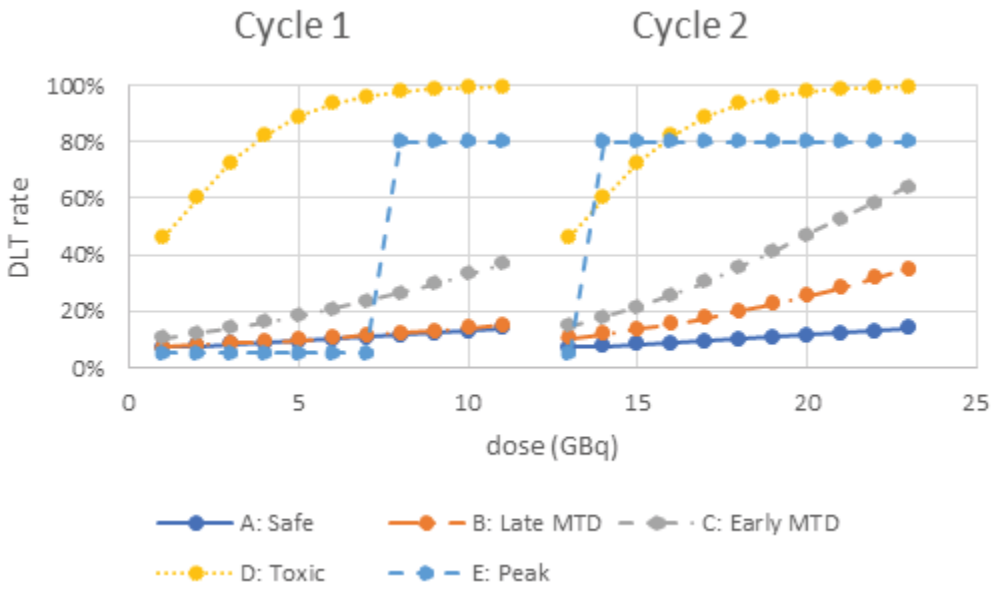


Table 12 Simulated Dose-DLT Probabilities

Dose (GBq)	A: Safe	B: Late MTD	C: Early MTD	D: Toxic	E: Peak
Cycle 1					
2.5	7%	7%	10%	46%	5%
3.0	8%	8%	12%	60%	5%
3.5	8%	8%	14%	72%	5%
4.0	9%	9%	16%	82%	5%
4.5	9%	10%	18%	89%	5%
5.0	10%	10%	21%	93%	5%
5.5	11%	11%	23%	96%	5%
6.0	11%	12%	26%	98%	80%
6.5	12%	13%	30%	99%	80%
7.0	13%	14%	33%	99%	80%
7.5	14%	15%	37%	100%	80%
Cycle 2					
5.0	7%	10%	15%	46%	5%
6.0	8%	12%	18%	60%	80%
7.0	8%	13%	21%	72%	80%
8.0	9%	15%	26%	82%	80%
9.0	9%	17%	30%	89%	80%
10.0	10%	20%	36%	93%	80%
11.0	11%	22%	41%	96%	80%
12.0	11%	25%	47%	98%	80%
13.0	12%	28%	53%	99%	80%
14.0	13%	32%	58%	99%	80%
15.0	14%	35%	64%	100%	80%

DLT=dose limiting toxicity, MTD=maximum tolerated dose.

19.5.4 Operational Characteristics

We used 1000 trial simulations to monitor the following properties of the adaptive design under the five scenarios:

- accuracy and precision of the MTSA and MTCA
- probability of archiving each of the four stopping rules (MTSA precision, last dose is safe, first dose is toxic, maximum sample size)
- total sample size after Cycle 1 and Cycle 2

- total number of cohorts
- number and proportion of subjects being overdosed during Cycle 1 and Cycle 2 (i.e. relative to the true MTSA and MTCA, respectively)
- subject distribution across dose levels.

Calculations were performed in R statistical software version 2.7.2 and using the BRugs package running on OpenBUGS version 2.2.0 for the Bayesian estimation. The posterior distribution was estimated using one MCMC chain based on 1000 iterations, after a burn-in of 2000 samples. The initial values were set to p_0=5%, MTD=5 GBq and β=0. Convergence was monitored by visual inspection of the diagnosis plots for a sample dataset spread across all five scenarios.

19.5.5 Simulation Results

The operational characteristics for the five trial simulation scenarios are presented in Table 13.

The mean (SD) sample size per dose is shown in Figure 5.

A box plot of the total sample size is in Figure 6 for Cohort 1 and in

Figure 8 for Cohort 2.

The number of cohorts is in

Figure 8 .

Overall, simulations performed as expected, under all scenarios, taking into account the constraints about the maximum fold-increase, the repeated dosing, the overdose control and the maximum sample size. The dose escalation for Cycle 1 was pursued up to the top single dose of 7.5 GBq under a similar pattern for the Safe, Early and Late scenarios, where the MTSA was either above the top dose (Safe, Late) or close to it (Early). Under the Toxic scenario, only low doses were administered, with an MTSA estimated near the first single dose (2.5 GBq) in most trials. When the MTSA and MTCA were within the dosage range (Peak), the escalation was performed up to the target dose of 5 to 5.5 GBq, followed by an adaptation around it. The MTSA and MTCA were found with precision in most trials and their relative errors remain good. There was a high proportion of trials stopped with the MTSA found (either based on CV or sample size criteria). As expected, sample size and cohort size were larger when escalation had to proceed up to the top doses (Safe, Late, Early) than when the MTSA was low (Toxic and Peak). In 80% of trial simulations, the total number of subjects was not larger than 28 in a maximum of seven cohorts. The number of overdoses was low in Cycle 1. It did not increase during Cycle 2, except when the second dose brought more toxicity (Early, Peak).

These results validate the use of the Bayesian model and the adaptive dose escalation plan for this study.

Table 13 Main Operational Characteristics for the Five Trial Simulation Scenarios

Criterion	A: Safe	B: Late	C: Early	D: Toxic	E: Peak
% stops for reason: 2.5 GBq is toxic				23.4	
% stops for reason: 7.5 GBq is safe	58.9	46.4	5.90		
% stops for reason: CV (MTSA)≤30%	34.0	42.4	69.0	34.1	92.1
% stops for reason: N≥6	7.10	11.2	25.1	42.5	7.90
% trials (MTSA>top dose)	94.9	92.5	48.8	.	0.8
% trials (MTSA<first dose)	.	.	.	38.1	.
Median MTSA (GBq)	10.5	9.9	7.4	2.7	4.8
Median MTSA Rel. Error (%) [a]	30.2%	29.2%	15.3%	34.2%	13.8%
Mean CV (MTSA) (%)	28.8%	28.9%	28.9%	43.5%	21.5%
Median MTCA (GBq)	17.4	14.7	9.5	4.2	6.2
Median MTCA Rel. Error (%) [a]	41.9%	19.7%	16.9%	112%	25.2%
Mean CV (MTCA) (%)	17.3%	26.9%	39.5%	54.2%	25.7%
Mean (SD) number of overdosed subjects (Cycle 1)	0.0 (0.0)	0.0 (0.0)	1.8 (2.1)	9.1 (3.6)	5.5 (1.5)
[Min, Max]	[0.0, 0.0]	[0.0, 0.0]	[0.0, 5.0]	[5.0, 19.0]	[0.0, 14.0]
Mean (SD) number of overdosed subjects (Cycle 2)	0.0 (0.0)	1.7 (1.5)	6.3 (2.9)	3.6 (1.9)	7.8 (1.9)
[Min, Max]	[0.0, 0.0]	[0.0, 3.0]	[0.0, 12.0]	[0.0, 9.0]	[0.0, 15.0]
Mean (SD) number of subjects (Cycle 1)	17.5 (3.0)	17.7 (3.3)	18.7 (4.3)	9.1 (3.6)	15.9 (2.5)
[Min, Max]	[5.0, 25.0]	[5.0, 28.0]	[5.0, 31.0]	[5.0, 19.0]	[5.0, 28.0]
Mean (SD) number of subjects (Cycle 2)	15.7 (2.5)	15.7 (2.7)	14.3 (3.3)	3.6 (1.9)	10.8 (2.0)
[Min, Max]	[2.0, 21.0]	[2.0, 21.0]	[2.0, 21.0]	[0.0, 9.0]	[2.0, 18.0]
Mean (SD) number of cohorts	5.3 (0.8)	5.3 (0.9)	5.1 (1.1)	2.0 (0.9)	4.4 (0.6)
[Min, Max]	[1.0, 7.0]	[1.0, 7.0]	[1.0, 7.0]	[1.0, 4.0]	[1.0, 7.0]

CV=coefficient of variation; Max=maximum; Min=minimum; MTSA=maximum tolerated single activity.

a Rel. Error=$|MTD_{true}-MTD_{median}|/MTD_{true}$

Figure 5 Mean (SD) Sample Size per Single or Cumulative Dose Level for the Five Simulation Scenarios

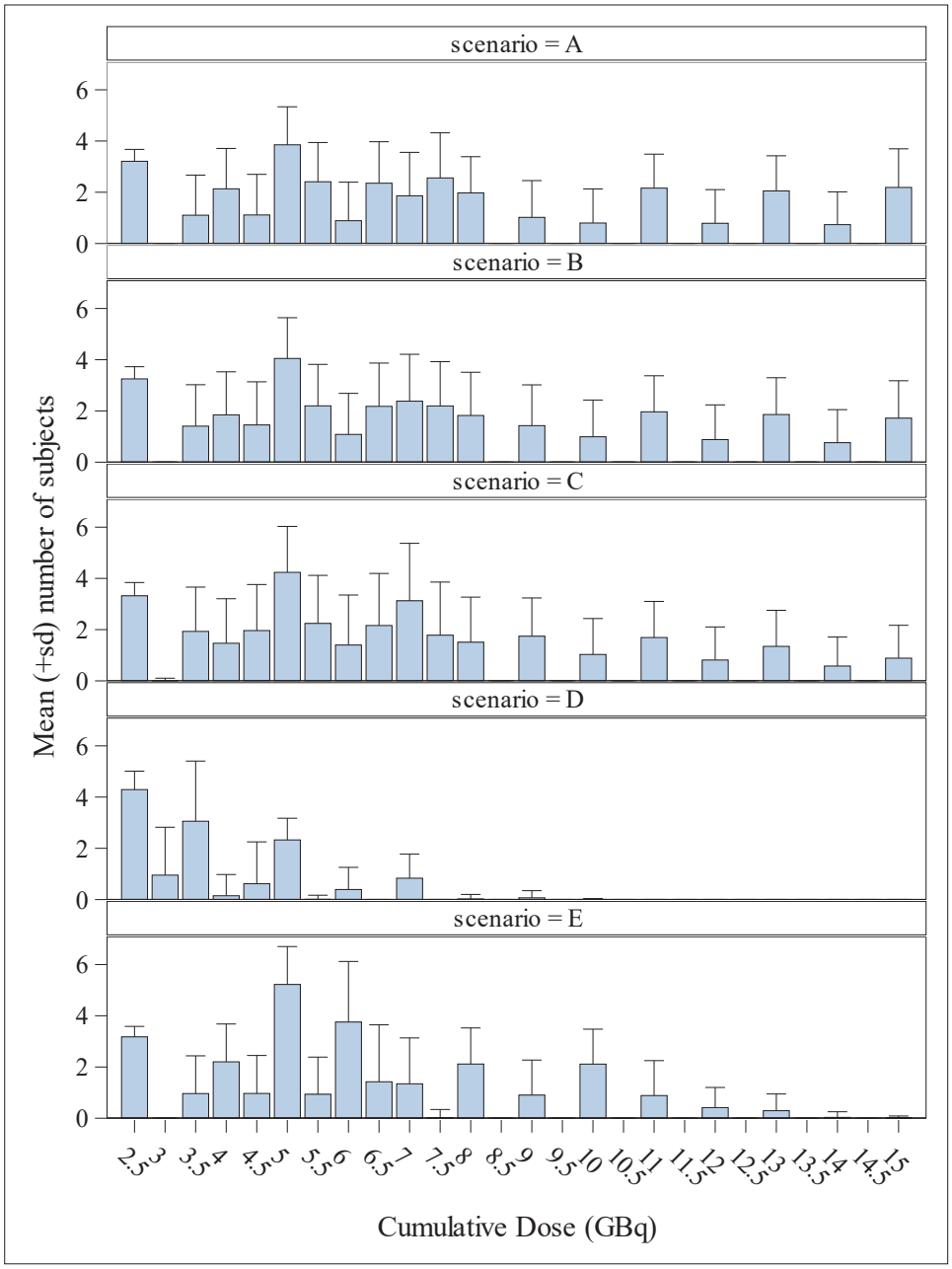


Figure 6 Boxplot of Total Number of Subjects During Cycle 1 for the Five Simulation Scenarios

