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Safety, distribution and metabolism of 89Zr-DFO-girentuximab in bodies of patients with masses of unknown nature on their kidneys.

Submission date 17/05/2023	**Recruitment status** No longer recruiting	[X] Prospectively registered [ ] Protocol [ ] Statistical analysis plan [ ] Results [ ] Individual participant data [ ] Record updated in last year
Registration date 23/05/2023	**Overall study status** Completed	
Last Edited 10/02/2025	**Condition category** Cancer	

Plain English summary of protocol

Background and study aims

With current imaging techniques, it can sometimes be difficult to assess whether there is kidney cancer or a benign (non-cancerous) growth, or if a patient with kidney cancer has recurrent or growing disease. A previous research study called ZIRCON tested a new imaging agent that shows brightness/contrast when using x-rays, called 89Zr-DFO-girentuximab. This imaging agent is also being investigated in this study. 89Zr-DFO-girentuximab combines the radionuclide (a radioactive molecule) known as zirconium-89 with the antibody girentuximab (a protein made in a lab). Girentuximab is known to specifically bind to proteins overly expressed by clear cell renal cell carcinoma (ccRCC), which means that it is taken up (engulfed) by the cancerous cells. The ZIRCON study successfully showed that 89Zr-DFO-girentuximab can identify kidney cancer lesions without requiring an invasive diagnostic process such as biopsy, which is currently the only available method for ccRCC diagnosis.

The aim of this study is to show similarity between 89Zr-DFO-girentuximab developed by three different manufacturing processes as described below:

- Group 1: Up to 5 evaluable patients to whom drug product 89Zr-TLX250 manufactured with girentuximab antibody produced by ADRM-free adapted cell lines will be administered on Day 0.
- Group 2: Up to 5 evaluable patients to whom drug product 89Zr-TLX250 manufactured with girentuximab antibody produced by original cell lines containing ADRM will be administered on Day 0.
- Group 3: Up to 5 evaluable patients to whom drug product 89Zr-TLX250 manufactured by animal derived raw materials

Regardless of the manufacturing process, the finished product is still the same, and the present study aims to demonstrate that.

Who can participate?

Male and female adults, aged at least 18 years, with morphological imaging evidence of a single renal mass of at least 7 cm in largest diameter on standard of care (SoC) imaging (CT/MRI) based on national standards, requiring further diagnostic work-up.

What does the study involve?
On the day of treatment, the participant will be injected with a small amount of 89Zr-DFO-girentuximab manufactured from either the legacy process or engineered process method. They may receive either version of the 89Zr-DFO-girentuximab. After that, they will undergo a few total PET/CT scans required for this study over a period of 6 days. The camera in PET/CT detects emissions coming from 89Zr, and a computer creates two and three-dimensional images of the area being examined. This PET/CT machine can detect the distribution of the 89Zr-DFO-girentuximab within their body and areas where the 89Zr-DFO-girentuximab gathers. These areas will appear 'brighter' on the images than the anywhere else in your body, making it clear the unknown kidney lesion is ccRCC.
89Zr-DFO-girentuximab is an experimental imaging agent/drug. This means that it is not approved by the Therapeutic Goods Administration (TGA) for use in Australia for any indication. Patients whose doctor may suspect they have a type of kidney cancer, known as clear cell renal cell carcinoma can participate in this study.

What are the possible benefits and risks of participating?
There will be no direct benefit to the participant for participating in this study. We hope that in the future the information learned from this study will benefit other people with this condition and help to further develop Zirconium-89 girentuximab and the use of PET / CT imaging as a valid technique for the diagnosis of clear cell renal cell carcinoma.
Medical treatments often cause side effects. The patients may have none, some or all of the side effects listed below. They may be mild, moderate, or severe. If the participants have any of the listed side effects, or are worried about them, they should talk with their study doctor. The study doctor will also be looking out for side effects.

