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# STATISTICAL ANALYSIS PLAN

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 AND DATE:**
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**Further to your review and agreement to the Statistical Analysis Plan version indicated above, please sign to indicate approval for your area of responsibility:**

| RESPONSIBILITY | NAME, TITLE & OFFICE | SIGNATURE | DATE |
|---|---|---|---|
| **Ipsen** PPD | PPD<br>Ipsen Innovation<br>5 Avenue du Canada<br>91940 Les Ulis, France | | |
| **Ipsen**<br>PPD | PPD<br>Ipsen Innovation<br>5 Avenue du Canada<br>91940 Les Ulis, France | | |
| **Ipsen** PPD | PPD<br>Ipsen Biopharm Ltd<br>102 Park Drive, Milton Park,<br>Abingdon, OX14 4RY,<br>United Kingdom | PPD | 09-Jul-2021 |
| **RESPONSIBILITY** | **NAME, TITLE & OFFICE** | **SIGNATURE** | **DATE** |
| PPD | PPD<br>Biotrial Biometrics<br>7-9 Rue Jean-Louis Bertrand<br>35042 Rennes Cedex, France | | |

IMPORTANT: This completed record (with additional sheets, where required), confirms the above-mentioned Statistical Analysis Plan version became the Final Statistical Analysis Plan

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# LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

| | |
|---|---|
| **AE:** | Adverse Event |
| **ALT:** | Alanine aminotransferase |
| **AST:** | Aspartate aminotransferase |
| **ATC:** | Anatomic Therapeutic Class |
| **BLQ:** | Below the Limit of Quantification |
| **BMI:** | Body Mass Index |
| **BOR:** | Best Overall Response |
| **BSAP:** | Bone Specific Alkaline Phosphatase |
| **CA:** | Cancer Antigen |
| **CEA:** | Carcinoembryonic Antigen |
| **ceCT/MRI:** | Contrast enhanced Computed Tomography/Magnetic Resonance Imaging |
| **cfDNA:** | Cell-Free DNA |
| **CI:** | Confidence Interval |
| **CR:** | Complete Response |
| **CRC:** | Colorectal Cancer |
| **CV:** | Coefficient of Variation |
| **DCR:** | Disease Control Rate |
| **DLT:** | Dose Limiting Toxicity |
| **DNA:** | Deoxyribonucleic acid |
| **DNA-DSB:** | Deoxyribonucleic acid-double strand breaks |
| **eCRF:** | Electronic Case Report Form |
| **ECG:** | Electrocardiogram |
| **ECOG:** | Eastern Cooperative Oncology Group |
| **ED:** | Early Discontinuation |
| **eGFR** | Estimated Glomerular Filtration Rate |
| **EOAC:** | End Of Additional Cycles |
| **EOCT:** | End Of Core Trial |
| **ES:** | Ewing Sarcoma |
| **FOV:** | Field of View |
| **GBq:** | Gigabecquerel |
| **GC:** | Gastric Cancer |
| **GIST:** | Gastrointestinal Stromal Tumours |

| | |
|---|---|
| **GST:** | alphaglutathione S-transferase |
| **GSTP1:** | glutathione S-transferase P1 |
| **Gy:** | Gray |
| **ICH:** | International Conference on Harmonisation |
| **IGF-1:** | Insulinlike Growth Factor 1 |
| **IMP:** | Investigational Medicinal Product |
| **i.v.** | Intravenous |
| **KIM-1:** | Kidney Injury Molecule-1 |
| **KM:** | Kaplan-Meier |
| **LDH:** | Lactate Dehydrogenase |
| **LOQ:** | Limit Of Quantification |
| **MACA:** | Maximum Administered Cumulative Activity |
| **MedDRA:** | Medical Dictionary for Regulatory Activities |
| **MTCA:** | Maximum Tolerated Cumulative Activity |
| **MTSA:** | Maximum Tolerated Single Activity |
| **NCA:** | Non-Compartmental Analysis |
| **NCI-CTCAE:** | National Cancer Institute - Common Terminology Criteria for Adverse Events |
| **NE:** | Not Evaluable |
| **NTSR1:** | Neurotensin receptor 1 |
| **ORR:** | Objective Response Rate |
| **OS:** | Overall Survival |
| **PD:** | Pharmacodynamics/Progressive Disease |
| **PDAC:** | Pancreatic Ductal Adenocarcinoma |
| **PFS:** | Progression-Free Survival |
| **PK:** | Pharmacokinetics |
| **PR:** | Partial Response |
| **PTH:** | Parathyroid Hormone |
| **QRS:** | QRS interval duration |
| **QT:** | Time interval for ventricular depolarisation and repolarisation |
| **QTc:** | Corrected QT interval |
| **RECIST:** | Response Evaluation Criteria in Solid Tumors |
| **SAP:** | Statistical Analysis Plan |
| **SAE:** | Serious Adverse Event |
| **SAS®:** | Statistical Analysis System® |

| | |
|---|---|
| **SCCHN:** | Squamous-Cell Carcinoma of Head and Neck |
| **SD:** | Standard Deviation/Stable Disease |
| **SI:** | International System |
| **SRC:** | Safety Review Committee |
| **SV:** | Sievert |
| **TEAE:** | Treatment Emergent Adverse Event |
| **TFLs:** | Tables, Figures and Listings |
| **TIAC:** | Time-Integrated Activity Coefficient |
| **TPA:** | Tissue Polypeptide Antigen |
| **TSH:** | Thyroid-Stimulating Hormone |
| **WHO-DD:** | World Health Organisation – Drug Dictionary |

Information reported in this document is only related to Phase I dose escalation part of the study.

# 1 INFORMATION TAKEN FROM THE PROTOCOL

## 1.1 Study objectives

### *1.1.1 Primary objective*

The primary objective is to establish the safety and tolerability of fractionated intravenous (i.v.) administrations of $^{177}$Lu-3BP-227 in subjects with unserectable, locally advanced or metastatic cancers expressing Neurotensin Receptor 1 (NTSR1).

### *1.1.2 Secondary Study Objectives*

The secondary objectives are:

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

• To determine the radiation dosimetry of $^{177}$Lu-3BP-227 (organ exposure to radiation) after each administration.

• To describe the preliminary antitumour activity of $^{177}$Lu-3BP-227.

### *1.1.3 Exploratory Study Objectives*

The exploratory objectives are:

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

• To explore renal safety by measuring urinary specific biomarkers.

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

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

• To collect gene mutation status for correlation with clinical outcome.

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

• To generate a model integrating PK, dosimetry, antitumour activity and safety data.

## 1.2 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. The purpose of the radioactivity escalation part is to determine the maximum tolerated cumulative (MTCA).

During phase I, it is planned to enrol subjects with unresectable, locally advanced, or metastatic tumours expressing NTSR1 originating from either the:

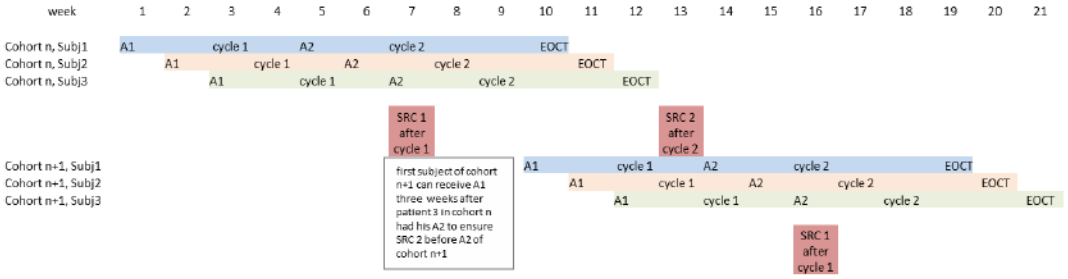
- Pancreas (Pancreatic Ductal Adenocarcinoma, PDAC);
- Colon and rectum (Colorectal Cancer, CRC);
- Stomach (Gastric Cancer, GC);
- Gastrointestinal Stromal Tumours, (GIST);

- Head and neck region (Squamous-Cell Carcinoma of Head and Neck, SCCHN);
- Bone (Ewing Sarcoma, ES).

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 MTCA level may be repeated in an additional cohort.

**Figure 1 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

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 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 Investigational Medicinal Product (IMP)-related Adverse Events (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 177Lu-3BP-227 to EOCT/ Early Discontinuation (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 m2).
- 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 delayed recovery to baseline or resolution of any AE to Grade ≤2 (exception of alopecia and lymphopenia).
- Grade 5 toxicity (death).

### *1.2.1 Study population*

CCI [redacted] and up to 30 subjects will receive the $^{177}$Lu-3BP-227 therapeutic dose.

### *1.2.2 Study duration*

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 administrations after the EOCT, provided the subject has an acceptable tolerability profile and the organ dose limits are not exceeded.

A long-term follow-up period will start after the last cycle is administered (after EOCT, ED visit or End Of Additional Cycles (EOAC)) 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.

## 1.3 Methods and procedures

### *1.3.1 Subject identification and allocation to study treatment*

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.

