An International Multicentre, Open-Label First in Human Phase I/II study to evaluate the safety, tolerability, biodistribution and antitumour activity of 177Lu-3BP-227 for the treatment of subjects with solid tumours expressing neurotensin receptor 1

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Primary objectivesPhase ITo establish the safety and tolerability of fractionated intravenous (i.v.) administrations of 177Lu-3BP-227 in subjects with unresectable, locally advanced or metastatic cancers expressing NTSR1.Phase IITo estimate ORR of...

Ethical review	Approved WMO
Status	Completed
Health condition type	Metastases
Study type	Interventional

Summary

ID

NL-OMON50308

Source
ToetsingOnline

Brief title
Ipsen D-FR-01087-001

Condition

- Metastases

Synonym
metastatic or locally advanced cancers expressing Neurotensin Receptor 1 (NTSR1).

Research involving
Human

Sponsors and support

Primary sponsor: Ipsen Pharma SAS
Source(s) of monetary or material Support: Industry

Intervention

Keyword: 177Lu-3BP-227, Neurotensin Receptor-1, phase I/II, tumour

Outcome measures

Primary outcome

Phase I

For the dose escalation, the primary endpoint is MTCA or the maximum administered cumulative activity (MACA), if the MTCA is not identified during the dose escalation part. The primary variables used for the MTCA determination will be the incidence of DLTs (as defined above) and the organ exposure to radiation during two cycles of treatment. The DLT period for the determination of the primary endpoint starts at the first administration of 177Lu-3BP-227 and ends 6 weeks after the second administration.

Safety evaluation will encompass DLTs, frequency and nature of adverse events (AEs), abnormal findings from physical examination, vital signs, 12-lead ECG and 24-hour 3 lead ECG Holter, ECOG performance status treatment related deterioration and clinical laboratory tests abnormalities (including haematology, blood biochemistry, hormone analysis, urinalysis and pregnancy test).

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

expectedness and frequency of AEs.

Phase II

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

Secondary outcome

Phase I

Pharmacokinetics, biodistribution and dosimetry

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

a) Maximal uptake (%); maximal concentration achieved (Cmax); time post injection to achieve maximal concentration (Tmax); area under the curve (AUC) at the target lesions, discernible organs and blood; terminal t1/2 of activity concentrations in blood.

b) Highest absorbed dose, specific absorbed dose to the target lesions (Gy/GBq), specific absorbed dose per organ (Gy/GBq) and cumulative absorbed organ doses (Gy).

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

c) Pharmacokinetic parameters including, but not limited to, Cmax, AUC, t1/2, clearance (CL), volume of distribution (Vd), cumulative amount of unchanged drug excreted into the urine (Ae), renal clearance of the drug from plasma

(CLR), as measured in plasma and urine at defined timepoints.

Pharmacodynamic/efficacy

a) Objective response rate and disease control rate (DCR), as determined by RECIST version 1.1 in subjects who received IMP.

b) Progression-free survival (PFS) and overall survival (OS) rates as determined from start of study treatment until occurrence of event and/or end of observation period.

c) Evaluation of metabolic tumour response using 18F-FDG-PET as determined by PERCIST (version 1.0) or practical PERCIST.

d) Changes in serum tumour markers relevant and specific to the underlying tumour disease from Day of the first treatment administration to EOCT, which is planned 6 weeks after the second 177Lu 3BP 227 dose administration.

Phase II

Efficacy

a) Disease control rate, time to progression, time to response, duration of response as per RECIST version 1.1.

b) Qualitative and quantitative changes in tumour-to-background uptake using PERCIST version 1.0

c) Progression-free survival (PFS) and OS as determined from start of study treatment until occurrence of event and/or 6 and 12 months after start of study treatment.

d) Changes in serum tumour markers relevant and specific to the underlying tumour disease from baseline to EOCT.

Subject Reported Outcomes

a) Changes in health-related quality of life scores from baseline to EOCT measured by validated questionnaires.

Safety

a) Safety and tolerability measured by the type, severity, expectedness and frequency of AEs.