Where is the study run from?
Telix Pharmaceuticals (Innovations) Pty Ltd. (Australia)

When is the study starting and how long is it expected to run for?
December 2022 to June 2025

Who is funding the study?
Telix Pharmaceuticals (Innovations) Pty Ltd. (Australia)

Who is the main contact?
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Additional identifiers

Protocol serial number
89Zr-TLX250-006

Study information

Scientific Title
A Phase 1, prospective study to compare safety, tolerability, biodistribution and pharmacokinetics of a single dose of 89Zr-TLX250 (89Zr-DFO-girentuximab) formulated by three unique processes in patients with indeterminate renal masses

Study objectives
Current study hypothesis as of 10/02/2025:

89Zr-DFO-girentuximab is composed of the monoclonal antibody girentuximab, labelled with 89Zr (zirconium-89) via DFO (desferrioxamine B), is currently subject to clinical development for the diagnosis of clear cell renal cell carcinoma (ccRCC) in the context of clinically suspected ccRCC. 89Zr-DFO-girentuximab targets carbonic anhydrase IX (CAIX) expressing tissues. Following administration to patients with ccRCC, 89Zr-DFO-girentuximab binds to CAIX, which in turn allows imaging of CAIX-expressing lesions by positron emission tomography (PET). Zirconium-89 is first coupled with antibodies via succinylated derivative of desferrioxamine B (DFO-TFP) as bifunctional chelate. Then, radiolabelled 89Zr undergoes intracellular catabolism and, as a result, stays in the target cells.

This study was designed to compare the safety, tolerability, pharmacokinetics, and biodistribution of 89Zr-TLX250 formulated by three unique processes: (1) the ADRM process, (2) the ADRM-free process, and (3) the commercial process.
The ADRM process produced the original drug product that utilized cell lines containing animal derived raw materials (ADRMs) in the manufacturing process. The ADRM-free process was free of animal-derived raw material that was produced via an adapted manufacturing process. Both of these processes were manual wherein only 3 doses were formulated per batch. The

commercial process is also free of ADRMs; however, the bioconjugation has also been optimized and upscaled to fit the requirements of commercial manufacturing.

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Previous study hypothesis:

89Zr-DFO-girentuximab is composed of the monoclonal antibody girentuximab, labelled with 89Zr (zirconium-89) via DFO (desferrioxamine B), is currently subject to clinical development for the diagnosis of clear cell renal cell carcinoma (ccRCC) in the context of clinically suspected ccRCC. 89Zr-DFO-girentuximab targets carbonic anhydrase IX (CAIX) expressing tissues. Following administration to patients with ccRCC, 89Zr-DFO-girentuximab binds to CAIX, which in turn allows imaging of CAIX-expressing lesions by positron emission tomography (PET). Zirconium-89 is first coupled with antibodies via succinylated derivative of desferrioxamine B (DFO-TFP) as bifunctional chelate. Then, radiolabelled 89Zr undergoes intracellular catabolism and, as a result, stays in the target cells.

As part of product development, the manufacturing process of the monoclonal antibody (mAb) girentuximab, has been adapted from a process that utilized animal derived raw material (ADRM) (original manufacturing process) to a process that is free of animal-derived raw material (ADRM-free adapted manufacturing process). The bioconjugation has also been optimized and upscaled during the development stage, to fit commercial needs. The current study will be undertaken to demonstrate comparability of biodistribution and safety between 89Zr DFO-girentuximab manufactured using the original manufacturing process and the adapted manufacturing process

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 08/05/2023, Northern A Health and Disability Ethics Committee (Ministry of Health, 133 Molesworth Street, PO Box 5013, Wellington, 6011, New Zealand; no telephone number provided; hdecs@health.govt.nz

Primary study design
Interventional

Study design
Phase I open label study

Study type(s)
Diagnostic

Health condition(s) or problem(s) studied
Diagnosis of clear cell renal cell carcimona in patients with unidentified renal masses

Interventions
Current interventions as of 10/02/2025:

Eligible patients will be enrolled in one of the three groups, which will enrol in parallel. At the discretion of the investigator and in consultation with the Sponsor, patients can be

simultaneously enrolled into Group 1, Group 2, or Group 3 until the full complement of patients have been recruited into each cohort.
The rest of the study processes before during and after IMP dosing will be identical between both the groups:
1. Screening Day 0:
- baseline assessments
- IMP dosing where IMP manufactured by one of the two processes mentioned above will be administered slowly over a minimum of 3 min.
- Radiation PK sample collection at 30min (± 3 min), 2h (± 5 min) and 4h (± 5 min) post dosing, and PET-CT scan at 4 hrs (± 20 min)post dosing.
2. PET/CT imaging and Radiation PK sample collection on days 1 (24h ± 2h), 3 (72h ± 12h) and 6 (144h ± 24h).
3. End of study visit on Day 21 (± 3 days).