### *1.3.2 Subjects assessments*

#### *1.3.2.1 Safety assessments*

- Adverse events (AEs) monitored from the time that the subject gives informed consent and throughout the study, elicited by direct, nonleading questioning or by spontaneous reports. All AEs, irrespective of causality, should be reported to the sponsor up to 6 month after the EOCT, ED and EOAC visit or until new antitumour treatment starts, whichever comes first. AEs reported after this timepoint up to the end of the 5-year follow-up should only be reported if evaluated as related to the IMP or study procedure by the investigator;
- Clinical safety assessments:
  - Physical examination assessed at screening, at Day 1 pre-dose (and up to 24 hours (replaced by up to 48 hours from protocol V7.0) before IMP infusion for cycle 1 only), Day 15 and Day 29 of both cycles 1 and 2, at EOCT/ED visit, at Day 1 and Day 29 of each additional cycle (if applicable), at EOAC/ED visit (if applicable) and every 3 months during long-term follow-up. Any clinically significant physical examination findings (abnormalities) observed during the study will be reported as AEs;
  - Vital signs measured at screening (prior to infusion, at the end of infusion, 30 minutes after infusion, 60 minutes after infusion (replaced by 90 minutes after infusion from protocol V7.0) and 4 hours after infusion), at Day 1 (prior to infusion, at the end of infusion, 30 minutes after infusion, 60 minutes after infusion (replaced by 90 minutes after infusion from protocol V7.0) and 4 hours after infusion), Day 2, Day 3, Day 8, Day 15, Day 22 and Day 29 of both cycles 1 and 2, at EOCT/ED visit, at Day 1 (prior to infusion, at the end of infusion, 30 minutes after infusion, 60 minutes after infusion (replaced by 90 minutes after infusion from protocol V7.0) and 4 hours after infusion), Day 2, Day 3, Day 8, Day 15, Day 22 and Day 29 of each additional cycle (if applicable), at EOAC/ED visit (if applicable) and every 3 months during long-term follow-up including supine systolic and diastolic blood pressures, supine heart rate and body temperature;
  - Body weight measured at screening, at Day 1 pre-dose (and up to 24 (replaced by up to 48 hours from protocol V7.0) hours before IMP infusion for cycle 1 only), Day 15 and Day 29 of both cycles 1 and 2, at EOCT/ED visit, at Day 1, Day 15 and Day 29 of each additional cycle (if applicable), at EOAC/ED visit (if applicable) and every 3 months during long-term follow-up;
  - 12-lead electrocardiograms (ECGs) measured at screening (a triplicate 12-lead ECG before infusion and a single 12-lead ECG at the end of infusion and 4 hours after the end of infusion), at Day 1 (a triplicate 12-lead ECG before infusion and a single 12-lead ECG at the end of

infusion and 4 hours after the end of infusion) and Day 2 at 24 hours of both cycles 1 and 2, at EOCT/ED visit, at Day 1 (a triplicate 12-lead ECG before infusion and a single 12-lead ECG at the end of infusion and 4 hours after the end of infusion) of each additional cycle (if applicable) and at EOAC/ED visit (if applicable), including corrected QT (QTc) calculated using Fridericia methodology as well as their clinical significance;

- 24-hour 3-lead holter ECGs starting before IMP infusion at Day 1 of both cycles 1 and 2;
- Clinical haematology and biochemistry laboratory tests measured at screening, at Day 1 pre-dose (and up to 24 hours (replaced by up to 48 hours from protocol V7.0) before IMP the infusion for cycle 1 only), Day 2 (for cycle 1 only) (removed from protocol V8.0), Day 8, Day 15, Day 22 and Day 29 of both cycles 1 and 2, at EOCT/ED visit, at Day 1, Day 2, Day 8, Day 15, Day 22 and Day 29 of each additional cycle (if applicable), at EOAC/ED visit (if applicable) and every 3 months during long-term follow-up:
  - Haematology: full blood count including red blood cells count, haemoglobin, haematocrit, mean corpuscular volume, white blood cell count with differential count (neutrophils, eosinophils, basophils, lymphocytes, monocytes), platelet count;
  - Blood biochemistry: urea, uric acid, creatinine, total bilirubin, conjugated bilirubin (direct) (only to be performed if the total bilirubin is abnormal i.e. outside the laboratory normal range from protocol V8.0), chloride, sodium, potassium, calcium, Alkaline phosphatase, Aspartate aminotransferase, Alanine aminotransferase, albumin, total protein, total cholesterol, triglycerides, fasting glucose, estimated Glomerular Filtration Rate (eGFR) and C reactive protein.
- Clinical urinalysis laboratory tests measured at screening, at Day 1 pre-dose (and up to 24 (replaced by up to 48 hours from protocol V7.0) hours before IMP the infusion for cycle 1 only), Day 2 (for cycle 1 only), Day 3 (for cycle 1 only) and Day 29 of both cycles 1 and 2, at EOCT/ED visit, at Day 1 and Day 29 of each additional cycle (if applicable), at EOAC/ED visit (if applicable) and every 3 months during long-term follow-up:
  - pH, proteins, ketones, glucose, nitrite, bilirubin, urobilinogen, leucocytes and blood as well as 24h sample creatinine clearance (removed from protocol V7.0) and protein excretion rate (only in case of positive dipstick).
- Clinical hormones laboratory tests measured at screening and at EOCT/ED visit:
  - Cortisol, Thyroid-Stimulating Hormone (TSH), ft4, Insulin-like Growth Factor 1 (IGF-1) and Parathyroid Hormone (PTH);

Hormones analysis will be analysed in 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).

- Eastern Cooperative Oncology Group (ECOG) performance status scale measured at screening, at Day 1 of both cycles 1 and 2, at EOCT/ED visit, at Day 1 of each additional cycle (if applicable), at EOAC/ED visit (if applicable) and every 3 months during long-term follow-up;
- Serum pregnancy tests measured at screening and urine pregnancy tests measured at Day 1 of both cycles 1 and 2, at EOCT/ED visit, at Day 1 of each additional cycle (if applicable) and at EOAC/ED visit (if applicable);
- CCI

*1.3.2.2 Pharmacodynamic/efficacy assessments*

- Tumour assessment according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria v1.1 for target and non-target lesions assessed locally (by ceCT/MRI) at screening, at Day 1 of cycle 1 (removed from protocol V7.0), at EOCT/ED visit, at Day 29 of second and fourth additional cycles (if applicable), at EOAC/ED visit (if applicable) and every 3 months during long-term follow-up;
- Tumour assessment according to PERCIST criteria v1.0 for target and non-target lesions assessed locally at Day 1 of cycle 1, at EOCT/ED visit and at EOAC/ED visit (if applicable);
- Tumour markers in serum assessed at Day 1 of both cycles 1 and 2, at EOCT/ED visit, at Day 1 of each additional cycle (if applicable) and at EOAC/ED visit (if applicable) including Carcinoembryonic antigen (CEA) (all subjects), Cancer Antigen (CA) 19-9 (all subjects except SCCHN), CA72-4 (subjects with GC) (removed from protocol V7.0), Tissue Polypeptide antigen (TPA) (subjects with SCCHN) (removed from protocol V7.0) and serum Lactate Dehydrogenase (LDH) and Bone Specific Alkaline Phosphatase (BSAP) for ES;

*1.3.2.3 Pharmacokinetics, biodistribution and dosimetry*

- Blood samples for pharmacokinetic evaluation of $^{177}$Lu-3BP-227 are collected just before the $^{177}$Lu-3BP-227 infusion (baseline), at the end of infusion (0), 5 minutes ±1 minute, 30 minutes ±5 minutes, 1 hour ±5 minutes (replaced by 90 minutes ±15 minutes from protocol V7.0), 4 hours ±30 minutes, 24 hours ±2 hours, 48 hours ±2 hours, 72 to 96 hours post infusion for both cycles 1 and 2 and for both first and third additional cycles (if applicable) and at 24 hours after the second and fourth additional cycles (if applicable);
- Urine collection for evaluation of the renal excretion of $^{177}$Lu-3BP-227 are collected during four different periods at cycle 1: from 0 (i.e. start of 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 IMP infusion to 6 hours after the end of the infusion only for US sites);

- Blood samples for pharmacokinetic evaluation of 3BP-227 are collected at cycle 1 only before the 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 (replaced by 90 minutes ±15 minutes from protocol V7.0), 4 hours ±30 minutes, 6 hours ±30 minutes, 10 hours ±1 hour (replaced by 8 hours ±1 hour from protocol V7.0), 24 hours ±2 hours and 48 hours ±2 hours after the end of infusion of $^{177}$Lu-3BP-227;
- Urine collection for evaluation of the renal excretion of 3BP-227 are collected during four different periods at cycle 1: from 0 (i.e. start of 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 IMP infusion to 6 hours after the end of the infusion only for US sites);
- Planar scintigraphy (whole body scan) are performed at screening after 177Lu-3BP-227 infusion, and at 0 to 1 hour (before urination) (removed from protocol V7.0), 4 (±2) hours, 24 (±6) hours, 48 (±6) hours, 72 to 96 hours (from protocol V7.0) and 138 to 168 hours (from protocol V8.0) after the end of 177Lu-3BP-227 infusion for both cycles 1 and 2 and for both first and third additional cycles (if applicable). After the second and fourth additional cycles (if applicable), a single planar scintigraphy at 48 (±6) hours will be performed.
- SPECT/CT are performed at screening after $^{177}$Lu-3BP-227 infusion, and at 0 to 1 hour (before urination) (removed from protocol V7.0), 4 (±2) hours, 24 (±6) hours, 48 (±6) hours, 72 to 96 hours (from protocol V7.0) and 138 to 168 hours (from protocol V8.0) after the end of $^{177}$Lu-3BP-227 infusion for both cycles 1 and 2 and for both first and third additional cycles (if applicable). After the second and fourth additional cycles (if applicable), a SPECT/CT at 48 (±6) hours will be performed.

Planar scintigraphy and SPECT/CT will enable assessment of the biokinetic of $^{177}$Lu-3BP-227 via an absolute quantification of radioactivity in target lesions and discernible organs.

#### *1.3.2.4 Exploratory assessments*

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*1.3.2.5 Other assessments*

- Demographics (sex, ethnicity, race) and baseline characteristics (age, body height, body weight, Body Mass Index (BMI));
- Post-menopausal status;
- Medical history, including ongoing medical history;
- Baseline signs and symptoms related to studied disease or previous studied disease therapy;
- Studied disease (Pancreatic Ductal Adenocarcinoma history, Colorectal Carcinoma history, Stomach Carcinoma history, GIST history, SCCHN history, Ewing Sarcoma history);
- Prior chemotherapy for studied disease;
- Prior immunotherapy for studied disease;
- Prior radiotherapy for studied disease;
- Prior surgical procedures for studied disease;
- Prior and concomitant medications;
- Concomitant medications for studied disease;
- Prior and concomitant non-drug therapies;
- Concomitant surgical procedures.