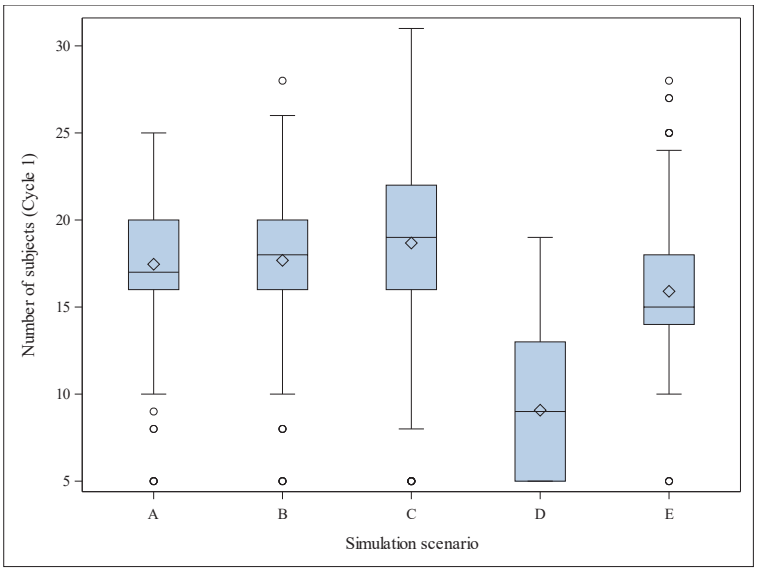


Figure 7 Boxplot of Total Number of Subjects During Cycle 2 for the Five Simulation Scenarios

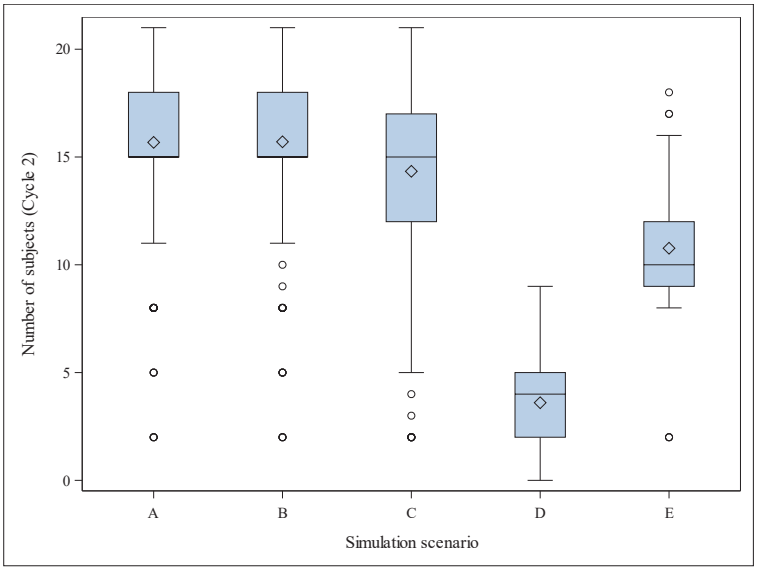
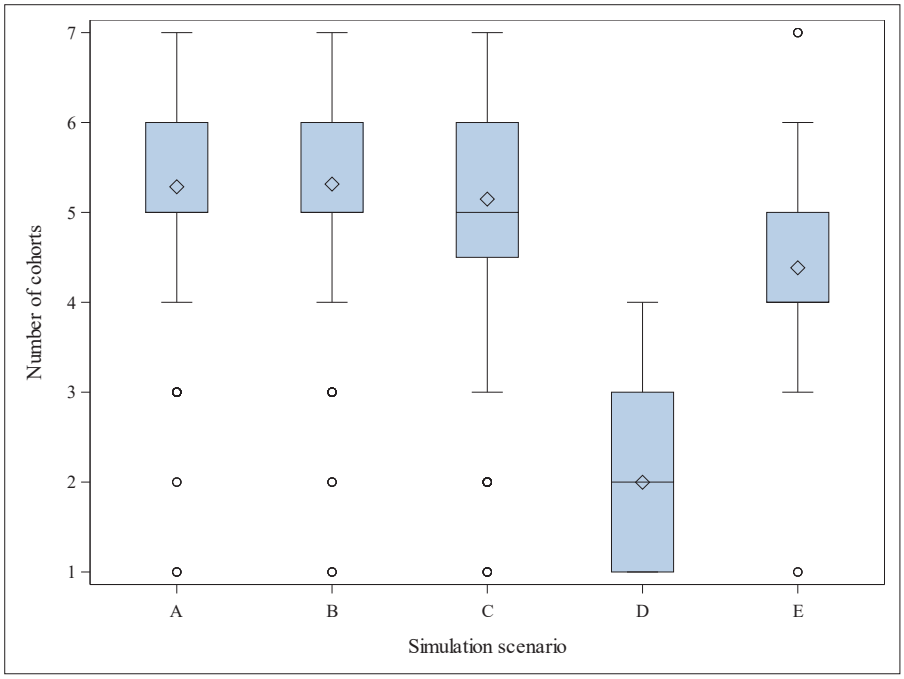


Figure 8 Boxplot of Total Number of Cohorts for the Five Simulation Scenarios



19.6 Attachment 6 – RECIST to PERCIST

TABLE 7. Comparison of EORTC and PERCIST 1.0 (36)

Characteristic	EORTC	PERCIST 1.0
Measurability of lesions at baseline	1. Tumor regions defined on pretreatment scan should be drawn on region of high ^{18}F-FDG uptake representing viable tumor. Whole tumor uptake should also be recorded. 2. Same ROI volumes should be sampled on subsequent scans and positioned as close to original tumor volume as possible. Coregistration method should be recorded. 3. Uptake measurements should be made for mean and maximal tumor ROI counts per pixel per second calibrated as MBq/L. 4. Alterations in extent of ^{18}F-FDG uptake should be documented, i.e., increase in orthogonal tumor dimensions including longest tumor dimension. 5. Partial volume may affect measurement of ^{18}F-FDG uptake. Tumor size from anatomic imaging in relation to PET scanner resolution should be documented where possible.	1. Measurable target lesion is hottest single tumor lesion SUL of "maximal 1.2-cm diameter volume ROI in tumor" (SUL peak). SUL peak is at least 1.5-fold greater than liver SUL mean + 2 SDs (in 3-cm spherical ROI in normal right lobe of liver). If liver is abnormal, primary tumor should have uptake > 2.0 × SUL mean of blood pool in 1-cm-diameter ROI in descending thoracic aorta extended over 2-cm *z*-axis. 2. Tumor with maximal SUL peak is assessed after treatment. Although typically this is in same region of tumor as that with highest SUL peak at baseline, it need not be. 3. Uptake measurements should be made for peak and maximal single-voxel tumor SUL. Other SUV metrics, including SUL mean at 50% or 70% of SUV peak, can be collected as exploratory data; TLG can be collected ideally on basis of voxels more intense than 2 SDs above liver mean SUL (see below). 4. These parameters can be recorded as exploratory data on up to 5 measurable target lesions, typically the 5 hottest lesions, which are typically the largest, and no more than 2 per organ. Tumor size of these lesions can be determined per RECIST 1.1.
Normalization of uptake	Scanners should provide reproducible data. Reporting would need to be accompanied by adequate and disclosed reproducibility measurements from each center. An empiric 25% was found to be a useful cutoff point, but reproducibility analysis is needed to determine appropriate cutoffs for statistical significance.	Normal liver SUL must be within 20% (and <0.3 SUL mean units) for baseline and follow-up study to be assessable. If liver is abnormal, blood-pool SUL must be within 20% (and <0.3 SUL mean units) for baseline and follow-up study to be assessable. Uptake time of baseline study and follow-up study 2 must be within 15 min of each other to be assessable. Typically, these are at mean of 60 min after injection but no less than 50 min after injection. Same scanner, or same scanner model at same site, injected dose, acquisition protocol (2- vs. 3-dimensional), and software for reconstruction, should be used. Scanners should provide reproducible data and be properly calibrated.
Objective response	CMR: complete resolution of ^{18}F-FDG uptake within tumor volume so that it was indistinguishable from surrounding normal tissue.	CMR: complete resolution of ^{18}F-FDG uptake within measurable target lesion so that it is less than mean liver activity and indistinguishable from surrounding background blood-pool levels. Disappearance of all other lesions to background blood-pool levels. Percentage decline in SUL should be recorded from measurable region, as well as (ideally) time in weeks after treatment was begun (i.e., CMR −90, 4). No new ^{18}F-FDG–avid lesions in pattern typical of cancer. If progression by RECIST, must verify with follow-up.

TABLE 7. continued

Characteristic	EORTC	PERCIST 1.0
	PMR: reduction of minimum of 15% ± 25% in tumor ^{18}F-FDG SUV after 1 cycle of chemotherapy, and >25% after more than 1 treatment cycle; reduction in extent of tumor ^{18}F-FDG uptake is not a requirement for PMR.	PMR: reduction of minimum of 30% in target measurable tumor ^{18}F-FDG SUL peak. Absolute drop in SUL must be at least 0.8 SUL units, as well. Measurement is commonly in same lesion as baseline but can be another lesion if that lesion was previously present and is the most active lesion after treatment. ROI does not have to be in precisely same area as baseline scan, though typically it is. No increase, >30% in SUL or size of target or nontarget lesions (i.e., no PD by RECIST or IWC) (if PD anatomically, must verify with follow-up). Reduction in extent of tumor ^{18}F-FDG uptake is not requirement for PMR. Percentage decline in SUL should be recorded, as well as (ideally) time in weeks after treatment was begun (i.e., PMR −40, 3). No new lesions.
	SMD: increase in tumor ^{18}F-FDG SUV < 25% or decrease of <15% and no visible increase in extent of ^{18}F-FDG tumor uptake (20% in longest dimension).	SMD: not CMR, PMR, or PMD. SUL peak in metabolic target lesion should be recorded, as well as (ideally) time from start of most recent therapy, in weeks (i.e., SMD −15, 7).
	PMD: increase in ^{18}F-FDG tumor SUV of >25% within tumor region defined on baseline scan; visible increase in extent of ^{18}F-FDG tumor uptake (20% in longest dimension) or appearance of new ^{18}F-FDG uptake in metastatic lesions.	PMD: >30% increase in ^{18}F-FDG SUL peak, with >0.8 SUL unit increase in tumor SUV peak from baseline scan in pattern typical of tumor and not of infection/treatment effect. OR: Visible increase in extent of ^{18}F-FDG tumor uptake (75% in TLG volume with no decline in SUL. OR: New ^{18}F-FDG–avid lesions that are typical of cancer and not related to treatment effect or infection. PMD other than new visceral lesions should be confirmed on follow-up study within 1 mo unless PMD also is clearly associated with progressive disease by RECIST 1.1. PMD should be reported to include percentage change in SUV peak, (ideally, time after treatment, in weeks) and whether new lesions are present/absent and their number (i.e., PMD, +35, 4, new: 5). Because SUL is continuous variable, dividing response criteria into limited number of somewhat arbitrary response categories loses much data. For this reason, PERCIST preserves percentage declines in SUV peak in each reported category. Because rapidity with which scan normalizes is important (faster appears better), PERCIST asks for time from start of treatment as part of reporting. For example, CMR 90, 1, is probably superior to CMR 90, 10, especially if latter patient were SMD 20, 1. More than one measurement of PET response may be needed at differing times, and it may be treatment type–dependent. PERCIST 1.0 evaluates SUL peak of only hottest tumor. This is possible limitation of approach, but lesions and their responses are highly correlated in general. Additional data are required to determine how many lesions should be assessed over 1. A suggested option is to include the 5 hottest lesions, or the 5 observed on RECIST 1.1 that are most measurable. Percentage change in SUL can be reported for single lesion with largest increase in uptake or smallest decline in uptake. Additional studies will be needed to define how many lesions are optimal for assessment.

