2. SYNOPSIS

Name of Sponsor: Institut de Recherches Internationales Servier (I.R.I.S.) 22, route 128 – 91190 Gif sur Yvette - France	*(For National Authority Use only)*
Name of finished product: Not applicable	
Name of active ingredient: ^{89}Zr-S095012 S095012	
Title of study: An open label, multicentre, positron emission tomography (PET) imaging study using Zirconium-89 to investigate the biodistribution and tumour uptake of a PD-L1x4-1BB bispecific antibody (S095012) in patients with advanced solid tumours. Protocol No.: CL1-95012-002 EudraCT No.: 2021-001764-20 CT.gov No: NCT05638334	
Principal investigator: Prof. Elisabeth GE de Vries, M.D., PhD, University Medical Centre Groningen, University of Groningen, Department of Medical Oncology DA11 - PO Box 30.001 9700 RB Groningen - The Netherlands	
Number of study centres and countries: In all, 3 participants were enrolled across 2 study centres based in The Netherlands.	
Studied period: Initiation date: 21 November 2022 (first visit first participant) Completion date: 13 July 2023 (last visit last participant) The study was prematurely terminated (as explained in the "Study design" and "Conclusions" sections).	
Phase of development of the study: Phase I	
Publication (reference): Not applicable	

Background and rationale for the study:
S095012 is a monoclonal antibody-like bispecific protein targeting the programmed death-ligand 1 (PD-L1) and the immune receptor 4-1BB.

Current treatments for advanced solid tumours include chemotherapies, targeted therapies, and immune checkpoint inhibitors. Despite their widespread use, these treatments are often limited by factors such as resistance, adverse effects, and suboptimal efficacy in certain patient populations. As a result, there is a critical need for new therapies that can offer more effective and durable responses in these patients. S095012, with its unique mechanism of action, represents a potential new therapeutic option in this context. The intended mechanism of action of S095012, involving simultaneous PD-1/PD-L1 axis inhibition and PD-L1 dependent 4-1BB activation, showed promising results in preclinical models.

A first-in-human (FIH) study, CL1-95012-001, was thus designed to further evaluate the safety profile, tolerability, and to determine the maximum tolerated dose (MTD) or maximum administered dose of S095012, as well as the pharmacokinetic (PK) profile, pharmacodynamic effects, and preliminary anti-tumour activity of S095012. The study was conducted in patients with advanced solid tumours, for whom no standard treatment existed, or where established treatments had failed. Most recently, the FIH study has enrolled participants to an already tested dose level of S095012 given after premedication with obinutuzumab. This pretreatment was intended to suppress the formation of anti-drug antibodies (ADAs) against S095012 and thereby prevent its rapid clearance. Early experience with this pretreatment showed increased liver toxicity compared to the same and higher doses of S095012 given without premedication. This experience prevented further dose escalation with obinutuzumab pretreatment.

Molecular imaging with PET is a powerful and non-invasive tool for in vivo visualisation, monitoring and quantification of the uptake of Zirconium-89 radiolabelled S095012 (^{89}Zr-S095012) compounds in tumours and tissues of interest in humans. Therefore, assessing the biodistribution and tumour 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 current study (CL1-95012-002) was conducted in a staggered manner with CL1-95012-001 and was designed to assess the whole-body biodistribution and tumour uptake of ^{89}Zr-S095012 at baseline and during treatment with S095012. The study was conducted in participants with histologically confirmed advanced and/or metastatic solid tumours. Pharmacodynamic effects of S095012 were followed through systemic 4-1BB specific biomarkers and CD8 T cell activation in the tumour (immunohistochemistry on biopsies). During this study, mass and treatment doses of S095012 administered were based on safety data collected during the FIH study. Reciprocally, safety data collected from the imaging study informed the safety profile of S095012 and was taken into account in the MTD (if any) and/or the recommended phase 2 dose determination. This study was planned to be conducted in 3 parts (Part A, and Part B and C). Participants from Part A were imaged at baseline only in order to determine the optimal non-therapeutic mass dose of S095012 to inject along with ^{89}Zr-S095012 and to select the optimal time points for PET/computerised tomography (CT) scan imaging. The first mass dose of S095012 was based on the results from the FIH PK data and data from the literature.