*1.3.2.6 Withdrawal/discontinuation*

In accordance with the Declaration of Helsinki and the applicable country's acceptance, each subject is free to withdraw from the study at any time for any reason.

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 blood-based or image-based dosimetry;
- cumulative liver dose exceeds 30 Gy;
- occurrence of a DLT for phase I dose escalation only.

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

CCI [redacted]

CCI

[redacted]

### *1.3.3 Schedule of assessments*

Here are the schedules of assessments extracted from the current version of the protocol:

**Table 1 Study Schedule of Assessments (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 | 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 18FDG-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.

**Table 1 Study Schedule of Assessments (dose escalation) (continued)**

| 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 177Lu 3BP-227 SPECT/CT following IMP screening administration, as soon as 177Lu 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 177Lu-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 177Lu-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 177Lu-3BP-227.

l ten blood samples will be collected at cycle 1. Blood samplings will be performed just before 177Lu-3BP-227 infusion (baseline), at the end of infusion of 177Lu-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 177Lu-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 177Lu-3BP-227 infusion.

**Table 1 Study Schedule of Assessments (dose escalation) (continued)**

| 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 177Lu-3BP-227 infusion (0) as well as 30±5 minutes, 90±15 minutes, 4 hours±30 minutes after the end of 177Lu-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 177Lu-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 177Lu-3BP-227 infusion (±15 minutes), at 4 hours after the end of 177Lu-3BP-227 infusion (±30 minutes) and on Day 2 at 24 hours after the end of 177Lu-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 177Lu-3BP-227 infusion, a 24-hour 3-lead continuous ECG Holter will be recorded.

**Table 1 Study Schedule of Assessments (dose escalation) (continued)**

| 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 [redacted] | | | | | | | | | | | | | | | | | | | | | |
| Tumour markers in serum | | x | | | | | | | | | x | | | | | | | | | x | |
| CCI [redacted] | | | | | | | | | | | | | | | | | | | | | |
| 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 [redacted]

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 177Lu-3BP-227 infusion (from the start of the infusion to 6 hours after the end of the infusion only for US sites).

u CCI [redacted]

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 177Lu-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 2 Study Schedule of Assessments (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 177Lu-3BP-227 infusion (baseline), at the end of infusion of 177Lu-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 177Lu-3BP-227 infusion (0) as well as 30±5 minutes, 90±15 minutes, 4 hours±30 minutes after the end of 177Lu-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 177Lu-3BP-227 infusion (±15 minutes) and at 4 hours (±30 minutes) after the end of 177Lu-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.

### *1.3.4 Planned sample size*

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.

The actual sample size required to adequately determine the MTCA/ Maximum Tolerated Single Activity (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. Based on experience, the chosen sample size of three to five subjects per cohort is considered sufficient to fulfill the objectives of the study. It is anticipated that approximately 30 subjects will be required to establish the MTCA or Maximum Administered Cumulative Activity (MACA).

## 2 SUBJECT POPULATIONS (ANALYSIS SETS)

### 2.1 Screened population

The screened population is all screened subjects in the study i.e. who signed the informed consent.

### 2.2 Included population

The included population is all screened subjects who are included in the study and received the therapeutic dose.

### 2.3 Safety population

The safety population is all subjects who received at least one dose of study medication (including screening administration).

### 2.4 Pharmacodynamic/Efficacy population

#### *2.4.1 Pharmacodynamic population*

The pharmacodynamic population is all subjects who received at least one therapeutic dose and with available post-baseline pharmacodynamics/efficacy data.

#### *2.4.2 Primary pharmacodynamic population*

The primary pharmacodynamic population for tumour response is all subjects who have received at least two therapeutic doses of $^{177}$Lu-3BP-227 and reached the end of Cycle 2 or EOCT visit with available post-baseline tumour assessment based on RECIST criteria v1.1 and with no major protocol deviations with an impact on the analysis.

### 2.5 Pharmacokinetic population

#### *2.5.1 $^{177}$Lu-3BP-227 Pharmacokinetic population*

##### *2.5.1.1 177Lu-3BP-227 blood pharmacokinetic population*

The $^{177}$Lu-3BP-227 blood pharmacokinetic population is all subjects with blood dosimetry data and with no major protocol deviations with an impact on $^{177}$Lu-3BP-227 blood PK analysis.

##### *2.5.1.2 $^{177}$Lu-3BP-227 urine pharmacokinetic population*

The $^{177}$Lu-3BP-227 urine pharmacokinetic population is all subjects with urine dosimetry data and with no major protocol deviations with an impact on $^{177}$Lu-3BP-227 urine PK analysis.

### *2.5.2 3BP-227 Pharmacokinetic population*

#### *2.5.2.1 3BP-227 plasma pharmacokinetic population*

The 3BP-227 plasma pharmacokinetic population is all subjects with plasma 3BP-227 concentration data and with no major protocol deviations with an impact on 3BP-227 plasma PK analysis.

#### *2.5.2.2 3BP-227 urine pharmacokinetic population*

The 3BP-227 urine pharmacokinetic population is all subjects with urine 3BP-227 concentration data and with no major protocol deviations with an impact on 3BP-227 urine PK analysis.

## 2.6 Dosimetry population

The dosimetry population is all subjects with organ dosimetry data and with no major protocol deviations with an impact on dosimetry analysis.

## 2.7 Primary population

The primary objective of this study is safety and tolerability, therefore the primary population for analysis is the safety population.

The pharmacodynamics/efficacy analyses will be based on the pharmacodynamic population, except analyses on tumour response which will be based on the primary pharmacodynamic population and overall survival which will be based on the included population.

The $^{177}$Lu-3BP-227 blood pharmacokinetic analyses will be based on the $^{177}$Lu-3BP-227 blood Pharmacokinetic population.

The $^{177}$Lu-3BP-227 urine pharmacokinetic analyses will be based on the $^{177}$Lu-3BP-227 urine Pharmacokinetic population.

The 3BP-227 plasma pharmacokinetic analyses will be based on the 3BP-227 plasma Pharmacokinetic population.

The 3BP-227 urine pharmacokinetic analyses will be based on the 3BP-227 urine Pharmacokinetic population.

The $^{177}$Lu-3BP-227 pharmacokinetic analyses in discernible organs and target lesions will be based on the dosimetry population.

# 3 STATISTICAL METHODS

## 3.1 Statistical analysis strategy

The statistical analyses will be performed in accordance with ICH E9 guideline [1].

Statistical analyses described in this document will be performed by Biotrial Biometrics, Rennes, France.

### *3.1.1 Safety endpoints*

The safety endpoints are:

- Treatment Emergent Adverse Events (TEAEs), including information on seriousness, intensity, drug relationship and DLTs;
- Clinical laboratory evaluations for haematology, biochemistry, urinalysis, hormones and shift tables;
- Clinical safety endpoints: physical examination, vital signs, body weight, BMI, 12-lead ECGs, 24h 3-lead holter ECGs, serum and urine pregnancy tests, ECOG and specific renal safety biomarkers.

### *3.1.2 Pharmacodynamic/efficacy endpoints*

The pharmacodynamics/efficacy endpoints are:

- Objective Response Rate (ORR): proportion of subjects with a best overall response (BOR) characterised as either a Complete Response (CR) or Partial Response (PR) according to RECIST criteria v1.1 relative to the total number of evaluable patients;
- Disease Control Rate (DCR): proportion of patients with a BOR characterised as Complete Response (CR), Partial Response (PR) or stable disease (SD) according to RECIST criteria v1.1 relative to the total number of evaluable patients;
- Progression-Free Survival (PFS) from first treatment administration until progression, according to RECIST criteria v1.1;
- Overall Survival (OS) from first treatment administration until death, according to RECIST criteria v1.1;
- Metabolic tumour responses according to PERCIST criteria v1.0;
- Changes in tumour markers in serum relevant and specific to the underlying tumour disease.

### *3.1.3 Pharmacokinetics, biodistribution and dosimetry endpoints*

#### *3.1.3.1 Biodistribution and pharmacokinetic endpoints for $^{177}$Lu-3BP-227*

The PK parameters will be derived by non-compartmental analysis (NCA) from individual blood concentrations of $^{177}$Lu-3BP-227 (calculated sample activity):

Concentrations will be decay-corrected for sampling time according to the following formula after substraction of pre-infusion concentration:

$$A_0 = A_t * \exp((\ln(2)/ t_{1/2}) * \Delta t) \text{ where } t_{1/2} = 6.647 \text{ days.}$$

With $A_t$ the radioactivity at the measurement time, $A_0$ radioactivity at the sampling time and $\Delta t$ the time between sampling and measurement time in days.