TABLE 7. continued

Characteristic	EORTC	PERCIST 1.0
	Nonmeasurable disease: CR, disappearance of all known disease, confirmed at ≥4 wk; PR, estimated decrease of ≥50%, confirmed at 4 wk; PD, estimated increase of ≥25% in existent lesions; NC, neither PR nor PD criteria met.	Nontarget lesions: CMR, disappearance of all ^{18}F-FDG–avid lesions: PMD, unequivocal progression of ^{18}F-FDG–avid nontarget lesions or appearance of new ^{18}F-FDG–avid lesions typical of cancer; non-PMD: persistence of one or more nontarget lesions or tumor markers above normal limits.
Overall response		1. Best response recorded in measurable disease from treatment start to disease progression or recurrence. 2. Non-PMD in measurable or nonmeasurable nontarget lesions will reduce CR in target lesion to overall PMR. 3. Non-PMD in nontarget lesions will not reduce PR in target lesions.
Duration of response		1. Overall CMR: from date CMR criteria are first met; to date recurrent disease is first noted. 2. Overall response: from date CMR or PMR criteria are first met (whichever status came first); to date recurrent disease is first noted. 3. SMD: from date of treatment start to date PMD is first noted.

TLG = total lesion glycolysis; CMR = complete metabolic response; PMR = partial metabolic response; PD = progressive disease; SMD = stable metabolic disease; PMD = progressive metabolic disease; CR = complete remission; PR = partial remission; NC = no change.

For PERCIST: Single-voxel SUL is commonly used but has been reported to be less reproducible than SUL peak, especially with very small single-voxel values. It is suggested, but not required, that lesions assessed on PERCIST be larger than the 1.5-cm-diameter volume ROI used to minimize partial-volume effects. Percentage changes are proposed to deal with SUL peak changes. Use of maximal SUL could be explored. If 5 lesions are used as exploratory approach, it is suggested that sum of SULs of baseline 5 lesions serve as baseline for study. After treatment, sum of same 5 lesions should be used. Percentage change in SUL is based on change in these sums from study 1 to study 2. Exploratory analysis can include calculating percentage change in SUL in individual lesions and averaging them. This may produce different result. We believe summed SUL approach will be less prone to minor errors in measurements.

For total lesion glycolysis: Exploratory analysis can include either all foci of tumor with maximal SUL > 2 SDs above normal liver, 5 lesions with highest SUL, or lesion with highest SUL. It is suggested that threshold approach, typically at 2 SDs above normal liver SUL, be used to generate lower bounds of ROI (3 SDs could be used for very active tumors). We believe this approach will be less variable than methods based on maximal SUL with percentage of maximal cutoff. Criteria for progression include 75% growth in TLG for SUL and are conservatively placed at 75% increase. Because 20% increase in EORTC linear size scales to 73% volume increase, the figures are comparable. Progression is judged from best response if being assessed after first scan was performed. For response by TLG, we propose 45% reduction as useful starting point, but more data are needed to make firm recommendations. If TLG is determined, explicit methodologic details should be provided. It should not be a primary metric, but a secondary endpoint at this time.

19.7 Attachment 7 – Protocol Amendment #7 Summary

PROTOCOL VERSION 8.0

STUDY NUMBER:	D-FR-01087-001
PROTOCOL TITLE:	An international multicentre, open-label first in human phase I/II study to evaluate the safety, tolerability, biodistribution and antitumour activity of ^{177}Lu-3BP-227 for the treatment of subjects with solid tumours expressing neurotensin receptor 1
AMENDED PROTOCOL VERSION NUMBER AND DATE	Version 8.0: 12 June 2020

THE FOLLOWING AMENDMENTS ARE PROPOSED:

Section	Version 7.0, 20 June 2019 **WAS**	Version 8.0, 12 June 2020 **IS**	RATIONALE FOR CHANGE
Cover Page, Agreement	**Protocol Version 7.0, dated 20 June 2019**	**Protocol Version 8.0, dated 12 June 2020**	Administrative update
Cover Page	**Serious Adverse Event Reporting** Fax: PPD	**Serious Adverse Event Reporting** Fax **Number**: PPD **USA and Latin America Fax Number:** PPD	Administrative update
Cover Page	**Sponsor Authorised Protocol Approver** Name, Title: PPD	**Sponsor Authorised Protocol Approver** Name, Title: PPD	Administrative update
Cover page	**Sponsor Medical Monitor** Name, Title: PPD	**Sponsor Medical Monitor** Name, Title: PPD	Administrative update
Agreement	**Sponsor** Name: PPD	**Sponsor** Name: PPD	Administrative update
Synopsis, 2.1	**STUDY HYPOTHESIS** **Phase I** ^{177}Lu-3BP-227 is sufficiently well-tolerated to permit clinical investigation in ~~the~~ phase II ~~part~~.	**STUDY HYPOTHESIS** **Phase I** ^{177}Lu-3BP-227 is sufficiently well-tolerated to permit clinical investigation in phase II.	Clarification
Synopsis, 2.2	**STUDY HYPOTHESIS** **Phase II**	**STUDY HYPOTHESIS** **Phase II**	FDA request to clarify the eligible subject population: inclusion

Section	Version 7.0, 20 June 2019 WAS	Version 8.0, 12 June 2020 IS	RATIONALE FOR CHANGE
	^{177}Lu-3BP-227 yields higher objective response rates in subjects who have NTSR1 expressing ~~metastatic or~~ locally advanced ~~cancers~~, based on RECIST version 1.1 by central review and as compared with the historical ORR obtained by current standard-of-care treatment for each tumour type.	^{177}Lu-3BP-227 yields higher objective response rates in subjects who have NTSR1 expressing **cancers that are unresectable,** locally advanced **or metastatic**, based on RECIST version 1.1 by central review and as compared with the historical ORR obtained by current standard-of-care treatment for each tumour type.	criterion should clearly state nonresectable locally advanced disease.
Synopsis, 1.5, 1.7, 3.1.1, 3.1.2, 4.1, 4.2.1, 4.3	...subjects with ~~metastatic or~~ locally advanced...	...subjects with **unresectable,** locally advanced **or metastatic**...	FDA request to clarify the eligible subject population: inclusion criterion should clearly state nonresectable locally advanced disease
Synopsis, 3.2.1	*Secondary objectives* **Phase I** … b) To determine the radiation dosimetry of ^{177}Lu-3BP-227 (organ exposure to radiation) ~~after each administration~~.	*Secondary objectives* **Phase I** … b) To determine the radiation dosimetry of ^{177}Lu-3BP-227 (organ exposure to radiation).	Clarification
Synopsis, 3.3.1	*Exploratory objectives* **Phase I/II** a) To explore the correlation between the tumour uptake of ^{177}Lu-3BP-227 and the NTSR1 expression on tumours. b) To explore renal ~~and haematological~~ safety by measuring urinary specific biomarkers ~~and deoxyribonucleic acid double strand breaks (DNA DSB) in peripheral lymphocytes (at selected centres)~~. c) To evaluate the tumour microenvironment, transcriptomics, and other markers of interest for the disease through assessment of tumour biopsies. d) To explore genomic alterations in circulating cell-free DNA (cfDNA) ~~as compared to~~ germline DNA.	*Exploratory objectives* **Phase I/II** a) To explore the correlation between the tumour uptake of ^{177}Lu-3BP-227 and the NTSR1 expression on tumours. b) To explore renal safety by measuring urinary specific biomarkers. c) To evaluate the tumour microenvironment, transcriptomics, and other markers of interest for the disease through assessment of tumour biopsies. d) To explore genomic alterations in circulating cell-free DNA (cfDNA) **and in** germline DNA.	Assessment of haematological safety markers (DNA-DSB in peripheral lymphocytes) removed and clarification of the genomic alteration assessment
Synopsis, 4.4.3	Exploratory endpoints • Tumour microenvironment and other markers of interest (such as NTSR1 expression, Ki67, gene	Exploratory endpoints • Tumour microenvironment and other markers of interest (such as NTSR1 expression, Ki67, gene	Clarification

Section	Version 7.0, 20 June 2019 WAS	Version 8.0, 12 June 2020 IS	RATIONALE FOR CHANGE
	expression and DNA ~~DSB~~) in tumour biopsies taken at baseline, at EOCT visit or at disease progression, whichever occurs earlier;	expression and DNA **damage**) in tumour biopsies taken at baseline, at EOCT visit or at disease progression, whichever occurs earlier;	
Synopsis, 4.4.3	Exploratory endpoints ~~(c) Number of DNA-DSB per cell in peripheral lymphocytes and the correlation with absorbed dose in the blood at baseline and , 4 and 72 to 96 hours after each administration (in selected centres only).~~	Exploratory endpoint deleted	Assessment of haematological safety markers (DNA-DSB in peripheral lymphocytes) removed
Synopsis, 4.2.1.1, 19.5.1	The MTCA is defined as the maximum tolerated cumulative activity that may be administered following fractionated i.v. administrations of at least 4 weeks apart, so that: • No more than 33% of the subjects experience a dose limiting toxicity (DLT) during Cycle 1 or 2 and • The cumulative radiation in each target organ does not exceed the acceptability limits.	The MTCA is defined as the maximum tolerated cumulative activity that may be administered following fractionated i.v. administrations of at least 4 weeks apart, so that: • No more than 33% of the subjects experience a dose limiting toxicity (DLT) during Cycle**s** 1 **and/**or 2 and • The cumulative radiation in each target organ does not exceed the acceptability limits.	Clarification
Synopsis, 4.7.1.1	The DLTs are defined ... DLT assessment period (from the first administration of ^{177}Lu-3BP-227 to EOCT/ED): ... • Grade 4 thrombocytopenia for~~—~~seven or more consecutive days; • ~~bleeding requiring transfusion with Grade 3 thrombocytopenia;~~ • any Grade 3 ~~or higher laboratory abnormalities on haemoglobin requiring transfusion for >4 weeks~~; • any Grade 3 or higher laboratory abnormalities ~~on~~ aspartate amino transferase/alanine amino transferase (AST/ALT) ~~and/or bilirubin, which do not resolve in ≤4 weeks~~; • any Grade 3 or higher ~~chronic kidney disease~~ (estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2), ~~which does not resolve within 1~~	The DLTs are defined ... DLT assessment period (from the first administration of ^{177}Lu-3BP-227 to EOCT/ED): ... • Grade **3 or** 4 thrombocytopenia **(platelet count decreased) with clinically meaningful bleeding (i.e. requiring urgent hospitalisation or transfusion to manage the bleeding);** • Grade 4 thrombocytopenia for seven or more consecutive days; • **A**ny Grade 3 **anaemia (Hb<8.0 g/dL; transfusion indicated) or Grade 4 anaemia (life-threatening consequences; urgent intervention indicated);** • **A**ny Grade 3 or higher laboratory abnormalities **in** aspartate aminotransferase/alanine aminotransferase (AST/ALT) **with accompanying Grade 2 or higher bilirubin (Hy's law);**	FDA request to revise the DLT criteria to adequately describe the grading as stated in the CTCAE v5.0 dictionary: - Grade 4 thrombocytopenia with a clinically significant bleeding is a DLT, irrespective of the duration of thrombocytopenia. In addition, revised the DLT criterion so a Grade 3 thrombocytopenia with a clinically meaningful bleeding (i.e. requiring urgent hospitalisation or transfusion) is a DLT. - Clarified the haemoglobin DLT criterion - Revised the ALT/AST DLT criteria so a Grade 3 ALT/AST