Pharmacokinetics, biodistribution and dosimetry

a) For PK, biodistribution and dosimetry, the endpoints will be similar as for phase I

Biobanking (optional):

Serum and whole blood ribonucleic acid samples will be stored for further biomarker analysis after the end of the study. Analysis of additional biomarkers from the biobank samples will be performed outside the scope of the main study and reported separately.

Study description

Background summary

This phase I/II study will be the first administration of 177Lu-3BP-227 in humans under controlled study conditions. The study will generate safety and antitumour activity data and is expected to provide a better understanding of the mechanism of action of 177Lu-3BP-227.
The results observed in terms of antitumour activity during dose escalation, will determine whether phase I expansion cohorts will be conducted to further investigate the safety of other activity levels and/or other administration schedule (e. g. hyperfractionation) or the investigation of efficacy of 177Lu-3BP-227 in the context of indication-specific cohorts or over multiple indications.

Study objective

Primary objectives
Phase I
To establish the safety and tolerability of fractionated intravenous (i.v.) administrations of 177Lu-3BP-227 in subjects with unresectable, locally advanced or metastatic cancers expressing NTSR1.
Phase II
To estimate ORR of fractionated i.v. administrations of 177Lu-3BP-227 in subjects with unresectable, locally advanced or metastatic cancers expressing NTSR1.

Secondary objectives
Phase I
a) To determine the whole-body distribution of 177Lu-3BP-227 and pharmacokinetics (PK) of both 177Lu-3BP-227 and 3BP-227.
b) To determine the radiation dosimetry of 177Lu-3BP-227 (organ exposure to radiation).
c) To describe the preliminary antitumour activity of 177Lu-3BP-227
Phase II
a) To further evaluate the safety profile of 177Lu-3BP-227 at the radioactivity recommended by the phase I results.
b) To further assess the response to treatment with 177Lu-3BP-227 using RECIST version 1.1 and/or positron emission tomography (PET) Response Criteria in Solid Tumours (PERCIST) version 1.0 criteria.
c) To further characterise the whole-body distribution and dosimetry of 177Lu-3BP-227 and PK of both 177Lu-3BP-227 and 3BP-227.
d) To describe the influence of 177Lu-3BP-227 on the health-related quality of life of treated subjects.

Study design

This is a multicentre, open-label phase I/II study of 177Lu-3BP-227 in subjects with metastatic or locally advanced solid tumour expressing NTSR1 who have exhausted their available standard-of-care treatment options and/or are deemed suitable for treatment with 177Lu-3BP-227 as per the investigator's clinical assessment and/or their individual disease state. The study consists of a phase I with a dose escalation part (and potential expansion cohorts) and a phase II either in selected or over multiple indications in a basket approach.

Phase I
During phase I, it is planned to enrol subjects with advanced, recurrent and/or metastatic tumours expressing NTSR1 originating from either the:
- Pancreas (pancreatic ductal adenocarcinoma, PDAC)
- Colon and rectum (Colorectal cancer, CRC)
- Stomach (gastric cancer, GC; adenocarcinoma or Gastrointestinal Stromal Tumours, (GIST)) or
- Head and neck region (squamous-cell carcinoma of head and neck, SCCHN).
- Bone (Ewing Sarcoma, ES)

For the dose escalation part, it is anticipated that approximately 30 subjects will be included, in up to six escalation steps. Three to five subjects will be treated per activity level in order to yield a minimum of three subjects treated at the full planned radioactivity amount fractionated into two administrations. Once the dose escalation part has been completed, the maximum tolerated cumulative activity (MTCA) level will be repeated in an additional cohort.

The cumulative starting activity will be 5 GBq fractionated into two administrations (2×2.5 GBq). The cumulative maximum activity will be 15 GBq activity (2×7.5 GBq). However, if the MTCA is not reached and if limiting organ dose levels are not exceeded, an additional cohort with three administrations at 7.5 GBq may be added, leading to a cumulative activity of 22.5 GBq.

Of note, for each cohort in the dose escalation part, subjects may receive up to four additional administrations of 177Lu-3BP-227 after the end of the core trial (EOCT), if they have clinical benefit and acceptable tolerability profile according to investigator's jugement, and if the organ dose limits are not exceeded.