The PK parameters are the following:

- $C_{max}$ (Bq/mL): Maximum observed $^{177}$Lu-3BP-227 concentration ;
- $T_{max}$ (h): Time of maximal observed $^{177}$Lu-3BP-227 concentration ;
- $AUC_{0\text{-}48}$ (MBq/mL*h): Area under the concentration-time curve of $^{177}$Lu-3BP-227 from start of infusion to 48 hours;
- $AUC_{0\text{-}tlast}$ (MBq/mL*h): Area under the concentration-time curve of $^{177}$Lu-3BP-227 from start of infusion to time t corresponding to the last quantifiable concentration;
- $AUC_{0\text{-}\infty}$ (MBq/mL*h): Area under the concentration-time curve from start of infusion to calculated as follows:

  $$AUC_{0\text{-}\infty} = AUC_{0\text{-}tlast} + C_{last}/\lambda_z,$$

  with $C_{last}$ as the last quantifiable concentration
- $t_{1/2}$ (h): terminal half-life of activity concentrations of $^{177}$Lu-3BP-227;
- CL (L/h): Total clearance calculated as follows:

  $$CL = Dose / AUC_{0\text{-}\infty;}$$
- $Vd_z$ (L): Volume of distribution calculated as follows:

  $$Vd_z = CL / \lambda z.$$

- MRT (h): Mean residence time

$$MRT = AUMC_{0-\infty;}/AUC_{0-\infty;}$$

with $AUMC_{0-\infty}$: Area under the first moment curve from zero to infinity

The following PK parameters will be derived by NCA of the individual urine concentrations of $^{177}$Lu-3BP-227:

- Ci x Vi (Bq) at each time interval with Ci : concentrations (calculated sample activity) decay-corrected for start of infusion time (using the same formula as for blood) and Vi: collected volume
- Ae (Bq): Cumulative activity of drug excreted in urine during 48 hours, calculated as follows:

$$Ae = \sum Ci \times Vi$$

- Fe (%): fraction of the administered drug excreted in urine during 48 hours
- $CL_R$ (L/h): Renal clearance calculated as follows:

$$CL_R = Ae / AUC_{0-48}$$

The following biodistribution parameters will be derived for target lesions and organs of interest (healthy liver, bone marrow, left kidney, right kidney, spleen and pancreas) by NCA from individual activity uptake of $^{177}$Lu-3BP-227:

- $C_{max}$ (GBq): Maximum observed $^{177}$Lu-3BP-227 activity uptake;
- $T_{max}$ (h): Time of maximal observed $^{177}$Lu-3BP-227 activity uptake;
- $AUC_{0-tlast}$ (GBq*h): [(Area under the concentration-time curve of $^{177}$Lu-3BP-227 from start of infusion to time t corresponding to the last quantifiable activity uptake (%) in %*h) * Radioactivity administered in GBq];
- $AUC_{0-\infty}$ (GBq*h): [(Area under the concentration-time curve of $^{177}$Lu-3BP-227 from start of infusion to infinity in %*h) * Radioactivity administered in GBq];

$$AUC_{0-\infty} = AUC_{0-tlast} + C_{last}/\lambda_z,$$

with $C_{last}$ as the last quantifiable concentration

- MRT (h): Mean residence time

$$MRT = AUMC_{0-\infty;}/AUC_{0-\infty;}$$

with $AUMC_{0-\infty}$: Area under the first moment curve from zero to infinity

*3.1.3.2 Pharmacokinetic endpoints for 3BP-227*

The following PK parameters will be derived by NCA of the plasma concentration-time profiles during cycle 1:

- $C_{max}$ (ng/mL): Maximum observed 3BP-227 plasma drug concentration;
- $AUC_{0-tlast}$ (ng/mL*h): Area under the plasma concentration-time curve of 3BP-227 from start of infusion to time t corresponding to the last quantifiable concentration
- $AUC_{0-\infty}$ (ng/mL*h): Area under the plasma concentration-time curve of 3BP-227from start of infusion to infinity calculated as follows:

$$AUC_{0-\infty} = AUC_{0-tlast} + C_{last}/\lambda_z,$$

with $C_{last}$ as the last quantifiable concentration

- $t_{1/2}$ (h): Terminal elimination half-life calculated as follows:

$$t_{1/2} = Ln(2)/\lambda_z$$

- CL (L/h): Total clearance from plasma calculated as follows:

$$CL = Dose / AUC_{0-\infty}$$

- $V_z$ (L): Volume of distribution from plasma calculated as follows:

$$Vd_z = CL / \lambda z$$

- MRT (h): Mean residence time

$$MRT = AUMC_{0-\infty;}/AUC_{0-\infty;}$$

with $AUMC_{0-\infty}$: Area under the first moment curve from zero to infinity

The following PK parameters will be derived by NCA of the individual urine concentrations:

- Ci x Vi (ng) at each time interval with Ci : concentrations and Vi: collected volume
- Ae (ng): Cumulative amount of drug excreted in urine during 48 hours, calculated as follows:

$$Ae = \sum Ci \times Vi$$

- Fe (%): fraction of the administered drug excreted in urine during 48 hours
- $CL_R$ (L/h): Renal clearance calculated as follows:

$$CL_R = Ae / AUC_{0-tlast}$$

*3.1.3.3 Radiation dosimetry endpoints for $^{177}$Lu-3BP-227*

The following parameters will be evaluated (only in organs and target lesions showing uptake):

- Organs receiving the highest absorbed dose by cycle;
- Specific absorbed dose to the target lesions (Gy/GBq) by cycle;
- Specific absorbed dose per organ (Gy/GBq) by cycle;
- Time-Integrated Activity Coefficient (TIAC) (or residence time) per organ and to the target lesions by cycle;
- Whole body effective dose (Sv)
- Whole body effective dose per administered activity (Sv/GBq)
- Absorbed doses on cycle 1 and cumulative absorbed doses on cycles 1 and cycle 2 per organ and to the target lesions (Gy).

The absorbed dose to the target lesions and discernible organs (i.e. organs showing uptake) will be evaluated by image-based analysis. It relies on the visual identification of the regions of interest on the images and determination of activity and absorbed doses using Planet Dose solution (Dosisoft). The organs considered for $^{177}$Lu-3BP-227 image based dosimetry assessment will be the following: Healthy Liver, Total Liver, Bone marrow, Left Kidney, Right Kidney, Intestine (large & small), Spleen, Pancreas, Stomach wall, Right ovary, Left ovary, Uterus, Right testis, Left testis, Thymus, Right thyroid gland, Left thyroid gland, Prostate gland and total body. Additional organs may be added later on.

In addition to the image-based analysis, the absorbed doses of all organs will be evaluated by model-based analysis (OLINDA/EXM version 1.0) using TIAC estimates from the image-based analysis.

Effective dose will be evaluated by model-based analysis.

Finally, absorbed dose in red marrow will also be computed assuming proportionality on activity measures in blood samples (blood based method).

Absorbed doses and specific absorbed doses will be also presented on kidney (left+right) using the average of left kidney and right kidney.

Details on the different calculations are provided in the Dosimetry Analysis Plan of the study.

### *3.1.4 Exploratory endpoints*

Exploratory endpoints will be described in a dedicated SAP.

### *3.1.5 Multiplicity*

There is no plan for multiple testing adjustments in this study.

### *3.1.6 Significance testing and estimation*

All statistical tests will be one-sided at the 5% level of significance.

## 3.2 Analysis methods

### *3.2.1 Safety*

All safety data will be included in the data listings and summary tables will be based on the safety population.

#### *3.2.1.1 Adverse events*

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) latest version at Ipsen coding department at the time of corresponding database lock and NCI-CTCAE version 5.0 will be used for the grade's classification.

Listings will be presented by treatment group, subject, start date-time, primary system organ class, preferred term and reported term for all AEs recorded during the study, after IMP screening administration, for core trial, additional cycles and follow-up long term separately.

Listings of all AEs, serious adverse events (SAE), AEs leading to withdrawal and listing of deaths will also be presented.

TEAEs will be flagged (*) in the listing of AEs and will be summarised.

A TEAE for the IMP screening administration is defined as any AE that occurs after the IMP screening administration if:

- It was not present prior to IMP screening administration and it had onset before the first dose of IMP during core trial, or
- It was present prior to receiving the IMP screening administration but the grade increased between IMP screening administration and the first dose of IMP during core trial,
- It was present prior to receiving the IMP screening administration, the grade is the same but the causality changed to "related" between IMP screening administration and the first dose of IMP during core trial.

A TEAE for the core trial period is defined as any AE that occurs during the core trial period of the study if:

- It was not present prior to first dose of IMP during core trial period and it had onset before the EOCT/ED visit, or
- It was present prior to receiving the first dose of IMP during core trial period but the grade increased between first dose of IMP during core trial period and EOCT/ED visit,
- It was present prior to receiving the first dose of IMP during core trial period, the grade is the same but the causality changed to "related" between first dose of IMP during core trial period and EOCT/ED visit.

A TEAE for the additional cycles period is defined as any AE that occurs during the additional cycles period of the study if:

- It was not present prior to EOCT visit and it had onset before the EOAC/ED visit, or
- It was present prior to EOCT visit but the grade increased between EOCT visit and EOAC/ED visit,
- It was present prior to EOCT visit, the grade is the same but the causality changed to "related" between EOCT visit and EOAC/ED visit.

A TEAE for the long-term follow-up period is defined as any AE that occurs during the long-term follow-up period of the study if:

- It was not present prior to EOCT/ED visit or EOAC/ED visit, or
- It was present prior to EOCT/ED visit or EOAC/ED visit but the grade increased between EOCT/ED visit or EOAC/ED visit and end of study,
- It was present prior to EOCT/ED visit or EOAC/ED visit, the grade is the same but the causality changed to "related" between EOCT/ED visit or EOAC/ED visit and end of study.

In addition, adverse events will be assigned to a specific cycle of treatment for core trial and additional cycles. This assignment will be based on the start date of the adverse event: if the AE start date is on or after the date of treatment X and before the date of treatment X+1 (or if the subject does not receive a treatment X+1 or the treatment X+1 date is missing), then the TEAE will be assigned to Treatment Cycle X.

An overall summary table of all AEs will be presented by treatment group and overall, by cycle (if applicable) and overall, after IMP screening administration, for core trial, additional cycles and follow-up long term separately. In addition, an overall summary table will be presented by pooling cycles from core trial and additional cycles.

TEAEs will be summarised by treatment group and overall with the number and percentage of subjects with AEs classified by primary system organ class and preferred term, by cycle (if applicable) and overall, after IMP screening administration, for core trial, additional cycles and follow-up long term separately. The number of occurrences of a TEAE will also be presented.

In addition, summary tables will also be presented for related TEAEs, SAEs, related SAEs, non-serious TEAEs, TEAEs by decreasing frequency, TEAEs by NCI-CTCAE worst grade (for NCI-CTCAE worst grade ≥ 3) and TEAEs by most serious causality (category related only).

Summary of TEAEs and related TEAEs will be also summarised by pooling cycles from core trial and additional cycles.

DLTs during cycle 1 or 2 (i.e. occurring between the first administration of $^{177}$Lu-3BP-227 and EOCT/ED) will be summarised by treatment group and overall with the number and percentage of subjects with DLTs classified by primary system organ class and preferred term. The number of occurrences of a DLT will also be presented.