Section	Version 7.0, 20 June 2019 WAS	Version 8.0, 12 June 2020 IS	RATIONALE FOR CHANGE
	~~week on nephroprotective treatment (e.g. forced diuresis);~~ • any Grade 3 or higher GI AE ~~with the following specifications: Grade 4 (life threatening) nausea, vomiting, diarrhoea, constipation, dry mouth or Grade 3 nausea, vomiting, diarrhoea, constipation not resolved to Grade ≤2 within 48 hours despite optimal adequate medical management;~~ • any toxicity related to ^{177}Lu-3BP-227 resulting in a treatment delay of more than four weeks due to either delayed recovery to baseline or resolution of any AE ~~of~~ Grade ≤2 (exception of alopecia and lymphopenia). ...	• **A**ny Grade 3 or higher **renal injury/toxicity** (estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2); • **A**ny Grade 3 or higher GI AE, **not resolved to Grade ≤2 within 48 hours despite optimal adequate medical management, with the following specifications:** - **Grade 3 nausea, vomiting (inadequate oral caloric or fluid intake; tube feeding, total parenteral nutrition or hospitalisation indicated)** - **Grade 3 diarrhoea (increase of ≥7 stools per day over baseline; hospitalisation indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL) or Grade 4 diarrhoea (life-threatening consequences; urgent intervention indicated)** - **Grade 3 constipation (obstipation with manual evacuation indicated; limiting self-care activities of daily living) or Grade 4 constipation (life-threatening consequences; urgent intervention indicated);** • **A**ny toxicity related to ^{177}Lu-3BP-227 resulting in a treatment delay of more than four weeks due to either delayed recovery to baseline or resolution of any AE **to** Grade ≤2 (**with the** exception of alopecia and lymphopenia). ...	increase simultaneous with a Grade 2 increase in bilirubin is considered a DLT (Hy's law). - Revised the DLT criteria so Grade 3 renal injury/toxicity is a DLT, irrespective of the toxicity being "chronic" or acute. - Revised the DLT criteria to delete Grade 4 nausea and dry mouth (there is no Grade 4 nausea toxicity described in the CTACE v5.0 dictionary).
Synopsis, 4.2.1.4	**Study design following phase I dose escalation results** Upon ~~termination~~ of phase I dose escalation ~~and/~~or ~~determination~~ upon reaching MTCA and ~~stated~~ jointly by the safety review committee (SRC) and the sponsor, and in consideration of the accumulated subject data, cohorts of subjects will be studied to further characterise safety and efficacy of ^{177}Lu-3BP-227.	**Study design following phase I dose escalation results** Upon **completion** of **the** phase I dose escalation or upon reaching **the** MTCA and **confirmed** jointly by the safety review committee (SRC) and the sponsor, and in consideration of the accumulated subject data, cohorts of subjects will be studied to further characterise **the** safety and efficacy of ^{177}Lu-3BP-227.	Clarification

Section	Version 7.0, 20 June 2019 WAS	Version 8.0, 12 June 2020 IS	RATIONALE FOR CHANGE
Synopsis, 5.1.1	**Inclusion criteria:** (3a) Histologically or cytologically confirmed ~~metastatic or~~ locally advanced disease and ~~no compelling treatment option as per~~ standard-of-care and documented decision by a multidisciplinary oncology board including a specialist of the concerned pathology.	**Inclusion criteria:** (3) Histologically or cytologically confirmed **unresectable**, locally advanced **or metastatic** disease and **has received prior lines of** standard-of-care **chemotherapy/treatment and has no further suitable treatment options** and **a** documented decision by a multidisciplinary oncology board including a specialist of the concerned pathology.	FDA request to clarify the inclusion criterion to clearly state that no further suitable treatment options are available for subjects eligible for the study
Synopsis, 5.1.1	**Inclusion criteria:** (5) Tumour ~~tissue expressing NTSR1, as determined by~~ uptake of ^{177}Lu-3BP-227 (screening formulation) in ~~tumour lesions being~~ judged by the investigator to ~~more avid than in the non tumoral surrounding tissue based on whole body scan (planar scintigraphy); single photon emission computed tomography (SPECT)/ computed tomography (CT) can be performed as per investigator's judgement~~.	**Inclusion criteria:** (5) Tumour**s showing:** **(a)** uptake of ^{177}Lu-3BP-227 (screening formulation) in **known primary or metastatic sites as** judged by the investigator to **be greater** than **background**; **or** **(b) uptake of ^{111}In-3BP-227 in known primary or metastatic sites (for subjects who participated in Study D-FR-01087-002) as judged by the investigator to be greater than background.**	To allow inclusion of subjects screened for NTSR1+ in the D-FR-01087-002 phase I study (^{111}In-IPN01087) in the D-FR-01087-001 phase I (^{177}Lu-IPN01087) study.
Synopsis, 5.1.1	**Inclusion criteria:** (12~~a~~) Female subjects must not be pregnant or lactating at study entry and during the course of the study and must not become pregnant for at least 6 months following the last study treatment. Women of childbearing potential must agree to use a highly effective method of contraception (see note below). ~~Because CT scanning is part of the long term follow up (every 12 ±2 weeks), female subjects should not become pregnant until the end of study assessments.~~ (13~~a~~) …	**Inclusion criteria:** (12) Female subjects must not be pregnant or lactating at study entry and during the course of the study and must not become pregnant for at least 6 months following the last study treatment. Women of childbearing potential must agree to use a highly effective method of contraception (see note below). (13) …	Clarification that inclusion criteria are related to study treatment procedures
Synopsis, 5.2	**Exclusion criteria:** (1) Prior treatment received	**Exclusion criteria:** (1) Prior treatment received	Clarification

Section	Version 7.0, 20 June 2019 WAS	Version 8.0, 12 June 2020 IS	RATIONALE FOR CHANGE
	(a) Any antitumour treatment since last ~~documentation of~~ disease progression	(a) Any antitumour treatment since last **documented** disease progression	
Synopsis, 4.4.3	*Exploratory endpoints* … c) Genomic profiling in circulating cfDNA ~~as compared to~~ germline DNA.	*Exploratory endpoints* … c) Genomic profiling in circulating cfDNA **and in** germline DNA.	Clarification
1.5	**Rationale for the Study** ... ^{177}Lu-3BP-227 could be investigated in those subjects who ~~exhausted available effective~~ chemotherapy and their tumour tissue overexpresses NTSR1, knowing that the percentage of CRC tumours expressing NTSR1 is very high, with high degree of expression (see Section 1.7).	**Rationale for the Study** ... ^{177}Lu-3BP-227 could be investigated in those subjects who **have received prior lines of standard-of-care** chemotherapy/**treatment and have no further suitable treatment options** and their tumour tissue overexpresses NTSR1, knowing that the percentage of CRC tumours expressing NTSR1 is very high, with high degree of expression (see Section 1.7).	FDA request to clarify the inclusion criterion to clearly state that no further suitable treatment options are available for subjects eligible for the study
1.7	In this FIH study, the subject population enrolled to receive the IMP will be restricted to PDAC, CRC, GC, squamous-cell carcinoma of head and neck (SCCHN) and ES, which are locally advanced and expressing NTSR1. … Tumours/metastases expressing NTSR1 will be identified and documented through the lesion uptake of ^{177}Lu-3BP-227 (at low dose) during the screening period.	In this FIH study, the subject population enrolled to receive the IMP will be restricted to PDAC, CRC, GC, **GIST,** squamous-cell carcinoma of head and neck (SCCHN) and ES, which are u**nresectable**, locally advanced **or metastatic** and expressing NTSR1. … Tumours/metastases expressing NTSR1 will be identified and documented through the lesion uptake of ^{177}Lu-3BP-227 (at low dose) during the screening period. **Subjects who participated in the imaging study, Study D-FR-01087-002, with ^{111}In-3BP-227 (also called ^{111}In-IPN01087) and who have an uptake of ^{111}In-3BP-227 in tumour lesions that is more avid than in the nontumoural surrounding tissue based on whole body imaging (planar scintigraphy), as judged by the investigator, can also be considered for enrolment in this study, provided that they fulfil all other inclusion criteria and do not meet any of the exclusion criteria and were imaged with ^{111}In-3BP-227 before the first treatment administration (therapeutic dose) of ^{177}Lu-3BP-227.**	To allow inclusion of subjects screened for NTSR1+ in the D-FR-01087-002 phase I study (^{111}In-IPN01087) in the D-FR-01087-001 phase I (^{177}Lu-IPN01087) study.

Section	Version 7.0, 20 June 2019 WAS	Version 8.0, 12 June 2020 IS	RATIONALE FOR CHANGE
1.8	The participating subjects will be closely monitored during the study and during follow-up ~~for~~ ~~2~~ years ~~after the last administration~~.	The participating subjects will be closely monitored during the study and during **the long-term** follow-up **period until lost to follow-up, withdrawal of consent, death or a maximum of 5** years**, whichever occurs first**.	To extend the long-term follow-up period from 2 years to a maximum of 5 years based on peptide receptor radionuclide therapy experience on the risks of developing secondary malignancies, and the median time to occurrence of such malignancies. This will ensure continued benefit-risk assessment of ^{177}Lu-3BP-227 for a longer period of time after the end of treatment.
4.2.1	The study screening period includes a screening administration of ^{177}Lu-3BP-227 to assess the tumour uptake of each subject by whole body scan (planar scintigraphy)~~;~~ single photon emission computed tomography (SPECT)/CT ~~can be done~~ at the investigator's discretion ~~to further evaluate the tumour uptake;~~ ~~o~~nly subjects with a tumour uptake higher than nontumoural surrounding tissue (based on investigator's decision) will be deemed eligible for treatment.	The study screening period includes a screening administration of ^{177}Lu-3BP-227 to assess the tumour uptake of each subject by whole body scan (planar scintigraphy**, 1 or 2 timepoint(s) at the investigator's discretion**) **and optional** single photon emission computed tomography (SPECT)/CT **scans (up to 2** at the investigator's discretion**). O**nly subjects with a tumour uptake higher than nontumoural surrounding tissue (based on investigator's decision) will be deemed eligible for treatment.	After reviewing subjects' SPECT/CT images at different timepoints following the therapeutic dose of ^{177}Lu-IPN01087, it is concluded that the quality of SPECT image with respect to the background noise has substantially improved at the 48-hour and later timepoints. Considering the significant number of screen failures due to lack of radioactive uptake, which is contrary to the information available in the literature on the expression of NTSR1 receptor, the image acquisition timepoint has been moved to 48 hours after the screening dose.
4.2.1	… The screening period will last 3 weeks but can be extended by up to 2 weeks if this is required for logistical reasons.	The screening period will last 3 weeks but can be extended by up to 2 weeks if this is required for logistical reasons. **Subjects who participated in the imaging study, Study D-FR-01087-002, with**	To allow inclusion of subjects screened for NTSR1+ in the D-FR-01087-002 phase I study (^{111}In-IPN01087) in the

