Clinical trial results:
Title: A confirmatory, prospective, open-label, multi-centre phase 3 study to evaluate diagnostic performance of 89Zirconium-labelled girentuximab (89Zr-TLX250) to non-invasively detect clear cell renal cell carcinoma (ccRCC) by positron-emission tomography/CT(PET/CT) imaging in patients with indeterminate renal masses (ZIRCON study).

Trial design: This was a confirmatory, prospective, open-label, multi-centre phase 3 study (ZIRCON) designed to confirm the sensitivity and specificity of PET/ computed tomography (CT) imaging with 89Zr-TLX250 to non-invasively detect ccRCC in patients with a pre-study diagnosed indeterminate renal mass (IRM) of up to 7 cm (stage cT1) who were scheduled for partial or total nephrectomy. Histological confirmation served as standard of truth, to assess sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), as well as accuracy of 89Zr-TLX250 PET/CT imaging. The qualitative 89Zr-TLX250 PET/CT imaging assessment of 3 trained independent readers blinded to patient medical history was compared to their confirmed histology data for the primary analysis.

Approximately 250 adult patients were planned to be recruited in Europe, Australia, Canada, and the USA, who had access to PET/CT imaging. The number of enrolled patients was increased to 332 to ensure adequate power to calculate both sensitivity and specificity of 89Zr-TLX250 PET/CT imaging; 300 patients were dosed.

Following informed consent, a screening visit was performed during which baseline examinations were performed. The study schedule was planned considering a delivery timeline for 89Zr-TLX250 of 7-10 days from the central study radiopharmacy, an imaging interval of 5 ± 2 days post administration (p.a.), and planned nephrectomy any time after the PET/CT imaging visit, but no later than 90 days p.a. of 89Zr-TLX250 and after image acquisition.

Treatment consisted of a single administration of the diagnostic agent for each patient.

Summary

EudraCT number	2018-002773-21
Trial protocol	NL GB BE ES
Global end of trial date	07 November 2022

Results information

Result version number	v1 (current)
This version publication date	28 December 2023
First version publication date	28 December 2023

Trial information

Trial identification

Sponsor protocol code	89Zr-TLX250-003

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03849118
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	TELIX International Pty Ltd
Sponsor organisation address	Main Office, Suite 401, 55 Flemington Road, North Melbourne, Australia, VIC 3051
Public contact	clinical trials information, ABX-CRO advanced pharmaceutical services , 0049 351214440, info@abx-cro.com
Scientific contact	clinical trials information, ABX-CRO advanced pharmaceutical services , 0049 351214440, info@abx-cro.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	27 October 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 October 2022
Global end of trial reached?	Yes
Global end of trial date	07 November 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to evaluate the sensitivity and specificity of qualitative assessment of PET/CT imaging with 89Zr-TLX250 to non-invasively detect ccRCC in patients with indeterminate renal masses, using histology as standard of truth.
The qualitative 89Zr-TLX250 PET/CT imaging assessment of 3 independent readers was the primary imaging result.
Sensitivity was defined as the proportion of patients with a true positive (TP) 89Zr-TLX250 PET/CT scan (detection of clear cell carcinoma), relative to those with positive histopathological diagnosis for ccRCC.
Specificity was the proportion of patients with a true negative (TN) 89Zr-TLX250 PET/CT imaging result (no ccRCC), relative to those with a negative histopathological diagnosis of non-ccRCC.
The positive/negative predictive values (PPV/NPV) were the probabilities that, respectively, a positive/negative histopathology diagnosis was obtained given that the result of the 89Zr-TLX PET/CT scan was positive/negative (for ccRCC).

Protection of trial subjects:

Patient accrual and histological results were centrally evaluated and monitored by an Independent Data Monitoring Committee (IDMC) blinded to 89Zr-TLX250 PET/CT images as well as to PET/CT results from the independent image reviewers.

The study protocol, amendments, the informed consent/assent form(s), and information sheets were approved by the appropriate and applicable Independent Ethics Committees (IECs) or Institutional Review Boards (IRBs).

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Conference on Harmonisation (ICH) guideline E6: Good Clinical Practice (GCP).

An informed consent form explaining the procedures of the study, including potential hazards, was reviewed and approved by the corresponding IEC/IRB before the study was allowed to start at each site. Each patient was asked to read the informed consent form and it was also verbally explained to all patients by the study staff. Each patient was given the opportunity to ask questions and the time to discuss the study and its implications with their family and surrogates. Patients were assured of their right to withdraw from the study at any time without suffering any disadvantages and without having to provide a reason for their decision.

The patient was only allowed to undergo any study specific procedures after signing the informed consent form.

Background therapy:

Prior and concomitant medication were recorded in the eCRF beginning at screening and throughout the study from Day 0, until the end of study (EOS) visit.