The number of subjects with at least one DLT or NCI-CTCAE grade ≥ 2 (excluding hair loss) will be tabulated by treatment group and overall, by cycle and overall.

Listings of all DLTs will also be presented.

Depending on the number of cases, for all SAEs linked to COVID-19, a summary table will also be provided by treatment group and overall, presenting the number of patients by SOC and PT, by pooling core trial, additional cycles and follow-up long term. Listings of all SAEs linked to COVID-19 will also be presented.

In the event of multiple reports of the same preferred term being reported by the same subject, the NCI-CTCAE worst grade (grade 5 > grade 4 > grade 3 > grade 2 > grade 1) and the most serious causality (related > not related) will be chosen.

*3.2.1.2 Laboratory data*

Haematological and biochemistry toxicities will be recorded and graded according to the NCI-CTCAE criteria, version 5.0.

A separate listing of normal ranges for standard international (SI) units will be provided (by age and gender where relevant) for all laboratory data (whenever relevant) as well as a listing of NCI-CTCAE grades with corresponding laboratory ranges.

Laboratory data (haematology, biochemistry, urinalysis and hormones) will be listed in SI units and abnormal values will be flagged (High [H], Low [L], clinically significant [CS], NCI-CTCAE grade [G] (for haematology and biochemistry)) where applicable, for core trial, additional cycles and follow-up long term separately (only core trial for hormones). Any unscheduled laboratory assessments will be flagged [U] in the listings.

In addition, a listing will be presented of all values for a subject with at least a clinically significant abnormal laboratory value.

The baseline will be defined as the last available (and reliable if applicable) assessment collected prior to first IMP administration.

For haematology and biochemistry, summary statistics will be presented by treatment group at each scheduled assessment for actual values and changes from baseline, for core trial, additional cycles and follow-up long term separately.

Shift tables from baseline to each applicable post baseline visit will be presented by treatment group using the number and percentage of subjects with low, normal or high values, for core trial, additional cycles and follow-up long term separately.

The NCI-CTCAE worst grade by subject, by cycle and overall, will be summarised by treatment group, for core trial, additional cycles and follow-up long term separately as well as by pooling cycles from core trial and additional cycles. All non-missing post-baseline values (including unscheduled visits and retest measurements if any) will be used to derive the worst grade.

A listing of NCI–CTCAE grade 3 and 4 toxicities will be produced. For white blood cells, neutrophils, platelets and haemoglobin, with associated Grade 3 or 4 toxicities, nadir and day to nadir will be calculated and listed.

Additionally, a listing of out of range values with parameters that could not be graded using NCI-CTCAE grade will be provided with the H and L flags.

Box plots and scatter plots over time will be provided with all treatment groups on the same graph for the following parameters: haemoglobin, neutrophils, white blood cells, platelet count, ASAT, ALAT, alkaline phosphatase, creatinine, eGRF, total and conjugated bilirubin.

For continuous urinalysis, summary statistics will be presented by treatment group at each scheduled assessment for actual values and changes from baseline.

For categorical urinalysis (negative/trace/positive) frequency tables will be presented at each scheduled assessment by treatment group.

Shift tables from baseline to each applicable post baseline visit will be presented by treatment group using the number and percentage of subjects in each category, for core trial, additional cycles and follow-up long term separately.

For hormones, summary statistics will be presented by treatment group at each scheduled assessment for actual values and changes from baseline, for core trial.

Hormones analysis will be analysed in 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).

#### *3.2.1.3 Physical examination*

A listing with the date and status of assessment of test will be provided by treatment group, subject and date, for core trial, additional cycles and follow-up long term separately.

#### *3.2.1.4 Vital signs*

Vital signs (supine systolic and diastolic blood pressures, heart rate, weight, BMI and temperature) will be listed at each assessment by treatment group and subject, for core trial, additional cycles and follow-up long term separately. Any unscheduled vital signs will be flagged [U] in the listing.

The baseline will be defined as the last available (and reliable if applicable) assessment collected prior to first IMP administration.

Summary statistics by treatment group will be presented at each scheduled assessment for actual values and changes from baseline, whatever the position, for core trial, additional cycles and follow-up long term separately.

For interpretation of clinical significance (normal / abnormal, not clinically significant / abnormal, clinically significant / not evaluable), a frequency table will be presented by treatment group at each post-dose assessment, for core trial, additional cycles and follow-up long term separately.

#### *3.2.1.5 ECG*

ECG results will be listed at each assessment by treatment group and subject, for core trial and additional cycles separately. Any unscheduled ECG will be flagged [U] in the listing.

The baseline will be defined as the last available (and reliable if applicable) assessment collected prior to first IMP administration.

In case of triplicate ECGs, the mean will serve as analysable data.

#### *3.2.1.6 Holter ECG*

Holter ECG results will be listed at each assessment by treatment group and subject. Any unscheduled Holter ECG will be flagged [U] in the listing.

#### *3.2.1.7 ECOG*

ECOG will be summarised by treatment group at each scheduled assessment and will be listed at each assessment by treatment group and subject, for core trial, additional cycles and follow-up long term separately.

#### *3.2.1.8 Serum and urine pregnancy tests*

Results for serum and urine pregnancy tests will be summarised by treatment group at each scheduled assessment and will be listed at each assessment by treatment group and subject, for core trial and additional cycles separately.

#### *3.2.1.9 Specific renal safety biomarkers*

CCI

### *3.2.2 Missing data and outliers*

#### *3.2.2.1 Missing data*

No missing value will be replaced.

If a value required a retest, the last reliable non-missing value will be taken into account if measured before the first administration of IMP; and the first non-missing reliable value for post-baseline assessments. An assessment will be considered reliable if it is performed without any technical problem and if the result is within the range of plausible values.

Any repeat or additional assessments performed will be included in the individual subject data listings.

If there is a significant number of missing values for a subject (or if there is confirmed data appearing spurious), a decision will be made following consultation with the sponsor regarding the handling of these data in summaries, prior to database freeze.

#### *3.2.2.2 Missing or incomplete dates*

In all listings, missing or incomplete dates should be left as they have been recorded. However, for calculation / sorting / assignation based on dates, the following methods will be used:

The most conservative approach will be systematically considered (i.e. if the onset date of an AE/concomitant medication is missing / incomplete, it is assumed to have occurred during the study treatment phase (e.g. a TEAE for AEs) except if the partial onset date or other data [stop date, …] indicates differently).

A missing/incomplete date of medical history or disease diagnosis will be assumed to have occurred before any study treatment.

Where this is possible, the derivations based on a partial date will be presented as superior inequalities (e.g. for an AE started in FEB2004 after the administration performed on 31JAN2004, the days since last dose will be "≥ 2", similarly the duration of ongoing AEs or medication will be "≥ xx" according to the start and last visit dates).

#### *3.2.2.3 Outliers*

Any outlier identified prior to database lock which is impossible/unplausable will be excluded from the analysis. For other identified outliers, the impact should be assessed by performing the statistical analysis with the actual values and at least one other analysis eliminating or reducing the outlier effect.

### *3.2.3 Subject disposition*

The number of subjects screened, included, discontinued and completed at each step of the study (core trial, additional cycles and long-term follow-up) will be tabulated by treatment group and overall on the screened population for core trial and on the included population for additional cycles and long-term follow-up and corresponding information will be listed. The number of subjects exposed and impacted by COVID-19 pandemic as well as the number of discontinued subjects due to COVID-19 will be also tabulated by treatment group and overall, by pooling core trial, additional cycles and long-term follow-up.

The number of subjects included in each analysis population will be presented by treatment group and overall for the safety population.

A listing of the inclusion and exclusion criteria not met will be provided by treatment group and subject and subject eligibility will also be listed.

The reasons for subject exclusions from each population will also be tabulated by treatment group and overall on the included population.

A summary table will present the extent of subject duration in the study for each treatment group and overall on the included population, for both core trial and long-term follow-up. The definition of the length of study duration is calculated from the date of informed consent form to the last study visit in each period.

A listing of dates of assessments and dates of hospitalisation will be presented by subject for each treatment group, for core trial, additional cycles and long-term follow-up separately. The number and percentage of subjects at each planned visit during the study will be presented by treatment group and overall for the included population, for core trial, additional cycles and long-term follow-up separately.

A listing of subjects screened but not included with the reason for screen failure will be presented by subject.

### *3.2.4 Withdrawals*

Discontinued subjects will be listed with their reasons for withdrawal and a summary table of the number and percentage of subjects who withdrew from the study and the reasons for withdrawal will be presented by treatment group and overall for the included population, for core trial, additional cycles and long-term follow-up separately.

### *3.2.5 Demographic and baseline characteristics*

The baseline will be defined as the last available (and reliable if applicable) assessment collected prior to first IMP administration.

All demographic (sex, race and ethnicity) and baseline characteristics (age, height, body weight and BMI at baseline) as well as postmenopausal status will be listed by treatment group and subject.

Summary statistics will be provided for demographic and baseline characteristics by treatment group and overall on the included population.

### *3.2.6 Medical and surgical history*

Medical and surgical history will be coded using MedDRA latest version at Ipsen coding department at the time of database lock.

Listing will present the primary system organ class, the preferred term and the reported term. The listing will be sorted by treatment group, subject, start date, primary system organ class, preferred term and reported term.

A frequency table of the number and percentage of subjects will be provided for all medical and surgical history by primary system organ class and preferred term for each treatment group and overall for the included population.

### *3.2.7 Baseline signs and symptoms related to studied disease or previous studied disease therapy*

Baseline signs and symptoms will be coded using MedDRA latest version at Ipsen coding department at the time of database lock.

Listing will present the primary system organ class, the preferred term and the reported term. The listing will be sorted by treatment group, subject, start date, primary system organ class, preferred term and reported term.

A frequency table of the number and percentage of subjects will be provided for all baseline signs and symptoms by primary system organ class and preferred term for each treatment group and overall for the included population.