Section	Version 7.0, 20 June 2019 WAS	Version 8.0, 12 June 2020 IS	RATIONALE FOR CHANGE
		^{111}In-3BP-227 (also called ^{111}In-IPN01087) and who have an uptake of ^{111}In-3BP-227 in tumour lesions that is more avid than in the nontumoural surrounding tissue based on whole body imaging (planar scintigraphy), as judged by the investigator, can also be considered for enrolment in this study, provided that they fulfil all other inclusion criteria and do not meet any of the exclusion criteria and were imaged with ^{111}In-3BP-227 before the first treatment administration (therapeutic dose) of ^{177}Lu-3BP-227.	D-FR-01087-001 phase I (^{177}Lu-IPN01087) study.
4.2.1	A long-term follow-up ~~lasting 24 months~~ will start after the ~~end of last cycle (either~~ EOCT, early discontinuation (ED) ~~visit~~ or end of additional cycles (EOAC)~~)~~ and subjects will be followed up every 3 months (±2 weeks) until ~~24 months or~~ death~~,~~ whichever occurs first.	A long-term follow-up **period** will start after the EOCT, early discontinuation (ED) or end of additional cycles (EOAC) **visit** and subjects will be followed up every 3 months (±2 weeks) until **lost to follow-up, withdrawal of consent,** death **or a maximum of 5 years**, whichever occurs first.	Duration of long-term follow-up updated
4.2.1	**Figure 1** Long-term follow up ~~24 months~~	**Figure 1** Long-term follow up **5 years**	Figure updated to show new long-term follow-up period
4.2.1	**Figure 1** New footnote added	**Figure 1** Footnote added: **Note: Population screened includes subjects with unresectable disease.**	FDA request to clarify the eligible subject population, i.e. nonresectable locally advanced or metastatic disease.
4.2.1.2	The size of the cohorts will be three to five treated subjects, to secure a minimum of three evaluable subjects per cohort who completed 2 cycles of treatment. ~~Once five subjects receive one administration of ^{177}Lu-3BP-227 in a cohort, enrolment will be stopped in that cohort.~~ A cohort will be considered as completed once three subjects of the cohort complete Cycle 2 or early discontinue during Cycle 2 (except for cohort 1, see Proceeding to the Next Cohort described in Section 4.2.1.4).	The size of the cohorts will be three to five treated subjects, to secure a minimum of three evaluable subjects per cohort who completed 2 cycles of treatment. A cohort will be considered as completed once three subjects of the cohort complete Cycle 2 or early discontinue during Cycle 2 (except for cohort 1, see Proceeding to the Next Cohort described in Section 4.2.1.4). **If a subject replacement is needed to complete the cohort enrolment, see Section 4.7.1.3 for replacement rules.**	Clarification of the maximum number of subjects per cohort.
4.2.1.3	…	…	Clarification

Section	Version 7.0, 20 June 2019 WAS	Version 8.0, 12 June 2020 IS	RATIONALE FOR CHANGE
	In the first step, in order to minimise the number of subjects receiving subtherapeutic activity, the inter-cohort radioactivity escalation will be performed by increment of 3 GBq (1.5 GBq per administration), up to the first study drug related AE (Grade 2 or higher, except hair loss) or until a DLT occurs.	In the first step, in order to minimise the number of subjects receiving subtherapeutic activity, the inter-cohort radioactivity escalation will be performed by increment of 3 GBq (1.5 GBq per administration), up to the first study drug related **treatment-emergent** AE **(TEAE)** (Grade 2 or higher, except hair loss) or until a DLT occurs.	
4.5	For the phase I, the maximum duration of subject participation in the core trial is 21 weeks. However, if a clinical benefit ~~is observed~~, subject~~s~~ may receive up to four additional cycles after the EOCT, provided they have an acceptable tolerability profile~~,~~ the organ dose limits are not exceeded ~~and according to investigator's judgement~~, subject's discretion and must be discussed ~~with~~ and agreed ~~by~~ the sponsor.	For the phase I, the maximum duration of subject participation in the core trial is 21 weeks. However, if**, according to the investigator,** a **subject has** clinical benefit, **the** subject may receive up to four additional cycles after the EOCT, provided they have an acceptable tolerability profile **and** the organ dose limits are not exceeded**. This is at the** subject's discretion and must be discussed and agreed **with** the sponsor.	Clarification
4.5	In all cases, a long-term follow-up ~~lasting 24 months~~ will start after the ~~last cycle is administered (after~~ EOCT, ED ~~visit~~ or EOAC~~)~~ and subjects will be followed up every three months (±2 weeks).	In all cases, a long-term follow-up **period** will start after the EOCT, ED or EOAC **visit** and subjects will be followed up every three months (±2 weeks) **until lost to follow-up, withdrawal of consent, death or a maximum of 5 years, whichever occurs first**.	Duration of long-term follow-up updated
4.7.1	***Individual Discontinuation Rules*** ... If any of the following occur, no further treatment will be administered: • subject withdraws their consent to further treatment; ...	***Individual Discontinuation Rules*** ... If any of the following occur, no further treatment will be administered: • **life-threatening toxicities outside of the DLT reporting period** • subject withdraws their consent to further treatment; ...	FDA request to revise the discontinuation rules so if there are life-threatening toxicities outside of the DLT period, treatment is discontinued.
5.2	(1) Prior treatment received: … (b) Any chemotherapy within 3 weeks or nitrosourea prior to first treatment IMP administration	(1) Prior treatment received: … (b) Any chemotherapy within 3 weeks or nitrosourea **within 6 weeks** prior to first treatment IMP administration	Revision of inconsistent exclusion criteria between synopsis and core text.
6.2	New text added	**If the COVID-19 pandemic prevents subjects from coming to the site, subjects can have their study visit**	Clarification following COVID-19 pandemic.

Section	Version 7.0, 20 June 2019 WAS	Version 8.0, 12 June 2020 IS	RATIONALE FOR CHANGE
		assessments performed remotely as judged appropriate by the investigator. This must be discussed with the sponsor before being implemented. In such a case, the investigator will perform a telemedicine visit and will make every effort, where applicable, to contact the subject's general practitioner or specialist physician to ensure all important medical information and safety event(s) occurring since the last visit are collected. Guidance on how to collect protocol-planned assessments will be provided to the investigator in a separate document. This document will be filed in the electronic trial master file. Independent ethics committees (IECs)/institutional review boards (IRBs) will be notified of the changes as applicable locally. Of note, as the adapted visit deviates from the regular protocol plan, the changes will be recorded as protocol deviations related to COVID-19.	
6.2.2.2	If according to the investigator, a subject has clinical benefit, good tolerability ~~of the compound and if~~ the organ dose limits are not exceeded, he/she can receive up to four additional cycles after EOCT. For these subjects, an EOAC visit will be done 6 weeks after last dose administration.	If**,** according to the investigator, a subject has clinical benefit, **the subject may receive up to four additional cycles after the EOCT, provided they have an acceptable** tolerability **profile and** the organ dose limits are not exceeded. **This is at the subject's discretion and must be discussed and agreed upon with the sponsor.** For these subjects, an EOAC visit will be done 6 weeks after last dose administration.	Clarification
6.2.3	For both phase I and phase II, a long-term follow-up period will start after ED, EOCT or ~~after~~ EOAC and subjects will be followed up every 3 months (±2 weeks) until ~~24 months or~~ death, whichever occurs first.	For both phase I and phase II, a long-term follow-up period will start after **the** ED, EOCT or EOAC **visit** and subjects will be followed up every 3 months (±2 weeks) until **lost to follow-up, withdrawal of consent,** death **or a maximum of 5 years**, whichever occurs first.	Duration of long-term follow-up updated
6.2.3	… New text added	… **<u>Five Years After the EOCT, ED or EOAC Visit</u>**	Specific assessments to be performed during the long-term safety follow-up detailed.

Section	Version 7.0, 20 June 2019 WAS	Version 8.0, 12 June 2020 IS	RATIONALE FOR CHANGE
		In the long-term follow-up period, subjects will be followed up every 3 months (±2 weeks) until lost to follow-up, withdrawal of consent, death or a maximum of 5 years, whichever occurs first. The following safety assessments will be performed by the site: these assessments can be performed on-site or by remote visit: • **Survival status** • **Haematology and biochemistry tests (haemoglobin, platelet count, white blood cell count (absolute counts), AST, ALT, total bilirubin (with conjugated bilirubin if total bilirubin is abnormal i.e. outside the laboratory normal range), creatinine and urea) performed until the start of new antitumour treatment or up to 2 years after the EOCT, ED or EOAC visit, whichever comes first. Laboratory tests can be performed locally; results should be collected from the local laboratory.** • **All AEs and serious adverse events (SAEs) are to be reported up to 6 months after the EOCT, ED or EOAC visit or until new antitumour treatment starts, whichever comes first. Thereafter, only AEs and SAEs related to the IMP or study procedure should be reported for the remainder of the safety follow up period.** • **Subsequent antitumour treatment** **All collected data will be recorded in the eCRF.**	
6.3.1	…. New text added	… **Any further antitumour treatment for the disease under study that may have been taken during the long-term follow-up period should be reported on the prior and concomitant medications page of the eCRF.**	Details of requirements during the long-term safety follow-up added.

Section	Version 7.0, 20 June 2019 WAS	Version 8.0, 12 June 2020 IS	RATIONALE FOR CHANGE
7.1.1	One vial can contain up to 17.5 GBq of ^{177}Lu-3BP-227, this amount takes into account decay to ensure the administration of the highest planned activity of 7.5 GBq of ^{177}Lu-3BP-227 from the vial.	One vial can contain up to 17.5 GBq of ^{177}Lu-3BP-227 **at the end of manufacturing**, this amount takes into account decay to ensure the administration of the highest planned activity of 7.5 GBq of ^{177}Lu-3BP-227 from the vial.	Clarification
7.1.1.2	… The screening and treatment IMP are formulated in a solution of water for injection containing DiethyleneTriaminePentaAcetate (DTPA) to complex free ^{177}Lu and ~~ascorbic acid~~ to protect the drug product from radiolysis and to ~~have a longer~~ shelf life. The IMP consists of a sterile clear solution, free ~~from visible~~ particles, filled in 25 mL Type I borosilicate glass vials, closed with a chlorobutyl rubber stopper and crimped with aluminium seal.	… The screening and treatment IMP are formulated in a solution of **sterile** water for injection containing DiethyleneTriaminePentaAcetate (DTPA) to complex free ^{177}Lu and **ascorbate buffer** to protect the drug product from radiolysis and to **extend the** shelf life. The IMP consists of a sterile clear **to slightly yellow** solution, free **of suspended** particles, filled in 25 mL Type I borosilicate glass vials, closed with a chlorobutyl rubber stopper and crimped with aluminium seal.	Clarification
7.1.3	… In case of ~~central~~ manufacturing by the central manufacturing organisation, the IMP should be stored between +2°C and +8°C. Since the IMP shelf life will vary depending on the manufacturing ~~setup~~ (decentralised or centralised) and potentially on ~~any updates supported by available updated~~ supporting data during the conduct of the study, ~~it is referred to~~ the ~~IMP label for the~~ exact shelf life.	… In case of manufacturing by the central manufacturing organisation, the IMP should be stored between +2°C and +8°C. Since the IMP shelf life will vary depending on the **mode of** manufacturing (decentralised or centralised) and potentially on supporting data **generated** during the conduct of the study, the exact shelf **life is indicated on the IMP label**.	Clarification
8.1.1	… All AEs irrespective of causality up to 6 month ~~follow-up from end of treatment period should be reported to the sponsor~~. ~~AEs reported~~ after this timepoint up to ~~2~~-year follow-up should be reported if evaluated as related to the IMP by the investigator.	… All AEs**,** irrespective of causality**, are to be reported to the sponsor** up to 6 month**s after the EOCT, ED or EOAC visit or until new antitumour treatment starts, whichever comes first**. **A**fter this timepoint**,** up to **the end of the 5**-year follow-up **period, AEs** should **only** be reported if **the event is** evaluated as related to the IMP **or study procedure** by the investigator.	Clarification of reporting requirements during the long-term safety follow-up
8.1.1	… Events that ~~are reported during the study and~~ cannot be differentiated ~~with~~ PD should be captured as AE/SAEs. Death due to disease progression should be reported as	… Events that cannot be differentiated **from progressive disease (**PD**)** should be captured as AE/SAEs. Death due to disease progression should be reported as **an**	Clarification