Study Assessments
Pre-baseline contrast enhanced computerized tomography (CT)/magnetic resonance imaging (MRI) images will be collected for evidence of a renal mass and for precise volumetric tumor delineation and sent for central reading assessment.
For biodistribution and dosimetry analysis, whole body PET/CT scans (vertex of the skull to mid-thigh) will be acquired at the following imaging timepoints (post administration (p.a.) of 89Zr-DFO-girentuximab using static image acquisition):
• Visit 2 / Day 0: 4h±20 min
• Visit 3 / Day 1: 24h±2h
• Visit 4 / Day 3: 72±12h
• Visit 5 / Day 6±1: 144+24h
All attempts should be made for the first PET/CT scan to be a low dose CT scan without contrast agent, and for all subsequent time points to be ultra-low dose CT scans.
Tumor dosimetry will be performed in patients with visible 89Zr-DFO-girentuximab uptake in the tumor at PET/CT.
Organ and whole-body dosimetry will be centrally analysed using the phantom based MIRD methodology using OLINDA, considering individual anatomy, allowing a precise description of tumour absorbed doses.
Radiation Pharmacokinetics - blood sampling for radiation PK analysis will be performed at pre-dose and at the following timepoints p.a. of 89Zr-DFO-girentuximab:
• Visit 2 / Day 0: 0.5h±3min, 2h±5min, 4h±5min
• Visit 3 / Day 1: 24h±2h
• Visit 4 / Day 3: 72h±12h
• Visit 5 / Day 6±1: 144h±24 h
Days 0, 1, 3 and 6±1 will also be imaging visits. The time points will be calculated from the end of the 89Zr-DFO-girentuximab administration.
Safety assessments include continuous monitoring of concomitant medications and AEs.
Other assessments include qualitative and quantitative testing for the presence of Anti-drug Antibody (ADA) (Human Anti-Chimeric Antibody (HACA)) in sera of patients during the study.

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Previous interventions:

Patients will be enrolled into 2 separate groups which will be dosed sequentially. Either group may be enrolled first, as determined by the sponsor.
Up to 5 patients in the 1st group will be dosed with the IMP manufactured from girentuximab antibody produced by ADRM-free adapted cell lines while group 2 will have up to 5 patients

dosed with the same IMP manufactured with girentuximab antibody produced from the original (ADRM containing) cell lines.
The rest of the study processes before during and after IMP dosing will be identical between both the groups:
1. Screening Day 0:
- baseline assessments
- IMP dosing where IMP manufactured by one of the two processes mentioned above will be administered slowly over a minimum of 3 min.
- Radiation PK sample collection at 30min (± 3 min), 2h (± 5 min) and 4h (± 5 min) post dosing, and PET-CT scan at 4 hrs (± 20 min)post dosing.
2. PET/CT imaging and Radiation PK sample collection on days 1 (24h ± 2h), 3 (72h ± 12h) and 6 (144h ± 24h).
3. End of study visit on Day 21 (± 3 days).

Study Assessments
Pre-baseline contrast enhanced computerized tomography (CT)/magnetic resonance imaging (MRI) images will be collected for evidence of a renal mass and for precise volumetric tumor delineation and sent for central reading assessment.
For biodistribution and dosimetry analysis, whole body PET/CT scans (vertex of the skull to mid-thigh) will be acquired at the following imaging timepoints (post administration (p.a.) of 89Zr-DFO-girentuximab using static image acquisition):
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Safety assessments include continuous monitoring of concomitant medications and AEs.
Other assessments include qualitative and quantitative testing for the presence of Anti-drug Antibody (ADA) (Human Anti-Chimeric Antibody (HACA)) in sera of patients during the study.