Anaesthetics, analgesics, sedatives and laxatives given in routinely used regimen and dosage in connection with nephrectomy were not to be recorded in the eCRF.

Prior medications (within 30 days from planned dosing visit at Day 0) and all medications (including herbal medications) taken from Day 0 until EOS had to be recorded in the patient’s eCRF, including concomitant medication or physical therapy for AEs. Vitamins, herbal preparations and other nutritional supplements were permitted during this study but had to be recorded.

Patients were allowed to be vaccinated against COVID-19; the recommendation was for the patient to be asymptomatic and having recovered from any side effects due to immunisation prior to study drug administration. The vaccine had to be listed as a concomitant medication.

Planned antineoplastic therapies were not allowed for the study period between administration of study drug and imaging.

Evidence for comparator: -

Actual start date of recruitment	14 August 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 35
Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	France: 45
Country: Number of subjects enrolled	Netherlands: 38
Country: Number of subjects enrolled	Belgium: 29
Country: Number of subjects enrolled	Spain: 4
Country: Number of subjects enrolled	Turkey: 29
Country: Number of subjects enrolled	United States: 113
Country: Number of subjects enrolled	Canada: 6
Worldwide total number of subjects	300
EEA total number of subjects	116

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	176
From 65 to 84 years	121
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

Patients were recruited at 32 centres in 9 countries with access to PET/CT imaging. Recruitment into the study continued until the number of patients required to conduct a powered statistical analysis was recruited.

Pre-assignment

Screening details:

Following informed consent, a screening visit was performed during which baseline examinations were performed. These included medical history, physical exam, vital signs, haematology and serum chemistry, urinalysis, pregnancy test, and 12 lead ECG.

Period 1

Period 1 title	Baseline (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Not applicable.

Arms

Arm title	Safety analysis set (SAF) 89Zr-TLX250 PET/CT imaging

Arm description:

The safety analysis set (SAF) consisted of all patients who received 89Zr-TLX250. The qualitative 89Zr-TLX250 PET/CT imaging assessment was performed by 3 trained independent readers blinded to patient medical history and histology results.

Arm type	Experimental
Investigational medicinal product name	89Zr-TLX250
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

The dose was a single administration of 37 MBq (±10%) 89Zr-TLX250, containing a mass dose of 10 mg of girentuximab.

Each patient received a single slow intravenous (IV) administration over a minimum of 3 minutes on Day 0 (after pre-dose assessments), at the nuclear medicine centre of the respective study site.

No dietary restrictions prior to dosing were necessary.

Imaging results for this arm were compared against confirmed histopathology diagnoses.

Number of subjects in period 1	Safety analysis set (SAF) 89Zr-TLX250 PET/CT imaging
Started	300
Completed	275
Not completed	25
Consent withdrawn by subject	5
death	1

Adverse event, non-fatal	2
Other	11
Lost to follow-up	6

Baseline characteristics

Reporting groups

Reporting group title	Safety analysis set (SAF) 89Zr-TLX250 PET/CT imaging

Reporting group description:

The safety analysis set (SAF) consisted of all patients who received 89Zr-TLX250. The qualitative 89Zr-TLX250 PET/CT imaging assessment was performed by 3 trained independent readers blinded to patient medical history and histology results.

Reporting group values	Safety analysis set (SAF) 89Zr-TLX250 PET/CT imaging	Total	
Number of subjects	300	300	
Age categorical Units: Subjects			
Adults (18-64 years)	176	176	
From 65-84 years	121	121	
85 years and over	3	3	
Age continuous Units: years			
arithmetic mean	60.9		
standard deviation	± 11.8	-	
Gender categorical Units: Subjects			
Female	86	86	
Male	214	214	
Race Units: Subjects			
American Indian or Alaskan Native	0	0	
Asian	9	9	
Black or African American	13	13	
Native Hawaiian or Other Pacific Islander	0	0	
White	277	277	
Missing	1	1	
Ethnicity Units: Subjects			
Hispanic or Latino	28	28	
Not Hispanic or Latino	272	272	

End points

End points reporting groups

Reporting group title	Safety analysis set (SAF) 89Zr-TLX250 PET/CT imaging

Reporting group description:

The safety analysis set (SAF) consisted of all patients who received 89Zr-TLX250. The qualitative 89Zr-TLX250 PET/CT imaging assessment was performed by 3 trained independent readers blinded to patient medical history and histology results.

Subject analysis set title	Full analysis set (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

The Full Analysis Set (FAS) consisted of all enrolled patients who had evaluable PET/CT imaging and a confirmed histopathology diagnosis.