Section	Version 7.0, 20 June 2019 WAS	Version 8.0, 12 June 2020 IS	RATIONALE FOR CHANGE
	SAE irrespective of causality if reported during the study period and ~~its early follow up~~ up to 6 months after the last dose of study drug.	SAE irrespective of causality if reported during the study period and up to 6 months after the **end of the cycle of the** last dose of study drug.	
8.1.2.3	Any AE/SAE ~~occurring during the study, from informed consent~~ up to 6 months after ~~long term follow up period start (after~~ EOCT or EOAC ~~or ED), must be reported to the sponsor~~. Any AE considered related to IMP administration that the investigator becomes aware of after completion of the EOS/ED visit must be reported to the sponsor and will be recorded in the safety database. EOS for AE reporting is defined as the end of ~~24 month~~ follow-up or death.	Any AE**s**/SAE**s, irrespective of causality, are to be reported to the sponsor** up to 6 months after **the** EOCT, ED or EOAC **visit or until new antitumour treatment starts, whichever comes first**. **After this timepoint, up to the end of the 5-year follow-up period, AEs/SAEs should only be reported if the event is evaluated as related to the IMP or study procedure by the investigator.** Any AE considered related to IMP administration that the investigator becomes aware of after completion of the EOS/ED visit must be reported to the sponsor and will be recorded in the **eCRF**. EOS for AE reporting is defined as the end of **the 5-year** follow-up or death.	Clarification of reporting requirements during the long-term safety follow-up
8.1.3	New text added	**In addition to the above criteria, any additional AE that the sponsor or an investigator considers serious should be immediately reported to the sponsor. This includes any suspected or confirmed coronavirus COVID-19 (SARS CoV-2) infection (seriousness criteria should be "other medically significant" if no other seriousness criteria are present (e.g. hospitalisation)).** **In case of suspected or confirmed COVID-19 infection, the IMP administration may be temporarily discontinued depending on the subject's clinical presentation. In some cases, the investigator may request a subject be retested before the IMP administration is resumed.**	Clarification following COVID-19 pandemic.
8.1.3	~~Any appropriate means of notification may be used.~~	**Email is the preferred method of SAE notification. If email is not available, facsimile transmission is the alternative method. In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable.**	Clarification

Section	Version 7.0, 20 June 2019 WAS	Version 8.0, 12 June 2020 IS	RATIONALE FOR CHANGE
8.1.5	~~If~~ the investigator becomes aware of a pregnancy occurring in the partner of a subject participating in the study, this should be reported to the sponsor. After the partner has given written consent, the ~~investigator should counsel the woman, discuss the risks of continuing with the pregnancy and the possible effects on the foetus. Monitoring of the subject's partner should continue until conclusion of the pregnancy, which may involve follow-up after the subject's involvement in the study has ended.~~ Pregnancies with a conception date within 90 days after subject's dosing must also be reported to the investigator for onward reporting to the sponsor.	**T**he investigator **is to report to the sponsor if they** become aware of a pregnancy occurring in the partner of a subject participating in the study. **If the female partner gives her** consent, the **pregnancy outcome should be followed up and reported.** **If there is an abnormal pregnancy outcome or an AE reporting in the foetus/neonate/child following exposure to the IMP during an Ipsen-sponsored clinical study, the information will be collected in two clinical study SAE report forms, one for the mother and one for the foetus/neonate/child.** Pregnancies **(in female subjects and partners of male subjects)** with a conception date within 90 days after subject's dosing must also be reported to the investigator for onward reporting to the sponsor.	To provide guidance to the physician about the reporting requirements for pregnancy occurring in female partner of childbearing potential and separate reporting of AEs/SAEs for the foetus/neonate/child and mother.
8.2.4	… During screening period, a triplicate 12-lead ECG will be recorded to check eligibility criteria by measuring the ECG parameters, in particular the QTc (Fridericia's correction, QTcF) interval in order to exclude subjects with high/abnormal QT values before the screening administration. Afterwards, single 12-lead ECG recordings will be performed at the end of ^{177}Lu-3BP-227 screening infusion and 4 hours after the end of ^{177}Lu-3BP-227 infusion. At each treatment administration, a triplicate 12-lead ECG will be recorded on Day 1 before the infusion (baseline). Afterwards, single 12-lead ECGs, will be recorded on Day 1 just after ^{177}Lu-3BP-227 infusion, at 4 hours after the end of ^{177}Lu-3BP-227 infusion and on Day 2 at 24 hours after the end of ^{177}Lu-3BP-227 infusion as well as at EOCT and EOAC visits.	… During **the** screening period, a triplicate 12-lead ECG will be recorded to check eligibility criteria by measuring the ECG parameters, in particular the QTc (Fridericia's correction, QTcF) interval in order to exclude subjects with high/abnormal QT values before the screening administration **(minus 15 minutes)**. Afterwards, single 12-lead ECG recordings will be performed at the end of ^{177}Lu-3BP-227 screening infusion **(±15 minutes)** and 4 hours after the end of ^{177}Lu-3BP-227 infusion **(±30 minutes)**. At each treatment administration, a triplicate 12-lead ECG will be recorded on Day 1 before the infusion (baseline) **(minus 15 minutes)**. Afterwards, single 12-lead ECGs, will be recorded on Day 1 just after ^{177}Lu-3BP-227 infusion **(±15 minutes)**, at 4 hours **(±30 minutes)** after the end of ^{177}Lu-3BP-227 infusion and on Day 2 at 24 hours **(±4 hours)** after the end of ^{177}Lu-3BP-227 infusion as well as at EOCT and EOAC visits.	Clarification

Section	Version 7.0, 20 June 2019 WAS	Version 8.0, 12 June 2020 IS	RATIONALE FOR CHANGE
8.2.4	Table 6 Timepoints and Replicates of 12-lead ECG Recordings Timepoint column: Before infusion End of infusion 4 hours after the end of infusion Before infusion End of infusion 4 hours after the end of infusion 24 hours after the end of infusion	Table 6 Timepoints and Replicates of 12-lead ECG Recordings Timepoint column: Before infusion **(minus 15 minutes)** End of infusion **(±15 minutes)** 4 hours **(±30 minutes)** after the end of infusion Before infusion **(minus 15 minutes)** End of infusion **(±15 minutes)** 4 hours **(±30 minutes)** after the end of infusion 24 hours **(±4 hours)** after the end of infusion	Clarification
9.1.2	... The samples for urine total activity concentration analysis will be taken from urine collected during four different periods at Cycle 1 only: from the start of the ^{177}Lu-3BP-227 infusion to 6 hours, 6 to 12 hours, 12 to 24 hours and 24 to 48 hours after the end of infusion (from the start of the ^{177}Lu-3BP-227 infusion to 6 hours after the end of the infusion only for US sites)~~, with an initial~~ void ~~collection~~ shortly before the infusion and ~~a final collection 48 hours after~~ the end of ~~^{177}Lu-3BP-227 infusion~~.	... The samples for urine total activity concentration analysis will be taken from urine collected during four different periods at Cycle 1 only: from the start of the ^{177}Lu-3BP-227 infusion to 6 hours, 6 to 12 hours, 12 to 24 hours and 24 to 48 hours after the end of infusion (from the start of the ^{177}Lu-3BP-227 infusion to 6 hours after the end of the infusion only for US sites)**. Subjects should** void shortly before the **^{177}Lu-3BP-227** infusion **(not to be collected)** and **shortly before** the end of **the last collection period**.	Clarification
9.2	During the treatment period, to improve the determination of the biokinetics of ^{177}Lu-3BP-227 and perform an absolute quantification of radioactivity in target organs, whole body scans (planar scintigraphy) and SPECT/CT will be performed at Cycles 1 and 2 at the following timepoint ~~ranges~~ just after the end of ^{177}Lu-3BP-227 infusion: • Day 1: ~~0 to 1 hour (before urination) and 2 to~~ 4 hours • Day 2: ~~16 to~~ 24 hours • Day 3: ~~40 to~~ 48 hours • Day 4: 72 to 96 hours	During the treatment period, to improve the determination of the biokinetics of ^{177}Lu-3BP-227 and perform an absolute quantification of radioactivity in target organs, whole body scans (planar scintigraphy) and SPECT/CT will be performed at Cycles 1 and 2 at the following timepoint**s** just after the end of ^{177}Lu-3BP-227 infusion: • Day 1: 4 **(±2)** hours • Day 2: 24 **(±6)** hours • Day 3: 48 **(±6)** hours • Day 4: 72 to 96 hours • **Day 7s to 8: 138 to 168 hours**	To optimise the dosimetry evaluation through adaptation of the imaging schedule

Section	Version 7.0, 20 June 2019 WAS	Version 8.0, 12 June 2020 IS	RATIONALE FOR CHANGE
	~~At the timepoint between 16 to 24 hours~~, SPECT/ standard dose CT will be performed. For all other time points, SPECT/low dose CT will be performed.	**Within each cycle**, **a single** SPECT/standard dose CT will be performed. For all other time points, SPECT/low dose CT will be performed. **Details of the procedures will be provided in the Image Acquisition Guidelines.**	
9.2	… After the second and fourth additional administrations, a single whole body scan and SPECT/standard dose CT ~~between 16 and 24~~ hours will be performed.	… After the second and fourth additional administrations, a single whole body scan and SPECT/standard dose CT **at 48 (±6)** hours will be performed.	Change of timepoint to 48 hours where the quality of SPECT images (with respect to the background noise) is expected to be improved
9.3.2	… The samples for urine 3BP 227 concentration analysis will be taken from urine collected during four different periods at Cycle 1 only: from the start of the infusion to 6 hours, 6 to 12 hours, 12 to 24 hours and 24 to 48 hours after the start of infusion (from the start of the infusion to 6 hours after the end of the infusion only in US sites)~~, with an initial~~ void ~~collection~~ shortly before the infusion and ~~a final collection 48 hours after~~ the end of ~~^{177}Lu-3BP-227 infusion~~.	… The samples for urine 3BP 227 concentration analysis will be taken from urine collected during four different periods at Cycle 1 only: from the start of the infusion to 6 hours, 6 to 12 hours, 12 to 24 hours and 24 to 48 hours after the start of infusion (from the start of the infusion to 6 hours after the end of the infusion only in US sites)**. Subjects should** void shortly before the **^{177}Lu-3BP-227** infusion **(not to be collected)** and **shortly before** the end of **the last collection period**.	Clarification
10.1.2	… After EOCT or EOAC, subjects will be followed up every 3 months (±2 weeks) to further evaluate the efficacy (by CT or MRI) until ~~24 months~~, disease progression, administration of any other chemotherapy or radiotherapy, ~~or~~ death, whichever occurs first (see Section 6.2.3).	… After **the** EOCT**, ED** or EOAC **visit**, subjects will be followed up every 3 months (±2 weeks) to further evaluate the efficacy (by CT or MRI) until disease progression, administration of any other chemotherapy or radiotherapy, **lost to follow-up, withdrawal of consent,** death **or a maximum of 2 years**, whichever occurs first (see Section 6.2.3). **After disease progression is confirmed, no further CT/MRI scans will be required for tumour/disease assessment. The survival status and safety of the subjects will continue to be monitored as indicated in Section 8.1.2.3 until lost to follow-up, withdrawal of consent, death or a maximum of 5 years, whichever occurs first.**	Clarification of requirements during the long-term follow-up.