### *3.2.8 Prior chemotherapy for studied disease*

Prior chemotherapy for studied disease will be coded using WHO-DD with the latest version at Ipsen coding department at the time of database lock. The therapeutic class will correspond to the second level of Anatomic Therapeutic Class (ATC) code, which corresponds to the first three digits.

Listing will be presented for the therapeutic class, preferred name and reported name. The listing will be sorted by treatment group, subject, chronological start date, therapeutic class, preferred name and reported name.

A frequency table of the number and percentage of subjects with at least one prior chemotherapy for studied disease will be provided by therapeutic class and preferred name for each treatment group and overall on the included population.

### *3.2.9 Prior immunotherapy for studied disease*

Prior immunotherapy for studied disease will be coded using WHO-DD with the latest version at Ipsen coding department at the time of database lock. The therapeutic class will correspond to the second level of Anatomic Therapeutic Class (ATC) code, which corresponds to the first three digits.

Listing will be presented for the therapeutic class, preferred name and reported name. The listing will be sorted by treatment group, subject, chronological start date, therapeutic class, preferred name and reported name.

A frequency table of the number and percentage of subjects with at least one prior immunotherapy for studied disease will be provided by therapeutic class and preferred name for each treatment group and overall on the included population.

### *3.2.10 Prior radiotherapy for studied disease*

Listing will present the primary system organ class, the preferred term and the reported term. The listing will be sorted by treatment group, subject, start date, primary system organ class, preferred term and reported term.

A frequency table of the number and percentage of subjects with at least one prior radiotherapy and by number of radiotherapies will be provided by treatment group and overall on the included population.

### *3.2.11 Prior surgical procedures for studied disease*

Prior surgical procedures for studied disease will be coded using MedDRA Dictionary with the latest version at Ipsen coding department at the time of database lock.

Listing will present the primary system organ class, the preferred term and the reported term. The listing will be sorted by treatment group, subject, start date, primary system organ class, preferred term and reported term.

A frequency table of the number and percentage of subjects with at least one prior surgical procedure for studied disease will be provided by primary system organ class and preferred term for each treatment group and overall for the included population.

### *3.2.12 Studied disease*

A frequency table of the number and percentage of subjects in each type of disease will be provided by treatment group and overall on the included population.

Moreover, the following tumour characteristics will also be described by type of studied disease, by treatment group and overall on the included population:

- For PDAC:
  - Time since diagnosis (in months),
  - Time since first relapse after last treatment (in months),
  - Histological grade,
  - Mutation status,
  - TNM staging at first diagnosis and at last relapse.
- For CRC:
  - Time since diagnosis (in months),
  - Time since first relapse after last treatment (in months),
  - Location of the primary tumour,
  - Histological grade,
  - Mutation status,
  - TNM staging.
- For GC:
  - Time since diagnosis (in months),

- Time since first relapse after last treatment (in months),
- Location of the primary tumour,
- Type of tumour,
- Histological grade,
- Helicobacter pylori infection status,
- Mutation status,
- TNM staging.

• For GIST:
- Time since diagnosis (in months),
- Time since first relapse after last treatment (in months),
- Location of the primary tumour,
- Type of tumour,
- Histological grade,
- Helicobacter pylori infection status,
- TNM staging.

• For SCCHN:
- Time since diagnosis (in months),
- Time since first relapse after last treatment (in months),
- Location of the primary tumour,
- Histological grade,
- Viral infection status,
- Mutation status,
- TNM staging.

• For ES:
- Time since diagnosis (in months),
- Time since first relapse after last treatment (in months),
- Location of the primary tumour (axial skeleton/appendicular skeleton),
- Histological grade,
- Mutation status,
- TNM staging.

All information on the studied disease will be listed by treatment group and subject.

### *3.2.13 Subject compliance*

All treatment administration information will be listed by treatment group and subject, for core trial and additional cycles separately.

Number of cycles and cumulative therapeutic dose as well as overall cumulative dose (including the screening dose) will be also described by treatment group, for core trial and additional cycles separately.

Duration of each cycle as well as duration of study drug exposure in core trial and additional cycles will be also summarised.

All protocol deviations, defined prior to database freeze, will be listed by treatment group and subject, for core trial, additional cycles and long-term follow-up separately.

Major protocol violations will be summarised on the included population, for core trial, additional cycles and long-term follow-up separately.

Additionally, protocol deviations due to COVID-19 (minor and major separately) will be summarised on the included population, by pooling core trial, additional cycles and long-term follow-up.

### *3.2.14 Prior and concomitant medications*

Prior and concomitant medications will be coded using WHO-DD with the latest version at Ipsen coding department at the time of database lock. The therapeutic class will correspond to the second level of Anatomic Therapeutic Class (ATC) code, which corresponds to the first three digits.

The date and time of first study drug administration will be used as the cut-off date for the definition of prior and concomitant medications. A medication that started before study drug administration and is continuing at time of study drug administration will be considered as both, prior and concomitant. Prior, concomitant and both prior and concomitant medications will be flagged P, C and PC respectively, in all listings.

In the event of incomplete start date and/or stop date which will not allow the categorisation of medication, it will be considered as concomitant.

Listing will be presented for the therapeutic class, preferred name and reported name. The listing will be sorted by treatment group, subject, chronological start date, therapeutic class, preferred name and reported name, for core trial, additional cycles and long-term follow-up separately.

A frequency table of the number and percentage of subjects with at least one prior medication will be provided by therapeutic class and preferred name for each treatment group and overall.

A frequency table of the number and percentage of subjects with at least one concomitant medication will be provided by therapeutic class and preferred name for each treatment group and overall on the included population, for core trial, additional cycles and long-term follow-up separately.

### *3.2.15 Concomitant medications for studied disease*

Concomitant medications for studied disease will be coded using WHO-DD with the latest version at Ipsen coding department at the time of database lock. The therapeutic class will correspond to the second level of Anatomic Therapeutic Class (ATC) code, which corresponds to the first three digits.

Listing will be presented for the therapeutic class, preferred name and reported name. The listing will be sorted by treatment group, subject, chronological start date, therapeutic class, preferred name and reported name, for core trial, additional cycles and long-term follow-up separately.

A frequency table of the number and percentage of subjects with at least one concomitant medication for studied disease will be provided by therapeutic class and preferred name for each treatment group and overall on the included population, for core trial, additional cycles and long-term follow-up separately.

### *3.2.16 Prior and concomitant non-drug therapies*

Prior and concomitant non-drug therapies will be coded using MedDRA Dictionary with the latest version at Ipsen coding department at the time of database lock.

The date and time of first study drug administration will be used as the cut-off date for the definition of prior and concomitant therapies. A therapy that started before study drug administration and is continuing at time of study drug administration will be considered as both, prior and concomitant. Prior, concomitant and both prior and concomitant therapies will be flagged P, C and PC respectively, in all listings.

In the event of incomplete start date and/or stop date which will not allow the categorisation of therapy, it will be considered as concomitant.

Listing will present the primary system organ class, the preferred term and the reported term. The listing will be sorted by treatment group, subject, start date, primary system organ class, preferred term and reported term, for core trial, additional cycles and long-term follow-up separately.

A frequency table of the number and percentage of subjects with at least one prior non-drug therapy will be provided by therapeutic class and preferred name for each treatment group and overall.

A frequency table of the number and percentage of subjects with at least one concomitant non-drug therapy will be provided by primary system organ class and preferred term for each treatment group and overall for the included population, for core trial, additional cycles and long-term follow-up separately.

### *3.2.17 Concomitant surgical procedures*

Concomitant surgical procedures will be coded using MedDRA Dictionary with the latest version at Ipsen coding department at the time of database lock.

Listing will present the primary system organ class, the preferred term and the reported term. The listing will be sorted by treatment group, subject, start date, primary system organ class, preferred term and reported term, for core trial, additional cycles and long-term follow-up separately.

A frequency table of the number and percentage of subjects with at least one concomitant surgical procedure will be provided by primary system organ class and preferred term for each treatment group and overall for the included population, for core trial, additional cycles and long-term follow-up separately.

### *3.2.18 Pharmacodynamics/efficacy analyses*

All information related to tumour assessment according to RECIST criteria v1.1 will be listed by treatment group and subject, for core trial, additional cycles and long-term follow-up separately.

#### *3.2.18.1 Best Overall Response*

The BOR will be presented by treatment group at the end of the core trial, at the end of the additional cycles and at the end of the long-term follow-up.

BOR will be derived as the highest objective response achieved by the subject based on measurable lesions ((i.e. target, non-target and new lesions) from the time of first treatment until disease progression or the end of period and will be classified as: CR > PR > Non-CR/Non-PD (NCR/NPD) > SD> PD > NE.

If SD is believed to the best response, it must also meet the minimum time from baseline of 56 days. If the minimum time is not met, the subject's best response will be based on the subsequent assessments.

According to RECIST guideline, any response CR or PR must be confirmed at least 4 weeks later, or as close to this timepoint as possible.

*3.2.18.2 Objective Response Rate*

The proportion of subjects with a BOR characterised as either CR or PR according to RECIST criteria v1.1 relative to the total number of evaluable patients will be also presented by treatment group.

*3.2.18.3 Disease Control Rate*

The proportion of subjects with a BOR characterised as either CR, PR or SD according to RECIST criteria v1.1 relative to the total number of evaluable patients will be presented by treatment group.

*3.2.18.4 Progression-Free Survival*

The PFS according to local review will include investigator assessed PD and deaths. Other data will be censored. PFS will be assessed at the end of the core trial, at the end of the additional cycles and at the end of the long-term follow-up.

Definition of progression date:

The PD date is assigned to the first time at which PD can be declared.

Definition of censoring date:

Censoring dates are defined in subjects with no PD or death before end of period or withdrawal. In these subjects, the censoring date is defined as the last date on which progression status was 'adequately' assessed. This is taken to be the date of the last radiological assessment at which the target lesions were evaluated by local investigator review.

If no PD is documented, patient will be censored at the last available overall tumour assessment before start of the new anticancer therapy.

Definition of PFS time:

The PFS time will be calculated as the time from first treatment administration to either locally assessed PD or death.