The MTCA is defined as the maximum cumulative activity that may be administered following fractionated i.v. administrations of at least 4 weeks apart, so that:
- No more than 33% of the subjects experience a dose limiting toxicity (DLT) during Cycle 1 or 2 and
- The cumulative radiation in each target organ does not exceed the acceptability limits.

The DLTs are defined for any of the following IMP-related AEs according to National Cancer Institute - Common Terminology Criteria for Adverse Events (NCI-CTCAE) scale version 5.0:
- 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 more than seven 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 aspartate amino transferase/alanine amino transferase (AST/ALT) with accompanying Grade 2 or higher bilirubin (Hy*s law);
- any Grade 3 or higher renal injury/toxity (estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m2);
- any Grade *3 GI AE not resolved to Grade *2 within 48 hours despite optimal adequate medical management, with the following specifications:
- Grade 3 nausea, vomiting (inadequate oral caloric or fluid intake; tube feeding, total parenteral nutrition or hospitalisation indicated)
- Grade 3 diarrhoea (increase of *7 stools per day over baseline; hospitalisation indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL) or Grade 4 diarrhoea (life-threatening consequences; urgent intervention indicated)
- Grade 3 constipation (obstipation with manual evacuation indicated; limiting selfcare activities of daily living) or Grade 4 constipation (life-threatening consequences; urgent intervention indicated);
- any toxicity related to 177Lu-3BP-227 resulting in a treatment delay of more than four weeks due to delayed recovery to baseline or to Grade <2 AE (with the exception of alopecia and lymphopenia).

Study design following phase I dose escalation results
Upon completion of the phase I dose escalation or upon reaching the MTCA and confirmed jointly by the safety review committee (SRC) and the Sponsor, and in consideration of the accumulated subject data, cohorts of subjects will be studied to further characterise the safety and efficacy of 177Lu-3BP-227.

In the case of acceptable tolerability and evident antitumour activity across all enroled subjects in phase I, a phase II basket trial design will be utilised to study the antitumour activity of 177Lu-3BP-227 in subjects with NTSR1 expressing tumours. Sample size estimations for this design will be provided as part of a protocol amendment. However, if the antitumour activity is driven by a type of tumour, tumour-specific phase II cohort(s) will be initiated utilising an Optimal Simon's Two Stage design (see Phase II).

If safety evaluation and dose schedules cannot be fully explored during the

phase I dose escalation part, the expansion part will serve to accomplish this objective including, but not limited to, schedules of high loading doses followed by fractionated lower doses. The expansion part will also serve to clarify any uncertainties of antitumour responses.

The number of cohorts and subjects will be determined based on emerging data from the dose escalation part and the modelling and simulation approach.

Phase II
Phase II study will be conducted either with a basket design trial or indication specific cohorts with an Optimal Simon's Two Stage design, according to the scenarios described above.
At this time and based on available preclinical and clinical data, it is anticipated that most likely two cohorts of subjects, one with PDAC and another with CRC, will enrol approximately 125 subjects, using the administration schedule and radioactivity/smallmolecule doses derived from phase I. One or two further cohorts may be opened (subject to results emerging from ongoing preclinical studies and antitumour efficacy seen during dose escalation and amending the current protocol) likely to enrol subjects with GC and/or SCCHN.
- The PDAC cohort will enrol approximately 55 subjects and will investigate whether 177Lu3BP-227 attains an ORR superior to a clinically accepted historical threshold of current standard-of-care treatment for subjects with metastatic or locally advanced disease.
- The CRC cohort will enrol approximately 70 subjects and will investigate whether 177Lu3BP-227 attains an ORR superior to a clinically accepted historical threshold of current standard-of-care for subjects with metastatic or locally advanced disease.
The current protocol will be amended at the end of the phase I to document the rationale of the phase II design. In any case, the cumulative activity administered during phase II will not exceed the MTCA determined during phase I.

Intervention

For both screening and treatment formulations, the specific activity of the IMP is 25 µg 3BP-227 per 1 GBq of 177Lu.
The screening IMP formulation consists of 1 GBq in a total volume of 10 mL.
The treatment IMP formulation consists of 2.5 to 7.5 GBq of 177Lu-3BP-227 in a total volume of 20 mL.
The total radioactivity of the treatment IMP formulation will be fractionated and administered in two i.v. infusions separated by at least 4 weeks (28 days).
A 100 mL saline solution will be administered intravenously over a period of 30 minutes concomitantly with every IMP administration.