Primary: 89Zr-TLX250 PET/CT imaging - Reader 01

End point title	89Zr-TLX250 PET/CT imaging - Reader 01[1]

End point description:

The primary study objective was to evaluate the diagnostic efficacy in all patients by comparing the sensitivity and specificity of 89Zr-TLX250 PET/CT imaging to thresholds of 0.70 (sensitivity) and 0.68 (specificity) for the lower 95% CI, using histology as standard of truth.

The co-primary variables as part of the primary objective were sensitivity and specificity of 89Zr-TLX250 PET/CT imaging to detect clear cell renal cell cancer (ccRCC).

The sensitivity and specificity values were determined by 3 independent readers. This endpoint included all 284 patients from the FAS.

End point type	Primary

End point timeframe:

From baseline up to Day 90

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The analyses of the primary endpoint are not yet ready for publication.

End point values	Full analysis set (FAS)			
Subject group type	Subject analysis set			
Number of subjects analysed	284			
Units: Subjects				
True positive	159			
True negative	84			
False positive	11			
False negative	30			

Statistical analyses

No statistical analyses for this end point

Primary: 89Zr-TLX250 PET/CT imaging - Reader 02

End point title	89Zr-TLX250 PET/CT imaging - Reader 02[2]

End point description:

The primary study objective was to evaluate the diagnostic efficacy in all patients by comparing the sensitivity and specificity of 89Zr-TLX250 PET/CT imaging to thresholds of 0.70 (sensitivity) and 0.68 (specificity) for the lower 95% CI, using histology as standard of truth.

The co-primary variables as part of the primary objective were sensitivity and specificity of 89Zr-TLX250 PET/CT imaging to detect clear cell renal cell cancer (ccRCC).

The sensitivity and specificity values were determined by 3 independent readers. This endpoint included all 284 patients from the FAS.

End point type	Primary

End point timeframe:

From baseline to Day 90

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The analyses of the primary endpoint are not yet ready for publication.

End point values	Full analysis set (FAS)			
Subject group type	Subject analysis set			
Number of subjects analysed	284			
Units: Subjects				
True positive	161			
True negative	84			
False positive	11			
False negative	28			

Statistical analyses

No statistical analyses for this end point

Primary: 89Zr-TLX250 PET/CT imaging - Reader 03

End point title	89Zr-TLX250 PET/CT imaging - Reader 03[3]

End point description:

The primary study objective was to evaluate the diagnostic efficacy in all patients by comparing the sensitivity and specificity of 89Zr-TLX250 PET/CT imaging to thresholds of 0.70 (sensitivity) and 0.68 (specificity) for the lower 95% CI, using histology as standard of truth.

The co-primary variables as part of the primary objective were sensitivity and specificity of 89Zr-TLX250 PET/CT imaging to detect clear cell renal cell cancer (ccRCC).

The sensitivity and specificity values were determined by 3 independent readers. This endpoint included all 284 patients from the FAS.

End point type	Primary

End point timeframe:

From baseline to Day 90

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The analyses of the primary endpoint are not yet ready for publication.

End point values	Full analysis set (FAS)			
Subject group type	Subject analysis set			
Number of subjects analysed	284			
Units: Subjects				
True positive	165			
True negative	80			
False positive	15			
False negative	24			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From baseline to Day 90	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	25.1

Reporting groups	
Reporting group title	Safety analysis set (SAF)
Reporting group description:	
The safety analysis set (SAF) consisted of all patients who received 89Zr-TLX250.	

Serious adverse events	Safety analysis set (SAF)		
Total subjects affected by serious adverse events			
subjects affected / exposed	26 / 300 (8.67%)		
number of deaths (all causes)	2		
number of deaths resulting from adverse events	2		
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 300 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Arteriosclerosis			
subjects affected / exposed	1 / 300 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 300 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Death			

subjects affected / exposed	1 / 300 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 300 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	2 / 300 (0.67%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Acute pulmonary oedema			
subjects affected / exposed	1 / 300 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pleural effusion			
subjects affected / exposed	1 / 300 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumothorax			
subjects affected / exposed	1 / 300 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Post procedural haemorrhage			
subjects affected / exposed	7 / 300 (2.33%)		
occurrences causally related to treatment / all	0 / 7		
deaths causally related to treatment / all	0 / 0		
Arterial injury			
subjects affected / exposed	1 / 300 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Post procedural bile leak			
subjects affected / exposed	1 / 300 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Post procedural complication			
subjects affected / exposed	1 / 300 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Post procedural haematuria			
subjects affected / exposed	1 / 300 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Post procedural hypotension			
subjects affected / exposed	1 / 300 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Procedural pain			
subjects affected / exposed	1 / 300 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Procedural pneumothorax			
subjects affected / exposed	1 / 300 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Tachycardia			
subjects affected / exposed	1 / 300 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Syncope			
subjects affected / exposed	2 / 300 (0.67%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