The recent experience in the FIH study prevented further dose escalation. As a result, the investigation of the dose-dependency of ^{89}Zr-S095012 tumor uptake became unfeasible which led to Servier's decision to prematurely stop the CL1-95012-002 clinical study. Since the study was terminated during Part A, Part B and Part C of the study were not initiated.

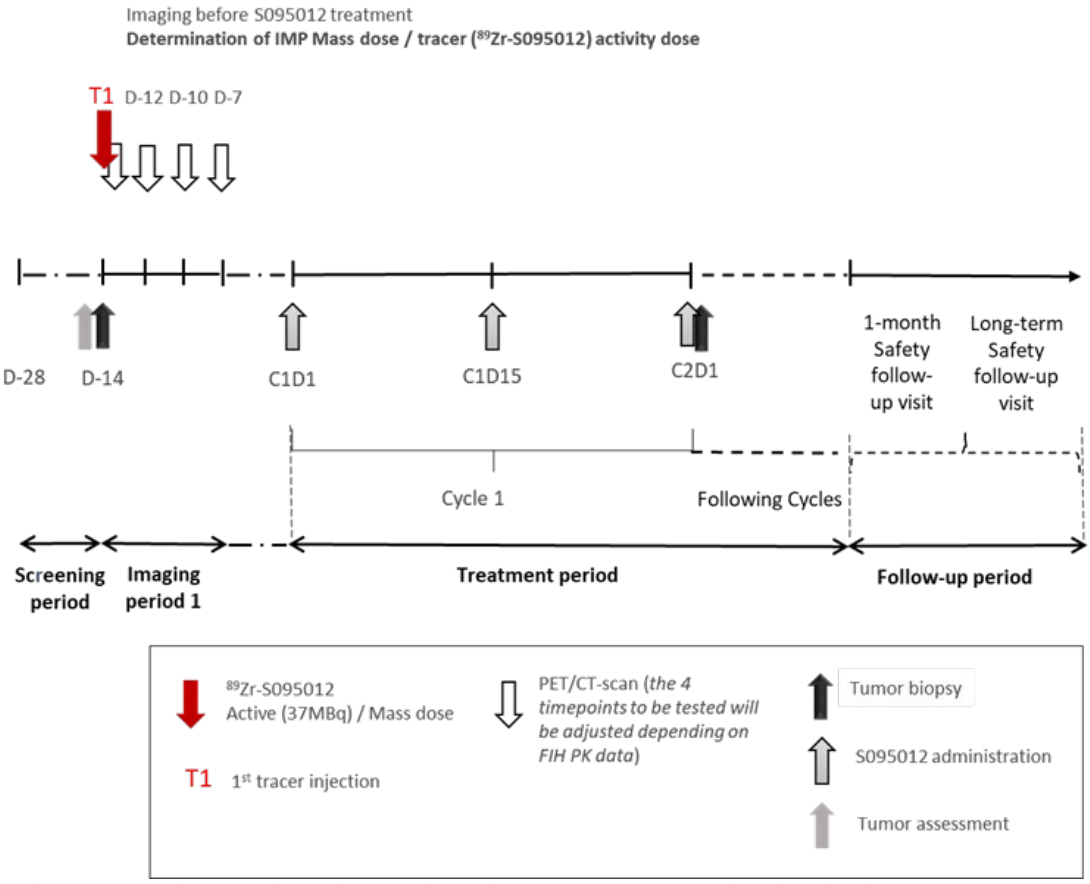
Objectives and endpoints:

Objectives	Endpoints
Primary	
- To establish the optimal mass dose of S095012 and optimal PET/CT scan time points for imaging of ^{89}Zr-S095012.	- Visual analysis of PET/CT scan images. - Parameters derived from PET scans for blood pool, organs and tumour lesions.
- To characterise whole-body biodistribution and PK of ^{89}Zr-S095012.	- Parameters derived from PET scan images to assess uptake in tumour lesions and normal tissues reported with standardised uptake value (SUV) and concentrations. - Serum PK parameters of ^{89}Zr-S095012.
- To investigate the treatment dose-dependent tumour uptake of ^{89}Zr-S095012.	- Comparison of ^{89}Zr-S095012 tumour uptake (as described using SUV and concentrations) before and on-treatment with different doses of S095012.
- To evaluate the safety and tolerability profile of ^{89}Zr-S095012 and S095012.	- Incidence and severity of adverse events (AEs). - Discontinuing study intervention due to an AE.
Secondary	
- To characterise the PK profile of S095012.	- Serum PK parameters of S095012.
- To measure the dosimetry of ^{89}Zr-S095012	- Organ and whole-body radiation exposure (milliSievert per Mega Becquerel [mSv/MBq]): Effective dose per organ and whole-body effective dose.
- To assess the preliminary anti-tumour activity of S095012.	- Assessment based on Response Evaluation Criteria in Solid Tumours (RECIST) V1.1, objective response rate.

Study design:

This was a Phase 1, multicentre, single-arm, open-label imaging study designed to assess the whole-body biodistribution and tumour uptake of ^{89}Zr-S095012 in participants with solid tumours treated with S095012. This study was conducted in a staggered manner with the FIH Phase 1/2 study (CL1-95012-001).

The study was planned in 3 parts (Part A, B, and C); however, participants were enrolled only in Part A due to the early termination of the study. The study plan for Part A is presented in the following figure:



C cycle; CT computed tomography; D day; FIH first-in-human; IMP investigational medicinal product; PET positron emission tomography; PK pharmacokinetics

Participants received ^{89}Zr-S095012, i.e., the tracer (37 MBq corresponding to 1.5 ± 0.5 mg in 10 mL) with different mass doses of S095012 at baseline. Imaging of ^{89}Zr-S095012 was performed using whole-body PET/CT scans.

This study was performed in strict accordance with Good Clinical Practice.

Number of participants (planned and analysed):

Planned:

No formal statistical power calculations to determine sample size were performed.
Overall, up to 9 participants (3 cohorts of 3 participants) were planned to be included in Part A and 24 participants (4 cohorts of 6 participants) were planned to be enrolled in Parts B and C (not performed).
Due to early termination of the study, participants were enrolled only in Part A.

Analysed:

A total of 3 participants were analysed in 3 cohorts:

- Cohort 1 (S095012 9 mg mass dose + S095012 36 mg every 2 weeks [Q2W] group): 1 participant
- Cohort 2 (S095012 24 mg mass dose + S095012 60 mg Q2W group): 1 participant
- Cohort 3 (S095012 24 mg mass dose + S095012 60 mg Q2W group): 1 participant

Although participants were enrolled into 3 distinct cohorts, the results are grouped for analysis by dosing regimens (S095012 9 mg mass dose + S095012 36 mg Q2W and S095012 24 mg mass dose + S095012 60 mg Q2W group).

Diagnosis and main criteria for inclusion/exclusion:
Main inclusion and exclusion criteria are presented hereafter.
Participants ≥ 18 years of age, with:

- Histologically confirmed diagnosis of unresectable, locally advanced or metastatic solid tumour for which standard treatment options were not available, no longer effective, or not tolerated.
- At least one measurable target lesion as per RECIST 1.1.
- Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1.
- Royal Marsden Prognosis Score of 0 to 1 (score based on lactate dehydrogenase value, albumin value and number of metastasis).
- Adequate organ function as assessed by laboratory tests (especially adequate hepatic function).