PFS time = [(Date of event – date of first treatment administration) + 1] / 7 (weeks)

The distribution of PFS times will be estimated using the Kaplan-Meier (KM) product limit method.

The Kaplan Meier method will provide hazard curves, life tables, median as well as corresponding 95% Confidence Interval (CI). These statistics will be presented for each treatment group.

*3.2.18.5 Overall Survival*

OS will be defined as the time from date of first treatment administration until death or last known alive. Any patient not known to have died at the time of analysis will be censored based at the last recorded date on which the patient was known to be alive (i.e. their status must be known at the censored date and should not be lost to follow up or unknown). OS will be assessed at the end of the core trial, at the end of the additional cycles and at the end of the long-term follow-up.

Definition of OS time:

The OS time will be calculated as the time from first treatment administration to death.

OS time = [(Date of death or last date known to be alive – date of first treatment administration) + 1] / 7 (weeks)

OS will be analyzed using the same methodology (Kaplan-Meier) as described for the PFS.

*3.2.18.6 Metabolic tumour response*

Evaluation of metabolic tumour response using PERCIST will be summarised at each scheduled assessment by treatment group, for core trial and additional cycles separately. Corresponding information will be listed at each assessment by treatment group and subject, for core trial and additional cycles separately.

*3.2.18.7 Tumour markers in serum*

Tumour markers in serum will be listed at each assessment by treatment group and subject, for core trial and additional cycles separately.

The baseline will be defined as the last available (and reliable if applicable) assessment collected prior to first IMP administration.

Summary statistics by treatment group will be presented at each scheduled assessment for actual values and changes from baseline, for core trial and additional cycles separately.

### *3.2.19 Pharmacokinetics, biodistribution and dosimetry analyses*

*3.2.19.1 Analysis methods*

*3.2.19.1.1 Descriptive statistics and listings*

The Ipsen requirements for "Clinical PK and Pharmacometrics" instruction [redacted] will be followed.

Listings of all parameters will be sorted by treatment group, subject, cycle (if applicable) and measurement time during core trial and additional cycles separately.

Descriptive summaries by treatment group and by cycle (if applicable), during core trial and additional cycles separately, will include arithmetic means, Standard Deviation (SD), Coefficient of Variation (CV%), geometric mean, geometric CV%, median, minimum, maximum, n and missing. Descriptive statistics should be displayed only if at least 2/3 of the data are available (not missing) and only if at least 2/3 of the parameters are accurately determined (unflagged); otherwise, only minimum and maximum are reported.

Of note, all BLQ (Below the Limit of Quantification) values must be replaced by missing/zero to compute descriptive statistics according to the rule set below:

- For plasma 3BP-227 concentrations, BLQ data must be substituted by 0 for concentrations measured before the first quantifiable concentration. Any embedded BLQ value (i.e. single BLQ value occurring between 2 quantifiable concentrations) and BLQ values following the last quantifiable concentration in a profile will be set to missing for the purposes of PK analysis. BLQ values substituted by 0 are included in the NCA calculation whereas missing values are ignored. In any case, when all concentrations from a concentration-time profile are BLQ, they must be substituted by 0 and included in the PK analysis dataset.
- For urine 3BP-227 concentrations, BLQ data have to be set as 0.
- No BLQ values are expected for $^{177}$Lu-3BP-227 blood and urine total activity concentrations.
- For biodistribution, the following nomenclature will be used:
  - "NA" (not applicable) for regions that are outside of the field of view (FOV) or for sex-specific organs: to be considered as missing.

- "NC" (not calculable) for regions inside the FOV, but where quantification is not possible or regions without segmentation: to be considered as missing.
- "AU" (absent uptake) for regions inside the FOV, but with no radiopharmaceutical uptake: to be considered as zero.

All BLQ concentrations or missing data will be labelled as such in the concentration data listings.

BLQ values substituted by 0 are included in the calculation of descriptive statistics whereas missing values are ignored.

*3.2.19.1.2 Graphical representations*

All BLQ values for 3BP-227 concentrations must be replaced by missing/zero for graphical representation according to the rule set below:

- For plasma 3BP-227 concentrations, BLQ data must be substituted by 0 for concentrations measured before the first quantifiable concentration, and missing for BLQ concentrations after the last quantifiable concentration. Any embedded BLQ value (i.e. single BLQ value occurring between 2 quantifiable concentrations) and BLQ values following the last quantifiable concentration in a profile will be set to missing;
- For urine 3BP-227 concentrations, BLQ data have to be set as missing.

Nominal times are to be used to display the concentration plots.

The graphic representation of PK parameters will be made only if at least 2/3 of the parameters are accurately determined.

*3.2.19.2 Analyses on blood pharmacokinetics of $^{177}$Lu-3BP-227*

Blood total activity concentrations (including PK blood sampling dates and times) and blood PK parameters will be listed and summarised as described in section 3.2.19.1.1. A summary will be also planned for both cycles of core trial.

The individual blood total activity concentration-time profiles of $^{177}$Lu-3BP-227 will be presented graphically on linear and log/linear coordinates with both cycles on the same graph, during core trial only. Spaghetti plots (overlay of individual concentration-time profile) will also be reported by treatment group, with both cycles on the same graph, during core trial only.

Graph of arithmetic mean (±SD) on linear and log/linear coordinates will be presented by cycle, with all treatment groups on the same graph, during core trial only.

Scatter plots will be also presented for the $AUC_{0\text{-tlast}}$ and $t_{1/2}$ with all treatment groups on the same graph for cycle 1 and for both cycles.

*3.2.19.3 Analyses on urine pharmacokinetics of $^{177}$Lu-3BP-227*

Urine total activity concentrations (including PK urine sampling dates and times) will be listed, amount of drug excreted in urine will be summarised by time interval and overall and urine PK parameters will be listed and summarised at cycle 1 as described in section 3.2.19.1.1.

Individual cumulative urine recovered activity versus time profiles of $^{177}$Lu-3BP-227 will be presented graphically at cycle 1 for each treatment group with all subjects on the same graph.

The graph of cumulative recovered activity in urine over time will be provided for urine total activity concentration of $^{177}$Lu-3BP-227 at cycle 1 with all treatment groups on the same graph.

*3.2.19.4 Analyses on plasma pharmacokinetics of 3BP-227*

Plasma concentrations (including PK plasma sampling dates and times) and plasma PK parameters will be listed and summarised at cycle 1 as described in section 3.2.19.1.1.

The individual plasma concentration-time profiles of 3BP-227 will be presented at cycle 1 graphically on linear and log/linear coordinates. Spaghetti plots (overlay of individual concentration-time profile) will also be reported by treatment group.

Graph of arithmetic mean (±SD) on linear and log/linear coordinates will be presented at cycle 1 with all treatment groups on the same graph.

Scatter plots will be also presented for $AUC_{0\text{-tlast}}$ and $AUC_{0\text{-inf}}$ with all treatment groups on the same graph for cycle 1 and for both cycles.

*3.2.19.5 Analyses on urine pharmacokinetics of 3BP-227*

Urine total activity concentrations (including PK urine sampling dates and times) will be listed, cumulative amount of drug excreted in urine will be summarised by time interval and overall and urine PK parameters will be listed and summarised at cycle 1 as described in section 3.2.19.1.1.

Individual urine cumulative recovered amount versus time profiles of 3BP-227 will be presented graphically at cycle 1 for each treatment group with all subjects on the same graph.

The graph of urine cumulative recovered amount (Ae) over time will be provided for urine concentration of 3BP-227 at cycle 1 with all treatment groups on the same graph.

*3.2.19.6 Biodistribution analysis for $^{177}$Lu-3BP-227*

Uptake activity (including assessment dates and times) and PK parameters for organs of interest (healthy liver, bone marrow, left kidney, right kidney, spleen and body) will be listed and summarised as described in section 3.2.19.1.1. PK parameters for target lesions will be summarised similarly. A summary will be also planned for both cycles of core trial for organs.

*3.2.19.7 Radiation dosimetry analysis of $^{177}$Lu-3BP-227*

A frequency table on the organ receiving the highest absorbed dose will be provided by cycle and treatment group, for core trial and additional cycles separately, using the results from image-based analysis.

The specific absorbed dose per organ will be summarised by cycle and overall (only for core trial), by treatment group and overall, for core trial and additional cycles separately, using the results from image-based analysis and model-based analysis.

The specific absorbed dose to the target lesions will be summarised for core trial and additional cycles separately using the results from image-based analysis, by treatment group and overall as follows:

- by localisation and overall and by cycle (only for core trial) and on overall cycles,
- by localisation and overall and by study disease, on overall cycles only.

The absorbed organ dose per organ and to the target lesions on cycle 1 and cumulative absorbed dose on cycles 1 and 2 will be analysed by treatment group for core trial using the results from image-based analysis.

The effective dose and specific effective dose will be summarised by cycle and overall (only for core trial) and by treatment group, for core trial and additional cycles separately, using the results from model-based analysis.

Both image-based and model-based analyses will be listed by treatment group, subject and cycle, for core trial and additional cycles separately.

Timing of planar scintigraphy and SPECT/CT assessments will be also listed by treatment group, subject and cycle, for core trial and additional cycles separately.

### *3.2.20 Exploratory analyses*

Exploratory analyses will be described in a dedicated SAP.

### *3.2.21 Derived data*

The derived data are variables which are calculated from the raw data in the eCRF and not included in the database and will be included in the listings (see Appendix 1).

### *3.2.22 Rules and data formats*

Data will be presented using an appropriate number of decimal places (i.e. the number of decimal places used does not imply undue precision). Raw data will be presented with the number of decimal places collected, and derived data will be presented to an appropriate number of decimal places. The appropriate number of decimal places will be determined by general practice, mathematical rationale or scientific rationale (e.g. age should be presented in whole numbers).

For PK/dosimetry data, all values will be reported with 3 significant digits for numbers < 1000, otherwise values will not be rounded.

For summary statistics, the following will be presented: n, arithmetic mean, standard deviation, median and the range (minimum, maximum).