Cerebrovascular accident			
subjects affected / exposed	1 / 300 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 300 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 300 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haemoperitoneum			
subjects affected / exposed	1 / 300 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intestinal obstruction			
subjects affected / exposed	1 / 300 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	1 / 300 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Retroperitoneal effusion			
subjects affected / exposed	1 / 300 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	1 / 300 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Hepatobiliary disorders			
Ischaemic hepatitis			
subjects affected / exposed	1 / 300 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Skin and subcutaneous tissue disorders			
Subcutaneous emphysema			
subjects affected / exposed	1 / 300 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Urinary retention			
subjects affected / exposed	2 / 300 (0.67%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Acute kidney injury			
subjects affected / exposed	1 / 300 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal impairment			
subjects affected / exposed	1 / 300 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Subcapsular renal haematoma			
subjects affected / exposed	1 / 300 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinoma			
subjects affected / exposed	1 / 300 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Haematoma muscle			

subjects affected / exposed	1 / 300 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Haematoma infection			
subjects affected / exposed	1 / 300 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infection			
subjects affected / exposed	1 / 300 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Klebsiella infection			
subjects affected / exposed	1 / 300 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 300 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyelonephritis			
subjects affected / exposed	1 / 300 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	1 / 300 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	2 / 300 (0.67%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hypovolaemia			

subjects affected / exposed	1 / 300 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Safety analysis set (SAF)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	86 / 300 (28.67%)		
Injury, poisoning and procedural complications			
Procedural pain			
subjects affected / exposed	11 / 300 (3.67%)		
occurrences (all)	11		
Vascular disorders			
Hypertension			
subjects affected / exposed	6 / 300 (2.00%)		
occurrences (all)	6		
Nervous system disorders			
Headache			
subjects affected / exposed	9 / 300 (3.00%)		
occurrences (all)	9		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	8 / 300 (2.67%)		
occurrences (all)	8		
Pain			
subjects affected / exposed	7 / 300 (2.33%)		
occurrences (all)	7		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	11 / 300 (3.67%)		
occurrences (all)	11		
Constipation			
subjects affected / exposed	8 / 300 (2.67%)		
occurrences (all)	8		
Diarrhoea			

subjects affected / exposed	8 / 300 (2.67%)		
occurrences (all)	8		
Vomiting			
subjects affected / exposed	6 / 300 (2.00%)		
occurrences (all)	6		
Abdominal pain			
subjects affected / exposed	5 / 300 (1.67%)		
occurrences (all)	5		
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	7 / 300 (2.33%)		
occurrences (all)	7		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 November 2018	Main changes were: o The section on benefit risk assessment was updated o Additional morphological CT imaging was removed from the study schedule to reduce the radioactivity burden. o patient identification was adapted to a five-digit number composed of two parts to reflect the situation on site
13 December 2018	Main changes were: o Dosimetry data from previous studies were added as justification o The need for a repeat anatomical CT scan during the study was omitted o The CT scan was changed to a low-dose CT for the purpose of attenuation correction of the PET data only. o As an administrative change, the contact details of the two central labs (for histology and for safety lab assessments) were added.
22 March 2019	Main changes were: o A calibrated ionization chamber for the individual measurement of the dose of 37 MBq of 89Zr-TLX250 was added to the protocol. o Total radiation exposure was changed to reflect the whole-body exposure as a result of the imaging modalities used during the study. o A cautionary note was inserted about the risks associated with this moderate exposure and the conditions of radiological protection for caregivers. o According to new stability data for 89Zr-girentuximab, shipping and storage conditions were changed. o In response to an investigator, ultrasound imaging was explicitly excluded from the standard of care imaging collected pre-baseline. o Preliminary safety data from the bridging dosimetry study ZIRDOSE were added to the protocol to confirm the good safety profile of 89Zr-girentuximab.
15 June 2021	Main changes were: o The first secondary objective/endpoint was also defined as primary objective/endpoint, to give two co-primary objectives/endpoints. o The ranking order of the remaining objectives and endpoints was also changed, and some details were added to the objectives and endpoints for clarity. o The statistical power was adjusted to accommodate for a higher percentage of non-ccRCC patients.
01 April 2022	Main changes were: o The secondary objectives were divided and reorganised into key secondary objectives and other secondary objectives to improve clarity and prioritise statistical evaluations. o Due to the actual numbers of patients observed during trial enrolment with cT1a tumours that were ccRCC positive and ccRCC negative, the total sample size was increased to ensure a minimum of negative patients to meet the aims of the study. Therefore, the statistical sample size calculation as well as the definition of statistical power were slightly changed to adapt for patient recruitment. o Due to the higher number of patients required to be enrolled to achieve a sufficient per-protocol population, the planned duration of the study had to be extended. o In addition, some explanatory statements were added to account for FDA comments.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported