An open label, multicentre, positron emission tomography (PET) imaging study using Zirconium-89 to investigate the biodistribution and tumor uptake of a PD-L1x4-1BB bispecific antibody (S095012) in patients with advanced solid tumors

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Objectives of Part A, B and C are the following: Part A: determination of the optimal mass dose of S095012 to inject with 89Zr-S095012 and optimal time point for PET scans for appropriate visualisation of 89Zr-S095012 through PET imaging. Part B…

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Miscellaneous and site unspecified neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON52007

Source
ToetsingOnline

Brief title
Immuno-PET study of 89Zr-S095012 in subject with advanced solid tumors.

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym

advanced solid tumors

Research involving
Human

Sponsors and support

Primary sponsor: Servier R&D Benelux
Source(s) of monetary or material Support: by the sponsor Servier

Intervention

Keyword: 89Zr-S095012, PET imaging study, solid tumors

Outcome measures

Primary outcome

Visual analysis of PET/CT scan images.

Quantitative parameters derived from PET scans for blood pool, organs and tumor lesions (time-uptake curves, tumor to background ratio, *).

- Quantitative parameters derived from PET scan images to assess uptake in tumor lesions and normal tissues reported with standardised uptake value (SUV) and concentration for each volume of interest (VOI).

Serum PK parameters of 89Zr*S095012.

Comparison of 89Zr*S095012 tumor uptake (as described using SUV and concentrations) before and on treatment with different doses of S095012.

- Incidence and severity of adverse events (AEs).

Discontinuing study intervention due to an AE.

Secondary outcome

Serum PK parameters of S095012.

-Organ and whole-body radiation exposure (mSv per Mega Becquerel (MBq):

Highest absorbed dose, specific absorbed dose to the target lesions, absorbed

dose per organ and cumulative absorbed organ doses.

-Assessment based on Response Evaluation Criteria in Solid Tumors (RECIST)

V1.1, objective response rate (ORR).

Study description

Background summary

S095012 is a monoclonal antibody (mAb)-like bispecific protein targeting the programmed death-ligand 1 (PD-L1) and the immune receptor 4-1BB. S095012 is constituted by the genetic fusion of a backbone-engineered anti-PD-L1 antibody and an agonistic 4-1BB-targeting moiety, based on Anticalin® technology, formulated as an aqueous solution for intravenous (IV) infusion. The antitumor activity of S095012 combine both the checkpoint inhibition via the PD-1/PD-L1 axis and the activation of the 4-1BB mediated anticancer effect to thereby provide a potent costimulatory signal to tumor antigen-specific activated-T cells.

Non-clinical pharmacology data support the intended mechanism of action of

Studies validated the use of immuno-PET with Zirconium 89 to directly visualise drug biodistribution in patients with a non-invasive approach, offering support to drug development.
.
Molecular imaging with PET is a powerful and non-invasive tool for in vivo visualisation, monitoring and quantification of the uptake of Zirconium-89 (89Zr)-labelled compounds in tumors and tissues of interest in humans. Therefore, assessing the biodistribution and tumor uptake of S095012 through PET imaging could provide important information to support dose and scheduling selection for efficacy testing, when correlated to pharmacodynamic markers.
The present imaging study will run in a staggered manner with a first-in-human (FIH) Phase 1/2 study (CL1-95012-001). The aim of the FIH study is to evaluate the safety profile, tolerability and determine the maximum tolerated dose (MTD) or maximum administered dose (MAD) of S095012, as well as the PK profile, pharmacodynamic effects and preliminary anti-tumor activity of S095012.
The imaging study is designed to assess the whole-body biodistribution and tumor uptake of 89Zr-S095012 at baseline and during treatment with S095012. The study will be conducted in participants with histologically confirmed advanced and/or metastatic solid tumors. Moreover, pharmacodynamic effects of S095012 will be followed through systemic 4-1BB specific biomarker and CD8 T cell activation in the tumor (immunohistochemistry (IHC) on biopsies). During this study, mass and treatment doses of S095012 administered will be based on safety

data collected during the FIH study. Reciprocally, safety data collected from the imaging study will inform the safety profile of S095012 and will be taken into account in the MTD (if any) and/or the RP2D determination.