Participants with no available archived material must have had one or more tumour lesions amenable to biopsy (optional for participants in Part A).
Participants with primary central nervous system malignancies and participants with Child-Pugh Class B8 or higher or C liver cirrhosis were excluded. Participants must not have had an active autoimmune disease or immune-related AEs currently requiring systemic anti-inflammatory agent > 10 mg/day prednisone or equivalent. Participants with a history of an opportunistic infection within a year before the administration of first study drug dose were excluded. Participants who received either systemic corticosteroids (> 10 mg per day of prednisone or equivalent) or other immunosuppressive medication during the 2 months prior to the first dose of the study drug were excluded. Serologic testing for cytomegalovirus (CMV) and Epstein-Barr virus (EBV) had to show absence of immunoglobulin M antibodies against CMV and EBV-Viral Capsid Antigen according to local standards. Participants with prior history of Grade ≥ 3 immune-related pneumonitis, colitis, hepatitis, or myocarditis were also excluded.

Investigational medicinal product:
- ***^{89}Zr-S095012 (tracer)***

^{89}Zr-S095012 contained 1.5 ± 0.5 mg ^{89}Zr-S095012 equivalent to approximately 37 MBq in 10 mL formulation buffer (50 mM histidine, 50 mM sodium chloride [NaCl], 200 mM arginine, 0.01% Polysorbate 80 [PS80], pH 6.5). The tracer was administered via an intravenous (IV) infusion over 10 minutes with a controlled rate.

- ***S095012***

S095012 drug product is a concentrate for solution for IV administration. It was supplied in 20 mL United States Pharmacopeia and European Pharmacopeia Type I glass vials filled with 16 mL of product at a concentration of 25 mg/mL. Each vial for administration contains 400 mg of S095012. For dosing, the required volume of product was diluted in saline with PS80 as a solvent (0.03% to 0.04% final concentration).

- S095012 mass dose

Three mass dose levels were anticipated to be tested in Part A: 3 mg, 9 mg and 24 mg. However, these doses might have been adjusted based on the S095012 PK profile observed in the FIH study, imaging data observed from previous cohorts, and emerging literature on molecules from the same class (bispecific monoclonal antibodies).

- Treatment dose of S095012

Treatment doses of S095012 were administered IV Q2W (Day 1 and Day 15 of each 28-day cycle) and never exceeded doses determined to be safe and tolerable after the 28-day dose-limiting toxicity observation period from the FIH study. In the FIH study, the starting dose planned was 12 mg, with a maximum dose of 1000 mg, based on the recommended dose of marketed anti-PD-L1 antibodies (atezolizumab, 1200 mg once every 3 weeks).

Comparator:
Not applicable

Duration of treatment:

For all participants, the study included:

- A ***screening period*** - inclusive of 14 days to check participants' eligibility criteria.
- An ***imaging period*** 1 of 7 days where participants were given the ^{89}Zr-S095012 tracer and an S095012 mass dose for imaging, followed by a series of PET/CT scans.
- A ***treatment period*** - participants received administrations of S095012 treatment, one cycle being 2 administrations (Q2W) and until one of the following criteria applied:
  - Adverse events.
  - Pregnancy.
  - Major protocol deviation if it interferes with the study evaluations and/or if it jeopardises participant's safety, *e.g.,* any medical event requiring administration of an unauthorised concomitant treatment.
  - Progressive disease (PD) confirmed radiographically.
  - Withdrawal of consent.
  - Other physician decision (physician decision other than AE or PD).
  - Other (for reasons that cannot be included in any of the criteria listed above, for example: participant's change of residence).

For all participants, the maximum duration of the treatment period did not exceed 1 year for participants with confirmed complete response and 2 years for participants with confirmed partial response. Longer treatment duration might have been permitted if the participant benefits outweigh the risks according to the investigator's judgement and after consultation with the Sponsor.