Section	Version 7.0, 20 June 2019 WAS	Version 8.0, 12 June 2020 IS	RATIONALE FOR CHANGE
10.1.3	After EOCT, subjects will be followed up every 3 months (±2 weeks) to further evaluate the efficacy (by CT or MRI) until ~~24 months~~, disease progression, administration of any other chemotherapy or radiotherapy, ~~or~~ death, whichever occurs first (see Section 6.2.3).	After **the** EOCT**, ED or EOAC visit**, subjects will be followed up every 3 months (±2 weeks) to further evaluate the efficacy (by CT or MRI) until disease progression, administration of any other chemotherapy or radiotherapy, **lost to follow-up,** death **or a maximum of 2 years**, whichever occurs first (see Section 6.2.3).	Updated long-term follow-up period.
10.4	**10.4 ~~DNA Double Strand Breaks in Peripheral Lymphocytes~~** CCI	Section deleted	Assessment of DNA-DSB in peripheral lymphocytes removed
10.5	**10.~~5~~ Genomic Profiling in Circulating Cell-free DNA** CCI	**10.4 Genomic Profiling in Circulating Cell-free DNA and Germline DNA** CCI	CCI

Section	Version 7.0, 20 June 2019 WAS	Version 8.0, 12 June 2020 IS	RATIONALE FOR CHANGE
		CCI	CCI
10.6	**10.7 Tumour Biopsy** CCI	**10.6 Tumour Biopsy** CCI	Clarification on biopsy collection and wording added for subjects participating in the imaging study

Section	Version 7.0, 20 June 2019 WAS	Version 8.0, 12 June 2020 IS	RATIONALE FOR CHANGE
CCI	[redacted]	[redacted]	[redacted]
12.3.1	Subjects in each phase of the study will have ~~2~~-year safety follow-up after the ~~end of the last~~ ^{177}~~Lu-3BP-227 cycle~~.	Subjects in each phase of the study will have **a 5**-year safety follow-up after the **EOCT, ED or EOAC visit**.	Updated long-term follow-up period.
19.1	Table 8 Schedule of Assessments for Phase I – Dose Escalation Timepoint changed: Cycle 1 Day ~~8~~	Table 8 Schedule of Assessments for Phase I – Dose Escalation Timepoint changed: Cycle 1 Day **7**	To amend the visit schedule to align with the change in imaging schedule
19.1	Table 8 Schedule of Assessments for Phase I – Dose Escalation Timepoint changed: Cycle 2 Day ~~8~~	Table 8 Schedule of Assessments for Phase I – Dose Escalation Timepoint changed: Cycle 2 Day **7**	To amend the visit schedule to align with the change in imaging schedule
19.1	Table 8 Schedule of Assessments for Phase I – Dose Escalation Timepoints updated	Table 8 Schedule of Assessments for Phase I – Dose Escalation	To optimise the dosimetry evaluation through adaptation of the imaging schedule

Section	Version 7.0, 20 June 2019 WAS	Version 8.0, 12 June 2020 IS	RATIONALE FOR CHANGE
		Timepoint added at Cycle 1 Day 7 and Cycle 2 Day 7 for: Planar scintigraphy SPECT/CT scan	
19.1	Table 8 Schedule of Assessments for Phase I – Dose Escalation Timepoint deleted: Haematology and biochemistry ~~at Day 2 of Cycle 1~~	Table 8 Schedule of Assessments for Phase I – Dose Escalation Timepoint deleted	Day 2 samples were initially proposed for the safety evaluation of the short-term effects (within 24 hours) of the IMP on laboratory parameters. Following evaluation of these results after IMP administration in the patients treated so far, there was no change in the laboratory parameters within 24 hours of IMP administration. Therefore, these laboratory tests do not add any value to the clinical safety or efficacy assessment. The sites can still perform the laboratory tests on Day 2, as on any other day, if needed.
19.1	Table 8 Schedule of Assessments for Phase I – Dose Escalation ~~Peripheral lymphocytes for DNA DSB (selected centres) [s] assessment at Day 1 of Cycle 1, Day 4 of Cycle 1, Day 1 of Cycle 2 and Day 4 of Cycle 2~~	Table 8 Schedule of Assessments for Phase I – Dose Escalation Assessment deleted	Assessment removed
19.1	Table 8 Schedule of Assessments for Phase I – Dose Escalation Timepoints deleted	Table 8 Schedule of Assessments for Phase I – Dose Escalation Timepoints were removed from the long-term follow-up for the following assessments: ECOG performance status Vital signs Body weight Urinalysis	Clarification of requirements during the long-term follow-up.
19.1	Table 8 Schedule of Assessments for Phase I – Dose Escalation	Table 8 Schedule of Assessments for Phase I – Dose Escalation	Clarification of requirements during the long-term follow-up.

Section	Version 7.0, 20 June 2019 WAS	Version 8.0, 12 June 2020 IS	RATIONALE FOR CHANGE
	New assessment added	New assessment added for the long-term follow-up: **Survival status**	
19.1	Table 8 Schedule of Assessments for Phase I – Dose Escalation Footnote b: follow-up visits will take place every 3 months and will start after the ~~last cycle of IMP administration~~.	Table 8 Schedule of Assessments for Phase I – Dose Escalation Footnote b: follow-up visits will take place every 3 months **(±2 weeks)** and will start after the **EOCT, ED or EOAC visit**. **Efficacy will be assessed until disease progression, administration of any other chemotherapy or radiotherapy, lost to follow-up, withdrawal of consent, death or a maximum of 2 years, whichever occurs first (see Section 6.2.3). After disease progression is confirmed, no further CT/MRI scans will be required for tumour/disease assessment. The survival status and safety of the subjects will continue to be monitored as indicated in Section 8.1.2.3 until lost to follow-up, withdrawal of consent, death or a maximum of 5 years, whichever occurs first.**	Clarification of requirements during the long-term follow-up.
19.1	Table 8 Schedule of Assessments for Phase I – Dose Escalation Footnote k: ~~ten~~ whole body scans (planar scintigraphy) and SPECT/CT acquisitions will be performed during the treatment period. Whole body scans (planar scintigraphy) and SPECT/CT scan will be performed ~~just after the end of the ^{177}Lu-3BP-227 infusion at 0 to 1 hour (before urination), 2 to 4 hours, 16 to 24 hours, 40 to 48 hours and at~~ 72 to 96 hours. SPECT/standard dose CT will be performed ~~at the 16 to 24 hour timepoint,~~ SPECT/low dose CT will be performed at all other timepoints.	Table 8 Schedule of Assessments for Phase I – Dose Escalation Footnote k: **eleven** whole body scans (planar scintigraphy) and SPECT/CT acquisitions will be performed during the treatment period. Whole body scans (planar scintigraphy) and SPECT/CT scan will be performed **at the following timepoints just after the end of ^{177}Lu-3BP-227 infusion: Day 1: 4 (±2) hours, Day 2: 24 (±6) hours, Day 3: 48 (±6) hours, Day 4:** 72 to 96 hours**, and Days 7 to 8: 138 to 168 hours**. **Within each cycle, a single** SPECT/standard dose CT will be performed**. A** SPECT/low dose CT will be performed at all other timepoints. **Details of the procedures will be provided in the Image Acquisition Guidelines.**	To optimise the dosimetry evaluation through adaptation of the imaging schedule
19.1	Table 8 Schedule of Assessments for Phase I – Dose Escalation	Table 8 Schedule of Assessments for Phase I – Dose Escalation	After reviewing subjects' SPECT/CT images at different

Section	Version 7.0, 20 June 2019 WAS	Version 8.0, 12 June 2020 IS	RATIONALE FOR CHANGE
	Footnote k: … At screening, planar scintigraphy will be performed after screening administration of ^{177}Lu-3BP-227~~; SPECT/CT can be performed as per investigator's judgement~~.	Footnote k: … At screening, planar scintigraphy **(1 or 2 timepoint(s) at the investigator's discretion) and optional** SPECT/CT **scans (up to 2 at the investigator's discretion)** will be performed after screening administration of ^{177}Lu-3BP-227.	timepoints following the therapeutic dose of ^{177}Lu-IPN01087, it is concluded that the quality of SPECT image with respect to the background noise has substantially improved at the 48-hour and later timepoints. Considering the significant number of screen failures due to lack of radioactive uptake, which is contrary to the information available in the literature on the expression of NTSR1 receptor, the image acquisition timepoint has been moved to 48 hours after the screening dose.
19.1	Table 8 Schedule of Assessments for Phase I – Dose Escalation Footnote n: prior to and at the end of ^{177}Lu-3BP-227 infusion (0) as well as 30±5 minutes, 90±15 minutes, 4 hours±~~1~~0 minutes after the end of ^{177}Lu-3BP-227 infusion.	Table 8 Schedule of Assessments for Phase I – Dose Escalation Footnote n: prior to and at the end of ^{177}Lu-3BP-227 infusion (0) as well as 30±5 minutes, 90±15 minutes, 4 hours±**3**0 minutes after the end of ^{177}Lu-3BP-227 infusion.	To homogenise the time window duration between vital signs and PK samples
19.1	Table 8 Schedule of Assessments for Phase I – Dose Escalation Footnote o: during the screening period, a triplicate 12-lead ECG will be recorded before the screening administration, and a single 12-lead ECG will be recorded at the end of ^{177}Lu-3BP-227 infusion and 4 hours after the end of infusion. At each treatment administration, a triplicate 12-lead ECG will be recorded on Day 1 before the infusion (baseline) and a single 12-lead ECG recordings at the end of ^{177}Lu-3BP-227 infusion, at 4 hours after the end of ^{177}Lu-3BP-227 infusion and on Day 2 at	Table 8 Schedule of Assessments for Phase I – Dose Escalation Footnote o: during the screening period, a triplicate 12-lead ECG will be recorded before the screening administration **(minus 15 minutes)**, and a single 12-lead ECG will be recorded at the end of ^{177}Lu-3BP-227 infusion **(±15 minutes)** and 4 hours **(±30 minutes)** after the end of infusion. At each treatment administration, a triplicate 12-lead ECG will be recorded on Day 1 before the infusion (baseline) **(minus 15 minutes)** and a single 12-lead ECG recordings at the end of ^{177}Lu-3BP-227	Clarification

Section	Version 7.0, 20 June 2019 WAS	Version 8.0, 12 June 2020 IS	RATIONALE FOR CHANGE
	24 hours after the end of ^{177}Lu-3BP-227 infusion as well as at EOCT. ~~In any case,~~ 12-lead computerised standard ECG , will be recorded in supine position after at least 5 minutes of rest.	infusion **(±15 minutes)**, at 4 hours after the end of ^{177}Lu-3BP-227 infusion **(±30 minutes)** and on Day 2 at 24 hours after the end of ^{177}Lu-3BP-227 infusion **(±4 hours)** as well as at EOCT. **All** 12-lead computerised standard ECGs will be recorded in **the** supine position after at least 5 minutes of rest.	
19.1	Table 8 Schedule of Assessments for Phase I – Dose Escalation Footnote s: ~~samples for DNA DSB will be taken, starting from Cohort 3, at each administration at the following timepoints: before infusion (baseline), 4 hours and 72 to 96 hours after the end of ^{177}Lu 3BP-227 infusion.~~	Table 8 Schedule of Assessments for Phase I – Dose Escalation Footnote s: **one blood sample for germline DNA will be collected at screening (after confirmation of ^{177}Lu-3BP-227 tumour uptake) or at Day 1 of Cycle 1 before the infusion**	Collection of germline DNA modified to allow more flexibility to the sites for biobanking blood collection and to avoid blood sampling from screening failure subjects.
CCI [redacted]			
19.1	Table 8 Schedule of Assessments for Phase I – Dose Escalation New footnote added	Table 8 Schedule of Assessments for Phase I – Dose Escalation Footnote **z**: **Any AEs/SAEs, irrespective of causality, are to be reported to the sponsor up to 6 months after the EOCT, ED or EOAC visit or until new antitumour treatment starts, whichever comes first. After this timepoint, up to the end of the 5-year follow-up period, AEs/SAEs should only be reported if the event is evaluated as related to the IMP or study procedure by the investigator.**	Clarification of requirements during the long-term follow-up.