Please describe which intervention is given; e.g. one group receives a 10 mg tablet of product X twice daily and the other group receives a placebo tablet

twice daily.

Study burden and risks

The duration of the study depends upon how many treatment cycles the subject will receive and how long he/she will be followed during the long-term follow-up. In case the subject has 2 treatment cycles and a long-term follow-up of 24 months, his/her participation will last for about 28 months and will includes 26 study visits. It consists of a screening visit, 8 visits per administration cycle, 1 follow-up visit and 8 visits during the long-term follow-up.
During the study the subject will undergo 3 to 4 MRI/CT scans, 1 PET scan, 1 or 2 tumor biopsies. At 9 visits a physical examination will be performed, at 14 visits blood will be collected and at 9 visits a urine sample will be taken. At 6 visits a ECG will be made and at day 1 of each cycle a hotter recording will be made.

Safety measures have been taken into consideration to minimise the risk. Each subject recruited across the sites will be hospitalised for 24 hours following administration for observation. The level of radioactivity will be monitored until it has fallen to safe levels for discharge.
The participating subjects will be closely monitored during the study and during the long-term follow-up period until lost to follow-up, withdrawal of consent, death or a maximum of 5 years whichever occurs first.

Even though promising safety data were collected from the treatment attempt, the safety, tolerability and efficacy of 177Lu-3BP-227 treatment for cancers expressing NTSR1, needs to be assessed in a well-designed prospective clinical study.
The dose escalation part of the study has been designed to primarily investigate the safety, tolerability, dosimetry and preliminary antitumour activity of 177Lu-3BP-227 following fractionated i.v. administrations in subjects with unresectable, locally advanced or metastatic cancers expressing NTSR1. This safety assessment also includes dosimetry studies to evaluate the radioactive exposure of organs. To optimise the benefit- risk ratio, it is essential to identify the proper target population for therapy. In this study, the target population will be identified by assessing the tumour uptake following the screening administration of 177Lu-3BP-227.

Subject-specific dosimetry will be performed on a regular basis for up to 48 hours, and optionally up to 72 hours, after each administration to describe the uptake by the tumour and organs identified at risk over the entire course of treatment. The cumulative organ doses of kidney, bone marrow and liver will be monitored on an ongoing basis as for the other organs identified at risk. If a previous cumulative radioactive dose indicates that the organ limit will be exceeded with the next cycle, the activity of the next cycle can be reduced or the cycle can be delayed.

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

Contacts

Public
Ipsen Pharma SAS

avenue du Canada 3
Les Ulis 91940
FR
Scientific
Ipsen Pharma SAS

avenue du Canada 3
Les Ulis 91940
FR

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Phase I
Eligible subjects meet all the following inclusion criteria:
(1) Signed informed consent form prior to all study procedures.
(2) Aged 18 years or older.
(3) Histologically or cytologically confirmed unresectable or locally advanced or metastatic disease and has received prior lines of standard-of-care chemotherapy/treatment and has no further suitable treatment option and a