- A ***follow-up period***:
  - 1-month safety follow-up visit: Participants were evaluated 30 days after the last investigational medicinal product (IMP) administration or prior to starting subsequent therapy, whichever occurred sooner. During this visit, participants were evaluated in order to assess any AEs regardless of the relationship with the IMP or experimental procedure.
  - Long-term safety follow-up visit: Participants were evaluated 60 and 90 days after the last IMP administration. During these visits, participant safety was evaluated through physical examination, vital signs, 12-lead electrocardiograms (ECGs), and laboratory assessments to assess AEs ongoing at the last study visit or new AEs related to the IMP or experimental procedure.

The ***end of the study*** was defined as the date of the last follow-up of the last participant, or the date of the last contact attempt if the last participant was declared lost to follow-up. The last follow-up corresponded to the last participant's last visit, which included the long-term safety follow-up visit, 90 days after the last dose of IMP.

Statistical methodology:

Analysis Sets:

- Enrolled Set (ES): This set included all screened participants who were eligible to take part in the study according to all inclusion and exclusion criteria.
- Included Set: This set corresponded to all included participants.
- Treated Set (TS): This set included all participants who received at least one dose of S095012.
- Pharmacokinetic Set (PKS): This set included all participants who received at least one dose of S095012 and for whom at least one reportable post-S095012 PK concentration was available.
- Immunogenicity Set**:** This set included all participants who received at least one dose of S095012 and for whom there were baseline and at least one post-S095012 immunogenicity assessment was available.

Efficacy analysis was performed on the TS and using all efficacy data before any subsequent anti-cancer therapy. The full study ***safety analysis*** (i.e., AEs, laboratory data, vital signs, and ECG analyses) were performed on the TS.

For Pharmacokinetic and Immunogenicity data, only individual listings were presented.

Study participants: disposition baseline characteristics and treatments analysis: Descriptive statistics were provided.

Summary of results and Conclusions

Disposition of participants:

A total of 3 participants were included in the study and treated with S095012: 1 participant with S095012 9 mg mass dose + S095012 36 mg Q2W, and 2 participants with S095012 24 mg mass dose + S095012 60 mg Q2W group. All 3 participants were withdrawn from the study due to PD.

Baseline characteristics:

A total of 2 participants received the S095012 24 mg mass dose + S095012 60 mg Q2W treatment, preceded by 1 participant who received the S095012 9 mg mass dose + S095012 36 mg Q2W treatment. Participants were male, under the age of 65, with body mass index values ranging from 26.64 to 33.74 kg/m^2 and body surface area between 1.91 and 2.40 m^2 The ECOG PS were 0 or 1 across participants. Participants across both dose groups had advanced-stage cancer, with primary tumour location in the colon or sigmoid region (colorectal cancer). All participants were in a state of relapse and metastasis. Disease duration ranged from 16.72 to 54.05 months, and treatment-free intervals varied between 0.03 and 1.12 months. Relapse duration was between 0.23 and 1.12 months. Participants had varying histories of comorbid conditions, including hypertension, hepatic cirrhosis, chronic hepatitis C, ureterolithiasis, myocardial infarction cholangitis, and constipation. Surgical interventions were common, with procedures such as ureteroscopy, stent placement, duodenal sphincterotomy, and endoscopic retrograde cholangiopancreatography performed prior to the study.

Extent of exposure:

The duration of treatment was between 1.87 and 2.76 months, and the participants withdrew the study after 2 to 3 cycles of treatment. The dose intensity was lower than planned, with a relative dose intensity of 50% to 83.3%.

Efficacy results:

All participants in the study experienced PD as the best overall response. Tumour size increased by 2.6% and 51.5% in the S095012 24 mg + 60 mg Q2W group and by 17.9% for the participant in the S095012 9 mg + 36 mg Q2W group.