Study objective

Objectives of Part A, B and C are the following:
Part A: determination of the optimal mass dose of S095012 to inject with 89Zr-S095012 and optimal time point for PET scans for appropriate visualisation of 89Zr-S095012 through PET imaging.
Part B: whole body distribution and tumor uptake of S095012 visualised by the administration of 89Zr-S095012 and PET imaging.
Part C: on treatment dose-dependent tumor uptake of 89Zr-S095012 in participant with tumor uptake at baseline (in Part B); visualised by the administration of 89Zr-S095012 on treatment and PET imaging. It is anticipated that 89Zr-S095012 uptake in tumor lesions will be inversely correlated with the level of saturation of tumor lesion by S095012.

Study design

This is a phase 1, multicentre, single arm, open-label, imaging study That will be conducted in 3 parts (Part A, and Part B and C). Participants from the Part A will be imaged at baseline only in order to determine the optimal non-therapeutic mass dose of S095012 to inject along with 89Zr*S095012 and to select the optimal time-points for PET/ computerised tomography (CT) scan imaging. The first mass dose of S095012 will be based on the results from the FIH PK data and data from literature. In the Part B and C, participants will be imaged at baseline (Part B) and on-treatment (Part C).

All participants from each part will receive S095012 treatment doses administered every two weeks as a 60-minute IV administration.
In participants included in Part A or Part B but not eligible for Part C, S095012 will be administered at the maximum treatment dose determined as tolerable and safe from the FIH study based on the 28-days DLT observation period.
In participants included in Part C, S095012 will be administered at 4 dose levels (60 mg, 180 mg, 500 mg and 1000 mg) in order to describe the relationship between tracer tumor uptake and treatment dose. These treatment dose could be adapted according to new information from this and the FIH study. In any case, the treatment will not exceed the maximum treatment dose determined as tolerable and safe from the FIH study based on the 28-days DLT observation period.
. The dose escalation will be stopped when a plateau in decrease of tumor uptake is reached and/or sufficient information to describe saturation of tumor uptake is obtained, or for safety reason, or for sponsor decision, whatever comes first.

Intra-participant dose escalation will be allowed in all participants up to the maximum treatment dose determined as tolerable and safe from the FIH study based on the 28-days DLT observation period, if not received before.

Intervention

For the Imaging Study, once or twice, depending on the group the patient is participating in, a radioactive tracer 89-ZrS95012 +- a mass dose of the Study drug S95012 will be administered, followed by 2 up to 4 PET-scans.
During the treatment part, the Study drug S95012 ill be administered intravenously every fortnight and the patients attends the Study visits. Blood and urine samples are taken, ECGs are made.
According to the group the patient is participating in, tumorbiopsies are made at baseline and during treatment.
Tumorevolution is followed with CT/MRI.

Study burden and risks

The burden for study participation for patients is to undergo the mandatory imaging part before having access to the treatment part of the study.
The imaging part involves 1 to 2 injections with 89-Zr S095012 and 4 PET-scans, resulting in a total radiation dose of 32 mSv for part A participants and 52 mSv for part B/C patients. (26 mSv if only participating to part B). Patients can go home after the procedure, no need to stay hospitalised.
The dose of the tracer used is the minimal dose mandatory for the measurement. Optimisation of the radiation dose is achieved via splitting of the protocol into parts. In conclusion, the radiation burden for this study has been optimised, is justified, and falls within the dose limits as discussed in the Netherlands Commission on Radiation, Report 26 (2016) and the International Commission on Radiological Protection, Publication 62 (1992). Dosimetry will be performed on the first participants included.
The burden for the treatment part is mainly because of the multiple site visits and exams mandatory to follow-up on the patient*s safety and to obtain information on the PK profile.
The risk: the doses of S95012 used in this study are dosages that have been evaluated as safe in a parallel study. Mandatory biopsies at baseline and on treatment are a risk for patients participating in part B/C. These biopsies are optional for patients taking part in part A and having archived tissue available. No information is available yet on the adverse reactions following S095012 administration

Contacts

Public

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Men and women of >= 18 years of age on the day the consent is signed.
2. Participants with histologically confirmed diagnosis of unresectable, locally advanced or metastatic solid tumor for which standard treatment options are not available, no longer effective, or not tolerated. Participant should have a documented disease progression on prior therapy before entry into this study.
3. Participants must have at least one measurable target lesion as per RECIST 1.1.
4. ECOG performance status of 0 or 1
5. For participants in part B/C (optional for part A): Participant with no available archived material must have one or more tumor lesions amenable to biopsy. Baseline biopsies are not mandatory if archived tumor biopsy specimens collected no later than 9 months before screening, are available. If no archived material is available, a fresh biopsy must be collected at baseline.
6. Adequate organ function as assessed by laboratory tests within 72 hours prior to the first IMP administration:

- Absolute neutrophil count (ANC) >= 1500/µL.
- Platelet count >= 75 000/µL (this criterion must be met without transfusion and thrombopoietin for at least two weeks prior to IMP administration).
- Haemoglobin >= 8 g/dL (this criterion must not be met with the use of transfusion and erythropoietin for at least two weeks prior to IMP administration).
- Glomerular filtration rate (GFR) or measured or calculated creatinine clearance (CrCl) >= 30 mL/min using the Cockcroft and Gault formula. Alternatively, the GFR can be estimated using the Modification of Diet in Renal Disease (MDRD) formula. However, the estimation of CrCl must be done using the same methodology for a given participant (see Appendix 5).
- Total bilirubin <= 1.5×upper limit of reference range (ULN) (or total serum bilirubin <3×ULN for participants with Gilbert*s disease).
- Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) <= 2.5×ULN.
- Serum albumin >= 3 g/dL

7. Woman must use a highly effective method of birth control during study treatment and until 120 days after last dose of IMP
In case of use of oral contraception, women should have been stable on the same contraceptive drug (same active principle) for at least 6 months prior to the first IMP administration.
8. A male participant with childbearing potential partners must use a condom during the study and until at least 120 days after the last dose of IMP.
Participants that are sterile or vasectomised must use a condom during sexual intercourse with a childbearing potential partner in order to avid exposure of an existing embryo/foetus. In addition, contraception should be considered for their female partner. Contraceptive measures do not apply if the participant is sterile, vasectomized or sexual abstinent. Sperm donation will not be allowed during the study and for 120 days after the last dose of IMP.
9. Human immunodeficiency virus (HIV)-infected participants must have well-controlled HIV or be on adequate antiretroviral therapy defined as:
CD4 lymphocyte count > 350 cells/µL at time of screening.
Achieving and maintaining virologic suppression defined as confirmed HIV ribonucleic acid (RNA) level below 50 or lower limit of detection by the local available assay at time of screening and for at least 12 weeks prior to screening.
10. Written informed consent obtained prior to performing any study procedure

Exclusion criteria

11. Pregnant and lactating women.
12. Unlikely to cooperate in the study.
13. Participation in another interventional study at the same time; participation in non-interventional registries or epidemiological studies is allowed.
14. Participant already included in the study (informed consent signed).

15. Participants with previously treated brain metastases may participate provided they are radiologically stable, clinically asymptomatic and are off immunosuppressive therapies for at least 4 weeks. Low dose of steroid < 10 mg/day prednisone or equivalent is allowed.
16. Participants with primary central nervous system malignancies.
17. Participants with Child-Pugh Class B8 or higher or C liver cirrhosis.
18. Participants who have received prior:
a. chemotherapy, Small molecule inhibitors, and/or other similar investigational agent: <= 2 weeks or 5 half-lives, whichever is shorter.
b. monoclonal antibodies, antibody-drug conjugates, or other similar experimental therapies: <= 3 weeks or 5 half-lives, whichever is shorter.
c. Radioimmunoconjugates or other similar experimental therapies <= 6 weeks or 5 half-lives, whichever is shorter.
19. Participants must have recovered from any AE (from previous anti-cancer therapy) to Grade 1 or lower by Common Terminology Criteria for Adverse Events (CTCAE) v5.0. Grade 2 neuropathy is acceptable. Participants receiving replacement hormone therapy due to previous AEs will not be excluded from participation in this study if the associated AE has recovered to Grade 1 with replacement therapy prior to the first IMP administration.
20. Participants who have received 4-1BB agonists in the past.
21. Participants who had a major surgery within 4 weeks prior to first administration of IMP.
22. Participants with an active autoimmune disease that is currently requiring systemic anti inflammatory treatment such as disease-modifying anti-rheumatic drugs, steroids, or immunosuppressants), except vitiligo, alopecia areata, asthma/atopy and psoriasis treated and controlled by topical therapies. Participants with auto-immune endocrinopathies that are well treated by replacement hormones therapies (e.g. thyroxine, insulin, physiological steroids for adrenal or pituitary deficits) are eligible.
23. Participants with a history of immune related AEs from a previous line of treatment must have recovered Grade <= 1 and have stopped any immunosuppressive/steroid therapy. Participants with prior history of Grade >= 3 immune-related pneumonitis, colitis, hepatitis, myocarditis.
24. Participants receiving systemic steroids at a dose of more than 10 mg per day equivalent of prednisone. Ocular, inhaled, intranasal, topical steroids are allowed. Local steroid injections (intra-articular and/or epidural) are allowed as a palliative therapeutic option only.
25. Participants who have received an allogenic solid organ or bone marrow transplant.
26. Participants with a history of interstitial lung disease, pneumonitis requiring systemic steroids for treatment, or current pneumonitis.
27. Participants with a clinically significant cardiovascular disease or condition, including:
a. New York Heart Association classification III or IV, known symptomatic coronary artery disease, or symptoms of coronary artery disease on systems review, or known cardiac arrhythmias (atrial fibrillation or supraventricular tachycardia).