Mean, median and standard deviation values will be reported with one decimal place greater than the raw/derived data that they summarise. Minimum and maximum values will be reported with the same precision as the raw data.

Percentages will be reported with 1 decimal place and 0% will not be presented. Percentages will be calculated using a denominator of all subjects in a specified population and by treatment group. The denominator will be specified in a footnote to the tables for clarification if necessary.

All values below or above a limit of quantification (e.g. < 0.1 or > 100) will be listed as such. For each safety parameter for which it is possible to have values below or above LOQ, the rule to be used in the statistical tables is to replace values below or above a limit of quantification by LOQ.

All text fields must be left justified and numeric or numeric with some text specification (e.g. not done, unknown, < 4.5, …) must be decimal justified. Dates will be presented in the format [yyyy-mm-dd] and times in the format [hh:mm].

### *3.2.23 Pooling of Centres*

It is not planned to perform a subgroup analysis on individual or groups of centres.

### *3.2.24 Interim analysis*

An interim analysis of the escalation cohort data will be done at the end of the core trial. In addition, tables of safety and efficacy data from cohort 2 (4 GBqx2) will be used to support the rationale for the starting dose of $^{177}$Lu-IPN01087 in phase I study combination with Chemotherapy (Gemcitabine-Nab paclitaxel).

### *3.2.25 Role of Safety Review Committee (SRC)*

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 modeling 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.

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

### *3.2.26 Covariates and analysis of subgroups*

It is not planned to perform an analysis of subgroups or use covariates.

## 4 COMPUTER SYSTEMS, SOFTWARE AND VALIDATION OF PROGRAMS

### 4.1 Hardware

The statistical analysis will be performed using Microsoft Windows 7 Enterprise.

### 4.2 Software

All TFLs will be produced and statistical analysis performed using SAS version 9.4 [2]. All outputs will be in Microsoft Word Format and compiled in bookmarked .pdf files as per ICH section (e.g. 14.1, 14.2 …).

### 4.3 Validation programs

Biotrial Biometrics will provide a validation plan to Ipsen identifying the methods of validation.

The study statistician is responsible for reviewing each output associated with the deliverable product. Program logs are checked by the statistical programmer for logical, syntax and fatal errors. The checks in SAS includes, but is not limited to, all ERRORS, WARNINGS, BY-VALUE merge messages, NOTES, and UNINITIALIZED variables. Program logs are also reviewed for accurate and consistent variable and observation counts following each procedure and data step.

The study statistician is responsible for checking and reviewing the work produced using whatever method he/she feels is appropriate (e.g. SAS code review, hand calculation, etc.) to reassure of the quality of the output.

Outputs are reviewed for typographical errors, misspellings and nonsensical values or results and to check the consistency with the statistical analysis plan. Outputs are

cross-checked against each other for accuracy and consistency. For statistical tables, listings, appendix listings, and figures, this procedure includes comparison of subject group numbers, counts of subjects at each observation point, and consistency of results for variables between outputs.

Findings of the quality control reviews are communicated to the party responsible for making necessary changes. The programs will be retested after modifications.

After final review, and when no further change is required to produce the deliverable, the statistical programmer and the study statistician have to complete and sign the quality control and statistical analysis results follow-up's validation checklist, to indicate that they have successfully performed all of their responsibilities. Copies of the internal quality control forms produced for the validation process will be provided to the sponsor to support the validation.

### 4.4 Restitution of the programs

All programs (including macros and analysis datasets) producing the tables, listings and statistical outputs along with associated logs should be given to the sponsor when the TFLs and statistical analyses have been finalised.

## 5 CHANGES FROM PROTOCOL

Not applicable.

## 6 REFERENCES

1. International Conference on Harmonisation (ICH) E9 and Federal register Vol. 63, No. 179 (September 1998).

2. SAS, Version 9.4. SAS Institute Inc., Cary, NC, USA, 2012.

3. Response Evaluation Criteria In Solid Tumours (RECIST) criteria version 1.1, Eisenhauer et al., European Journal of Cancer 45 (2009) 228 – 247.

# 7 APPENDICES TO THE SAP

## Appendix 1: Derived Data

The following derived data will be calculated:

- Study day

Study day will be defined as '-1' for the day prior to first IMP administration during core trial and as '1' for the day of first IMP administration during core trial (i.e. day 0 does not exist).

- BMI

BMI ($kg/m^2$) will be derived as Weight (kg)/[Height(cm)/100]$^2$ and rounded to the nearest decimal.

- Core trial duration

Core trial duration (days) will be calculated as (date of last visit attended during core trial - date of informed consent form) + 1.

- Long-term follow-up duration

Long-term follow-up duration (days) will be calculated as (date of last visit attended during long-term follow-up - date of informed consent form) + 1.

- Time since diagnosis

Time since diagnosis in months will be calculated as (date of informed consent form - date of diagnosis) + 1] / 30.4375.

- Time since first relapse after last treatment

Time since first relapse after last treatment in months will be calculated as (date of informed consent form - date of first relapse after last treatment) + 1] / 30.4375.

- Baseline

Baseline will be derived as the last available (and reliable if applicable) assessment before first IMP administration.

- Changes from baseline

Changes from baseline will be calculated as the difference from baseline (e.g. assessment at the visit – assessment at baseline).

- Duration of each cycle

Duration of each cycle (days) will be calculated as (date of infusion of the next cycle - date of infusion of the cycle) + 1.

For last cycle, duration will be calculated as (date of Day 29 of last cycle - date of infusion of the cycle) + 1.

- Study drug exposure during core trial

Study drug exposure (days) = (date of infusion of last cycle during core trial - date of infusion of cycle 1) + 29 days.

- Study drug exposure during additional cycles

Study drug exposure (days) = (date of infusion of last cycle during additional cycles - date of infusion of first cycle during additional cycles) + 29 days.

- Progression-Free Survival

PFS time (weeks) = [(Date of event – date of first treatment administration) + 1] / 7.

| Event | Decision | Date of event or censoring to consider for the analysis |
|---|---|---|
| Progression Disease | Not censored | Date of progression |
| No event | Censored | Last date of tumour assessment |
| Death | Not Censored | Date of death |

- Overall survival

OS time (weeks) = [(Date of death or last date know to be alive – date of first treatment administration) + 1] / 7.

| Event | Decision | Date of event or censoring to consider for the analysis |
|---|---|---|
| Death | Not censored | Date of death |
| No event | Censored | Date last known to be alive |

- Therapeutic Class

The therapeutic class will correspond to the first three digits of the ATC code. The decoding of the therapeutic class will be done from the WHO-DD (latest version at the time of database lock).

- Prior and concomitant flags

The date and time of baseline (study day 1) is used as the cut-off date for the definition of prior and concomitant medications. A medication started before study day 1 and continuing at time of Day 1 is considered as both, prior and concomitant. Prior, concomitant and both prior and concomitant will be coded as P, C and PC respectively.

In the event of incomplete start date and/or stop date which will not allow the categorisation of medication, it will be considered as concomitant.

- Medical and surgical history

The duration of medical and surgical history will be calculated as (end date – start date) + 1. If the recorded end date is CONT. (for continuing), the end date will be listed as "ongoing" and the duration will be approximated as "≥ (screening visit date – start date) + 1" day(s). If the start date or the end date are partial, the duration will be presented as a superior inequality "≥ xx"day(s) [i.e. ≥2 where start date=31JAN2004 and end date=FEB2004 or start date=JAN2004 and end date=01FEB2004] but if both are partial or one is missing the duration will not be presented.

- Prior and concomitant medication/Concomitant medications for studied disease /prior and concomitant non-drug therapies duration

If the start and end dates of the medication are identical then "<1" day will be presented with the duration in hh:mm recorded in the eCRF if it is available. If times are available, the duration of treatments will be calculated as (end date/time - start date/time). If at least one time is missing, the duration of concomitant treatments will be calculated as (end date - start date) + 1. If the recorded end date is continuing at the end of the study then the end date will be listed as "ongoing" and the duration will be approximated as "≥(last attended visit date – start date) + 1" day(s). If the start date or the end date are partial, the duration will be presented as an inequality "≥xx" day(s) [i.e. ≥2 where start date=31JAN2004 and end date=FEB2004 or start date=JAN2004 and end date=01FEB2004] but if both are partial or one is missing the duration will not be presented.

- AE duration

If the start and end dates of the AE are identical then "<1" day will be presented with the duration in hh:mm recorded in the eCRF if it is available. If times are available, the duration will be calculated as (end date/time – start date/time) and presented in days hh:mm. If at least one time is missing and if the duration is greater than 24 hours then it will be calculated as (end date - start date) + 1 and presented in days. If the recorded end date is continuing at the end of the study, the end date will be listed as "ongoing" and the duration will be approximated as "≥(last attended visit date – start date) + 1" day(s). If the start date or the end date are partial the duration will be presented as a superior inequality "≥xx" day(s) [i.e. ≥2 where start date=31JAN2004 and end date=FEB2004 or start date=JAN2004 and end date=01FEB2004].

- Time since last dose for adverse event

If the start date of the adverse event is identical to the date of last administration, then"<1" day will be presented with the duration in hh:mm recorded in the eCRF if it is available. Otherwise, it will be calculated as (start date/time - last administration date/time) and presented in days days hh:mm. If at least one time is missing and if the duration is greater than 24 hours then it will be calculated as (start date – last administration date) + 1 and presented in days. If the start date and the associated information do not allow to state about the last dose received (partial start date or start at administration day without knowing if it started before or after the drug intake), all the possible time since last dose will be presented [i.e.: if a subject received a daily administration and reported an AE at second administration day but without indication about before or after the drug intake the time since last dose will be as "2 / <1"]. If the start date is partial, the time since last dose will be presented as an superior inequality (i.e.: for an AE started in FEB2004 after the only administration performed on 31JAN2004, the time since last dose will be as "≥2" days). If the start date is missing the time since last dose will not be presented although the AE will be assigned to each dose received before its end date.

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