- Pharmacokinetic, pharmacodynamic, and other analyses results

Treatment with Zr-S095012 was administered without dose interruption to all participants. Serum drug concentration peaked within the first 6 hours post-infusion, followed by a decreased to below the quantitation limit between 96 and 168 hours after the end of infusion. PET scans showed strong uptake of ^{89}Zr-S095012 in the spleen, liver, and lymphoid tissue, and modest uptake in tumor lesions. Considering the early study termination of this trial and the low number of participants included, further characterisation was not possible.

Safety results:

- Treatment-emergent AEs

Treatment-emergent AEs (TEAEs) were reported in all 3 participants. In the S095012 9 mg mass dose + S095012 36 mg Q2W group, a total of 3 TEAEs were reported in 1 participant. In the S095012 24 mg mass dose + S095012 60 mg Q2W group, 5 and 6 TEAEs were reported in 2 participants, respectively.
Fatigue, weight decreased, and infusion-related reaction (IRR) were reported in 2 participants. All other events were reported in only 1 participant.
In the S095012 24 mg mass dose + S095012 60 mg Q2W group, 4 ***severe TEAEs*** (pneumonia, lipase increased, cholangitis, and IRR) were reported in 1 participant, all of which resolved by the end of the study.
All 3 participants experienced ***TEAEs related to study treatment***. In the S095012 9 mg mass dose + S095012 36 mg Q2W group, the participant experienced 2 TEAEs: pustular rash and fatigue. In the S095012 24 mg mass dose + S095012 60 mg Q2W group, 1 participant reported 5 TEAEs related to study treatment (influenza-like illness, rash maculo-papular, fatigue, headache, and IRR) while the second participant reported 1 TEAE related to study treatment (TEAE of IRR).
No ***deaths*** were reported during the study.
In the S095012 24 mg mass dose + S095012 60 mg Q2W group, 1 participant experienced 3 ***serious TEAEs***. These included pneumonia, cholangitis, and IRR, all classified as Grade 3 AEs, and all resolved by the end of study, without any changes made to treatment dose. The serious TEAE of IRR was considered related to the study treatment.

- Laboratory tests

In the S095012 24 mg mass dose + S095012 60 mg Q2W group, clinically significant abnormal values for TEAEs of lipase increase and bilirubin increase were reported in 1 participant.
No clinically relevant trends were observed during the study.

- Other observations

No clinically relevant trends were observed for vital signs during the study.
No ECG measurement was reported as TEAE.
All 3 participants were negative for ADA at screening and became positive under treatment, with titers ranging from 1024 to 262144. All ADA positive samples were positive for both 4-1BB and anti-PD-L1 epitopes.
No specific AE related to the radiolabelled compound was reported.

Conclusion:

This was a Phase 1, multicentre, single-arm, open-label, imaging study designed to assess the whole-body biodistribution and tumour uptake of ^{89}Zr-S095012 and to establish the optimal mass dose of S095012 in participants with solid tumours.

A total of 3 participants were included in the study and treated with S095012 until withdrawal from the study due to PD. After all participants had stopped treatment, and with no new included participants, the Sponsor decided to prematurely discontinue the study based on strategic considerations and due to safety concerns observed in the CL1-95012-001 FIH study.

All 3 participants experienced TEAEs related to S095012, including fatigue, IRR (in 2 participants, each), and influenza-like illness, pustular rash, headache, and rash maculo-papular (in 1 participant, each). Serious TEAEs were reported in 1 participant who experienced 3 non-fatal serious Grade 3 AEs: pneumonia, cholangitis, and IRR. Infusion-related reaction was considered to be S095012-related, while the other 2 serious AEs were not related to treatment.

No clear conclusion could be drawn regarding the assessed efficacy, PK results, or the safety and tolerability of S095012 due to the low number of participants included in the study. Imaging results showed major drug uptake in the lymphoid system and modest uptake in tumor lesions at the low protein tracer doses tested. However, the safety assessments at these doses informed the safety profile of the study drug and were considered in the conduct of the FIH study.

Date of the report: 09 January 2025