b. Any concomitant serious health condition, which, in the opinion of the investigator, would place the participant at undue risk from the study, including uncontrolled hypertension and/or diabetes, clinically significant pulmonary disease (e.g., chronic obstructive pulmonary disease requiring hospitalization within 3 months) or neurological disorder (e.g., seizure disorder active within 3 months). Participants with an active infection with a viral, bacterial, or fungal agent requiring systemic treatment within seven days before first IMP administration.
28. Participants with an active infection with a viral, bacterial, or fungal agent requiring treatment within seven days before first IMP administration.
29. Participants seropositive for and with evidence of active viral infection with hepatitis B virus (HBV). Participants who are hepatitis B surface antigen (HBsAg) negative and HBV viral deoxyribonucleic acid (DNA) negative are eligible.
a. Participants who had HBV but have received an antiviral treatment and show non-detectable viral DNA for 6 months are eligible.
b. Participants who are seropositive because of HBV vaccine are eligible.
Note: a quantitative polymerase chain reaction (PCR) test result of < 10 IU/mL is equivalent to being undetected (negative).
30. Participants seropositive for and with active viral infection with hepatitis C virus (HCV).
a. Participants who had HCV but have received an antiviral treatment and show no detectable HCV viral DNA for 6 months are eligible.
Note: a quantitative PCR test result of < 10 IU/mL is equivalent to being undetected (negative).
31. Participants with HIV who have Kaposi*s or Castleman*s disease.
32. Participants who have received a live vaccine within four weeks before the first IMP administration. Examples of live vaccines include but are not limited to measles, mumps, rubella, varicella zoster, yellow fever, rabies, Bacillus Calmette-Guérin (BCG), and typhoid vaccine. Seasonal injected influenza vaccines are generally killed virus vaccines and are allowed, however intranasal influenza vaccines are live attenuated vaccines and are not allowed.
33. Participants who have received any COVID-19 vaccine within 14 days prior to first dose of IMP or who have a dose planned during Cycle 1.
34. Participants with a history of clinically significant hypersensitivity to monoclonal antibodies or infused therapeutic proteins or any component of the IMP.
35. Participants with significant pulmonary compromise including a requirement for continuous supplemental oxygen to maintain adequate oxygenation.
36. Participants with any clinically significant medical condition (e.g. organ dysfunction) or laboratory abnormality likely to jeopardise the participant*s safety or to interfere with the conduct of the study, in the investigator*s opinion.
37. Any psychiatric or substance abuse condition rendering the participant unable to understand the nature, scope, and possible consequence of the study and or evidence of an uncooperative attitude.
38. Participants with known previous or coexisting cancer that is distinct in

primary site or histology from the cancers being evaluated in this study except for treated cervical cancer in situ, surgically removed prostate in situ cancer, treated basal cell carcinoma, treated superficial bladder tumors (non-invasive papillary carcinoma (Ta) and in situ carcinoma (Tis), all treated for more than 1-month before study entry or any localised cancer curatively treated < 3 years prior to study entry.

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	12-12-2022
Enrollment:	33
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	89Zr-S095012
Generic name:	89Zr-S095012
Product type:	Medicine
Brand name:	S095012
Generic name:	S095012

Ethics review

Approved WMO

Date:	23-02-2022

Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	12-08-2022
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	06-09-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	24-10-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	26-03-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	17-05-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	05-07-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	23-08-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	31-10-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Not approved Date:	20-02-2024

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	EUCTR2021-001764-20-NL
CCMO	NL76944.042.22