Intervention Type
Drug

Phase
Phase I

Drug/device/biological/vaccine name(s)

89Dr-DFO-girentuximab also known as 89Zr-TLX250; INN (proposed): Zirconium 89 girentuximab deferrioxamine

Primary outcome(s)
1. Safety and tolerability will be measured by comparing all the adverse events between patients treated with IMP containing girentuximab derived from ADRM-free medium versus patients treated with IMP containing girentuximab derived from ADRM-containing medium, at the end of the study.
2. Equivalence of uptake will be measured by comparing the injected activity (as a percentage) per organ mass in the major target organs including kidneys, liver, spleen, heart content and red marrow at the end of the study patients treated with IMP containing girentuximab derived from ADRM-free medium versus patients treated with IMP containing girentuximab derived from ADRM-containing medium, at the end of the study.

Key secondary outcome(s)
1. Radiation Pharmacokinetics (PK) will be measured by comparing the following between patients treated with IMP containing girentuximab derived from ADRM-free medium versus patients treated with IMP containing girentuximab derived from ADRM-containing medium, at the end of the study.
1.1. Whole blood radiation PK measurements will include Cmax, Tmax, elimination half-live (T1 /2), volume of distribution, and Area under the Curve (AUC0-inf) calculated from the radiation PK measurements
1.2. Radioactivity uptake in tumor lesions including SUVpeak, SUVmax and SUVmean, Time Activity Curve, and Time Integrated Activity Coefficient calculated from the PET/CT images
1.3. 89Zr retention on the tumour by AUC0-inf obtained from the images calculated from the PET /CT images
1.4. Tumour to background ratio during imaging on days 0, 1, 3 and 6 calculated from the PET/CT images
1.5. Radioactivity uptake in major target organs calculated from the PET/CT images
1.6. Normalized whole body effective radiation calculated from the PET/CT images
1.7. Normalized absorbed organ and tumor radiation calculated from the PET/CT images
2. Patient safety will be measured by comparing the following between patients treated with IMP containing girentuximab derived from ADRM-free medium versus patients treated with IMP containing girentuximab derived from ADRM-containing medium, at the end of the study.
2.1. Serious Adverse Events
2.2. Changes in safety laboratory assessments that are clinically significant
2.3. Changes in ECG parameters that are clinically significant
2.4. Changes in physical examination results that are clinically significant
2.5. Changes in vital signs that are clinically significant

Completion date
30/06/2025

Eligibility

Key inclusion criteria
Current inclusion criteria as of 10/02/2025:

1. Patients ≥18 years of age at time of informed consent signature
2. Have morphological imaging evidence of a single renal mass of ≤7 cm in largest diameter on standard of care (SoC) imaging (CT/MRI) based on national standards, requiring further

diagnostic work-up, including participants who have simple cysts (Bosniak I to II) in addition to the single indeterminate renal mass and participants with suspected recurrence based on previous imaging. Patients with a history of ccRCC and renal lesion of unclear origin during follow-up may also be included
3. Life expectancy of at least 6 months
4. Availability of a pre-study morphological image (contrast-enhanced CT or MRI scan) showing a renal mass within 90 days prior to dosing with 89Zr-DFO-girentuximab.
5. Have the capacity to understand the study and be willing and able to comply with all protocol requirements.
6. Negative serum pregnancy tests in female patients of child-bearing potential at screening. Confirmation of negative pregnancy test results from urine within 24 hours prior to receiving investigational product.
7. Participants must agree to practice adequate precautions to prevent pregnancy, including male patients with female of child-bearing potential partners and to avoid potential problems associated with radiation exposure to the unborn child (Refer to 10.2, Appendix 2).
8. Participants must comply with the radiation protection rules that are used by the treating institution in order to protect their close contacts and the general public.
9. Participant agrees not to participate in another interventional study while participating in the present study.