documented decision by a multidisciplinary oncology board including a specialist of the concerned pathology.
(4) Subjects have:
(a) PDAC or,
(b) CRC or,
(c) GC or,
(d) GIST or
(e) SCCHN or
(f) ES.
(5) Tumour showing:
(a) uptake of 177Lu-3BP-227 (screening formulation) in known primary or metastatic sites as judged by the investigator to be greater than background; or
(b) uptake of 111In-3BP-227 in known primary or metastatic sites (for subjects who participated in Study D-FR-01087-002) as judged by the investigator to be greater than background.
(6) Measurable disease (based on RECIST version 1.1).
(7) Criterion 7 is removed by protocol amendment.
(8) Documentation of progressive disease in the 6 months prior to study start (treatment).
(9) Eastern Cooperative Oncology Group performance status of 0 or 1 (unless disability is related to surgery in ES and agreed by the sponsor).
(10) Adequate organ function as evidenced by:
(a) Leukocytes *3000/*L
(b) Absolute neutrophil count *1500/*L
(c) Platelets *75,000/*L
(d) Hb >9 g/dL or >10 g/dL (if history of cardiac disease)
(e) Total serum bilirubin *2 times upper normal institutional limits (ULN)
(f) Aspartate aminotransferase/alanine aminotransferase (ALT) *2.5×ULN (or *5×ULN, if subject has liver metastases)
(g) eGFR *55 mL/min.
(11) Estimated life expectancy of 3 months.
(12) Female subjects must not be pregnant or lactating at study entry and during the course of the study and must not become pregnant for at least 6 months following the last study treatment. Women of childbearing potential must agree to use a highly effective method of contraception (see note below).
(13) Male subjects must not father children during the study and for at least 6 months after the last study treatment and in addition must agree to use a condom for this period to protect his partner from contamination with the IMP. For males with partners who are of child bearing potential, effective contraception is a combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods), but these are not considered to be highly effective. A man is considered to be infertile if he has had bilateral orchidectomy or successful vasectomy. Effective contraception includes a female partner of childbearing potential if she is using highly efficacious contraception (see note below), but the male subject must agree to use a condom to protect his partner as described above.
(14) Must be willing and able to comply with study restrictions and to remain

at the clinic for the required time during the study period and willing to return to the clinic for the followup evaluation, as specified in the protocol.

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

Exclusion criteria

Phase I/II
Eligible subjects must not have any of the following conditions:
(1) Prior treatment received
(a) Any antitumour treatment since last documented disease progression
(b) Any chemotherapy within 3 weeks or nitrosourea within 6 weeks prior to first treatment IMP administration
(c) Any curative radiotherapy within 4 weeks, or palliative radiotherapy within 7 days prior to first treatment IMP administration
(d) Any monoclonal antibodies within 4 weeks or tyrosine kinases inhibitors within 2 weeks prior to the first treatment IMP administration (e) Any other IMP within 2 weeks prior to first treatment IMP administration, if the previous compound is a mechanism-based molecularly targeted agent whose t1/2 is not well-characterised.
(2) Brain metastases.
(3) Nephrectomy, renal transplant or concomitant nephrotoxic therapy putting the subject at high risk of renal toxicity during the study.
(4) Only non measurable metastatic bone lesions
(5) Existing or planned colostomy during study participation.
(6) Any history of inflammatory bowel disease.
(7) Any uncontrolled significant medical, psychiatric or surgical condition or laboratory finding, that would pose a risk to subject safety or interfere with study participation or interpretation of individual subject results.
(8) Clinically significant abnormalities on ECG at screening including corrected QT interval (Fridericia's formula) >450 msec for males or 470 msec for females at screening.
(9) Previously received external beam irradiation to a field that includes more than 30% of the bone marrow or kidney.
(10) Criterion 10 is removed by protocol amendment.
(11) Any unresolved NCI-CTCAE Grade 2 or higher toxicity (except alopecia) from previous antitumour treatment and/or medical/surgical procedures/interventions
(12) Known allergy to IMP or its excipients administered in this study, including imaging contrast media
(13) Positive pregnancy test (female subjects).
(14) Likely to be uncompliant or uncooperative during the study, in the judgment of the investigator.

(15) Unable to understand the nature, scope and possible consequences of the study, in the judgment of the investigator.
(16) Sponsor employees or investigator site personnel directly affiliated with this study, and their immediate families. Immediate family is defined as a spouse, parent, child or sibling, whether biological or legally adopted.

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

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	15-05-2020
Enrollment:	30
Type:	Actual

Medical products/devices used

Product type:	Medicine
Generic name:	177Lu-3BP-227

Ethics review

Approved WMO

Date:	05-09-2018
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Approved WMO

Date:	04-11-2019
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	09-12-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	18-02-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	10-08-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	11-12-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	02-04-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2017-001263-20-NL
ClinicalTrials.gov	NCT03525392
CCMO	NL64607.042.18

Study results

Date completed: 06-08-2021

Results posted: 26-01-2022

First publication
20-12-2021