Section	Version 7.0, 20 June 2019 WAS	Version 8.0, 12 June 2020 IS	RATIONALE FOR CHANGE
CCI [redacted]			
19.1	Table 9 Schedule of Assessment for Additional Cycles in Case of Clinical Benefit and Good Tolerability Timepoint changed: Additional cycles Day ~~8~~	Table 9 Schedule of Assessment for Additional Cycles in Case of Clinical Benefit and Good Tolerability Timepoint changed: Additional cycles Day **7**	To amend the visit schedule to align with the change in imaging schedule
19.1	Table 9 Schedule of Assessment for Additional Cycles in Case of Clinical Benefit and Good Tolerability Timepoints updated	Table 9 Schedule of Assessment for Additional Cycles in Case of Clinical Benefit and Good Tolerability Timepoint added at Day 7 for: Planar scintigraphy SPECT/CT scan	To optimise the dosimetry evaluation through adaptation of the imaging schedule
19.1	Table 9 Schedule of Assessment for Additional Cycles in Case of Clinical Benefit and Good Tolerability Footnote a: ceCT/MRI will be done at Cycles 4 and 6 only.	Table 9 Schedule of Assessment for Additional Cycles in Case of Clinical Benefit and Good Tolerability Footnote a: ceCT/MRI will be done **every 2 cycles during additional administrations, to confirm the clinical benefit after 2 additional administrations (i.e. at Cycle 4 and EOAC). In case of early discontinuation,**	Clarification of when ceCT/MRI scans should be performed during additional cycles, to be consistent with the core trial period assessments.

Section	Version 7.0, 20 June 2019 WAS	Version 8.0, 12 June 2020 IS	RATIONALE FOR CHANGE
		the CeCT/MRI should be performed at the ED visit, to confirm any disease progression.	
19.1	Table 9 Schedule of Assessment for Additional Cycles in Case of Clinical Benefit and Good Tolerability Footnote b: full dosimetry assessment will be performed after the first and third additional administrations as described for Cycles 1 and 2. After the second and fourth additional administrations, only a single SPECT/standard dose CT at ~~16 to 24~~ hours will be performed	Table 9 Schedule of Assessment for Additional Cycles in Case of Clinical Benefit and Good Tolerability Footnote b: full dosimetry assessment will be performed after the first and third additional administrations as described for Cycles 1 and 2. After the second and fourth additional administrations, only a single SPECT/standard dose CT at **48 (±6)** hours will be performed	Change of timepoint to 48 hours where the quality of SPECT images (with respect to the background noise) is expected to be improved
19.1	Table 9 Schedule of Assessment for Additional Cycles in Case of Clinical Benefit and Good Tolerability Footnote c: After the first and the third additional administration, blood samplings will be performed just before ^{177}Lu-3BP-227 infusion (baseline), at the end of infusion of ^{177}Lu-3BP-227 (0), 5 minutes ±1 minute, 30 minutes ±5 minutes, ~~1 hour ±5 minutes~~ and 4 hours ±30 minutes, ~~6 hours ±30 minutes, 8 hours ±1 hour~~, 24 hours ±2 hours and 48 hours ±2 hours, and 72 to 96 hours ±2 hours. After the second and fourth additional administrations a single blood collection will be performed at 24 hours only (as close as possible to the SPECT/CT).	Table 9 Schedule of Assessment for Additional Cycles in Case of Clinical Benefit and Good Tolerability Footnote c: After the first and the third additional administration, blood samplings will be performed just before ^{177}Lu-3BP-227 infusion (baseline), at the end of infusion of ^{177}Lu-3BP-227 (0), 5 minutes ±1 minute, 30 minutes ±5 minutes, **90** minutes **±15 minutes** and 4 hours ±30 minutes, 24 hours ±2 hours and 48 hours ±2 hours, and 72 to 96 hours ±2 hours. After the second and fourth additional administrations a single blood collection will be performed at 24 hours only (as close as possible to the SPECT/CT).	Clarification of inconsistency between core trial period assessments and additional cycle assessments
19.1	Table 9 Schedule of Assessment for Additional Cycles in Case of Clinical Benefit and Good Tolerability Footnote d: prior to and at the end of ^{177}Lu-3BP-227 infusion (0) as well as 30±5 minutes, 90±15 minutes, 4 hours±~~1~~0 minutes after the end of ^{177}Lu-3BP-227 infusion.	Table 9 Schedule of Assessment for Additional Cycles in Case of Clinical Benefit and Good Tolerability Footnote d: prior to and at the end of ^{177}Lu-3BP-227 infusion (0) as well as 30±5 minutes, 90±15 minutes, 4 hours±**3**0 minutes after the end of ^{177}Lu-3BP-227 infusion.	Clarification of inconsistency between core trial period assessments and additional cycle assessments
19.1	Table 9 Schedule of Assessment for Additional Cycles in Case of Clinical Benefit and Good Tolerability Footnote e: at each cycle, a triplicate 12-lead ECG will be recorded on Day 1 before the infusion (baseline). A single 12-lead computerised standard ECG, with	Table 9 Schedule of Assessment for Additional Cycles in Case of Clinical Benefit and Good Tolerability Footnote e: at each cycle, a triplicate 12-lead ECG will be recorded on Day 1 before the infusion (baseline) **(minus 15 minutes)**. A single 12-lead computerised standard	Clarification

Section	Version 7.0, 20 June 2019 WAS	Version 8.0, 12 June 2020 IS	RATIONALE FOR CHANGE
	paper printout, will be recorded in supine position after at least 5 minutes of rest during each cycle on Day 1 at the end of ^{177}Lu-3BP-227 infusion and at 4 hours after the end of ^{177}Lu-3BP-227 infusion as well as at EOAC.	ECG, with paper printout, will be recorded in supine position after at least 5 minutes of rest during each cycle on Day 1 at the end of ^{177}Lu-3BP-227 infusion **(±15 minutes)** and at 4 hours **(±30 minutes)** after the end of ^{177}Lu-3BP-227 infusion as well as at EOAC.	
CCI [redacted]			
19.2	Assessment in blood sampling summary table: **Core trial** Clinical laboratory tests [a] -Maximum blood volume per sample (mL): 25 -Maximum number of blood samples: ~~11~~ -Maximum total volume (mL): ~~275~~ CCI [redacted]	Assessment in blood sampling summary table: **Core trial** Clinical laboratory tests [a] -Maximum blood volume per sample (mL): 25 -Maximum number of blood samples: **10** -Maximum total volume (mL): **250** CCI [redacted]	Amend blood volumes to reflect change in assessments

Section	Version 7.0, 20 June 2019 WAS	Version 8.0, 12 June 2020 IS	RATIONALE FOR CHANGE
	-Maximum number of blood samples: ~~1~~ -Maximum total volume (mL): ~~10~~	-Maximum number of blood samples: **2** -Maximum total volume (mL): **20**	
19.2	Assessment in blood sampling summary table: **EOCT/ED** CCI [redacted]	Assessment in blood sampling summary table: **EOCT/ED** CCI [redacted]	Amend blood volumes to reflect change in assessments
19.2	Blood sampling summary table: Total volume over study period: Approximately ~~900~~ mL	Blood sampling summary table: Total volume over study period: Approximately **820** mL	CCI [redacted]
19.3	The following assessments in the haematology table were removed from the LTFU: RBC count Haematocrit MCV	LTFU timepoints deleted	Clarification of requirements during the long-term follow-up.
19.3	Footnote added to the clinical chemistry table	Footnote added to the clinical chemistry table: a only to be performed if the total bilirubin is abnormal i.e. outside the laboratory normal range	The testing of conjugated bilirubin has been made optional because the differentiation between conjugated vs unconjugated bilirubin is usually needed only if the total bilirubin is elevated, to find the cause of hyperbilirubinemia. Hence the conjugated bilirubin test is not required if the value of total bilirubin is within the laboratory normal range.
19.3	LTFU assessment added	The following assessment in the clinical chemistry table was added to the LTFU: Total bilirubin	Clarification of requirements during the long-term follow-up.
19.3	The following assessments in the clinical chemistry table were removed from the LTFU: Albumin	LTFU timepoints deleted	Clarification of requirements during the long-term follow-up.

Section	Version 7.0, 20 June 2019 WAS	Version 8.0, 12 June 2020 IS	RATIONALE FOR CHANGE
	ALP Calcium Chloride CRP eGFR Glucose Potassium Sodium Total bilirubin Total cholesterol Total protein TG Uric acid		
19.3	Assessment in clinical chemistry table Glucose ~~(fasting)~~	Assessment in clinical chemistry table Glucose	Clarification
19.3	Urinalysis table New assessment added	Urinalysis table Specific gravity added	Clarification for consistency with the eCRF
19.3	The following assessments in the urinalysis table were removed from the LTFU: Bilirubin Blood Glucose Ketones Leucocytes Nitrite pH Protein Proteinuria Urobilinogen Proteinuria (urine collection)	LTFU timepoints deleted	Clarification of requirements during the long-term follow-up.

SUMMARY & OUTCOME OF CHANGES:

STUDY NUMBER	D-FR-01087-001		
AMENDED PROTOCOL VERSION NUMBER AND DATE	Version 8.0, 12 June 2020		
SUBSTANTIAL ☒	**NON-SUBSTANTIAL** ☐		
REASON(S) FOR CHANGES	The protocol was amended to update the following: • Clarification of the inclusion criteria for subject selection as follows: - to clearly state nonresectable locally advanced disease - to clearly state that no further suitable treatment options are available for subjects eligible for the study • Allow subjects screened and found positive for NTSR1 in the ^{111}In-IPN01087 phase I diagnostic study to take part in this study without having the diagnostic dose of ^{177}Lu-IPN01087 during the screening phase • Extend the long-term follow-up period from 2 years to a maximum of 5 years or until lost to follow-up, withdrawal of consent or death, whichever occurs first. • Revision of the DLT criteria to adequately describe the grading as stated in the CTCAE v5.0 dictionary • Revision of the subject discontinuation rules so if there are life threatening toxicities outside of the DLT period, treatment will be discontinued • Optimise the dosimetry evaluation through adaptation of the imaging schedule • Clarification of biopsy collection • Clarification about COVID-19 added following the recent pandemic • CCI [redacted] • Make various clarifications and minor corrections for consistency		
Other Action Required?	CRF UPDATE	Yes ☒ No ☐ *(tick one)*	
	LOCAL CONSENT FORM UPDATE	Yes ☒ No ☐ *(tick one)*	
	DATABASE UPDATE	Yes ☒ No ☐ *(tick one)*	
	STATISTICAL ANALYSIS PLAN (SAP) UPDATE	Yes ☒ No ☐ *(tick one)*	