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Previous inclusion criteria:

1. Patients ≥18 years of age at time of informed consent signature
2. Have morphological imaging evidence of a single renal mass of ≤7 cm in largest diameter on standard of care (SoC) imaging (CT/MRI) based on national standards, requiring further diagnostic work-up a. Patients with a history of ccRCC and renal lesion of unclear origin during follow-up may also be included
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5. Have the capacity to understand the study and be willing and able to comply with all protocol requirements.
6. Negative serum pregnancy tests in female patients of child-bearing potential at screening. Confirmation of negative pregnancy test results from urine within 24 hours prior to receiving investigational product.
7. Participants must agree to practice adequate precautions to prevent pregnancy, including male patients with female of child-bearing potential partners and to avoid potential problems associated with radiation exposure to the unborn child (Refer to 10.2, Appendix 2).
8. Participants must comply with the radiation protection rules that are used by the treating institution in order to protect their close contacts and the general public.
9. Participant agrees not to participate in another interventional study while participating in the present study.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Upper age limit
99 Years

Sex
All

Key exclusion criteria
1. Other radiopharmaceutical administered within ten physical half-lives (of the radionuclide) of intended administration of 89Zr-DFO-girentuximab (i.e., within ten physical half-lives of Day 0)
2. Exposure to any experimental diagnostic or therapeutic agent within 30 days of planned administration of 89Zr-DFO-girentuximab (i.e., within 30 days of day 0).
3. Known uncontrolled hyperthyroidism.
4. Any planned antineoplastic therapies to be administered between administration of 89Zr-DFO-girentuximab and imaging.
5. Established diagnosis of renal cell carcinoma in the renal mass
6. Any clinically significant abnormalities detected during screening blood tests or physical exam that in the opinion of the investigator would adversely affect the participants' ability to participate in the study.
7. Known allergy, hypersensitivity, or intolerance to girentuximab or any of the components of the investigational agent.
8. Psychiatric, cognitive, or other condition that, in the opinion of the investigator, compromises full compliance with the requirements of the study.
9. Women who are pregnant or breast-feeding
10. Exposure to murine or chimeric antibodies within the last 5 years
11. Serious but non life-threatening diseases or any other health conditions which the investigator determines may impact patient safety, compliance, and the integrity of the study data.
12. Chemotherapy, radiotherapy, or immunotherapy within 4 weeks prior to the planned administration of 89Zr-DFO-girentuximab or continuing adverse effects (> Grade 1) from such therapy (Common Terminology Criteria for Adverse Events [CTCAE] version 5.0).
13. Planned antineoplastic therapies (for the period between IV administration of 89Zr-DFO-girentuximab and imaging)
14. Known hypersensitivity to girentuximab or DFO.
15. Renal insufficiency with GFR ≤ 45 mL/min/ 1.73 m^2

Date of first enrolment
12/06/2023

Date of final enrolment
30/06/2025

Locations

Countries of recruitment

Australia

New Zealand

Study participating centre
Austin Health
145 Studley Rd
Heidelberg
Australia
3084

Study participating centre
Mercy Hospital
98 MOUNTAIN ROAD, EPSOM,
AUCKLAND
New Zealand
1149

Study participating centre
Westmead Hospital
Sydney
Australia
2145

Sponsor information

Organisation
Telix International Pty Ltd

Funder(s)

Funder type
Industry

Funder Name
Telix International Pty Ltd

Results and Publications

Individual participant data (IPD) sharing plan

The datasets generated during and/or analysed during the current study are not expected to be made available due to data being the property of the study sponsor. However, the data will be analysed and shared as tables, listings and figures (TLFs) to be published in the clinical study report. The data will be analyzed using agreed-upon statistical methods to show the study end-points.
While the report may be submitted to health authorities, the relevant TLFs will likely be published in high impact journals and be presented at various conferences.
All patient data will be collected only after obtaining their consent to study participation. No patient-identifying information will be collected, or any information used which could be traced back to the patient. This study has be reviewed by various Ethics committees and they are in agreement with the sponsor's approach to maintain patient privacy and data integrity.

IPD sharing plan summary

Not expected to be made available