A confirmatory, prospective, open-label, multi-centre phase 3 study to evaluate diagnostic performance of ^{89}Zirconium-labelled girentuximab(^{89}Zr-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)

Short Title	^{89}Zr-TLX250 for PET/CT imaging of ccRCC – ZIRCON-Study		
Test Product:	^{89}Zr-girentuximab		
Study Purpose:	Evaluation of sensitivity and specificity of PET/CT imaging with ^{89}Zr-TLX250 in patients with indeterminate renal masses suspicious of ccRCC		
Clinical study phase:	3	**Date:**	01-APR-2022
Registration:	EudraCT/IND no. 2018-002773-21	**Version no.:**	8.0, Amendment 07
Sponsor's study no.:	^{89}Zr-TLX250-003		
Sponsor:	TELIX International Pty Ltd Main Office, Suite 401, 55 Flemington Road North Melbourne VIC 3051, Australia		

Document History:

Date	Version	Amendment
31-Aug-2018	2.0 (Initial Protocol)	NA
07-Nov-2018	3.0	Amendment 01
13-Dec-2018	4.0	Amendment 02
22-Mar-2019	5.0	Amendment 03
10-Sep-2019	5.1 (Belgium only)	Amendment 04
30-Sep-2019	6.0 (USA and Canada only)	Amendment 05
15-Jun-2021	7.0	Amendment 06
01-Apr-2022	8.0	Amendment 07

The study will be conducted in compliance with the protocol, ICH-GCP and any applicable regulatory requirements

Sponsor Approval Signature Page

We agree to conduct this trial in accordance with this clinical study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki
- Good Clinical Practice of the European Community/International Conference on Harmonisation (CPMP/ICH/135/95)
- All applicable laws and regulations.

Study title: **A confirmatory, prospective, open-label, multi-centre phase 3 study to evaluate diagnostic performance of ^{89}Zirconium-labelled girentuximab (^{89}Zr-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)**

Version: **8.0, Amendment 07**

Date: **01-Apr-2022**

DocuSigned by:
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Dr. Colin Hayward, Telix Chief Medical Officer	Signature	01-Apr-22 Date
Albert Chinhenzva Biostatistician ABX-CRO	Signature	01 APRIL 2022 Date

Principal Investigator Agreement Page

Study title: **A confirmatory, prospective, open-label, multi-centre phase 3 study to evaluate diagnostic performance of ^{89}Zirconium-labelled girentuximab (^{89}Zr-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)**

Version: **8.0, Amendment 07**

Date: **01-Apr-2022**

Principal Investigator Signature:

I confirm that I have read and that I understand this protocol and other appropriate related documentation for ^{89}Zr-girentuximab provided by the Sponsor and the coordinating CRO.

I agree to perform this study in accordance with this protocol, the ethical principles that have their origin in the Declaration of Helsinki, the International Conference on Harmonisation (ICH) guideline for Good Clinical Practice (GCP), and the applicable regulatory requirement(s).

I will also appropriately direct and assist the personnel at the trial site who will be involved in the conduct of the study.

(Name and Function) **(Signature)**	**Date**

Serious Adverse Event Reporting

Notification in case of Serious Adverse Events	
Pharmacovigilance **Medwork Pharma** **Research & Consulting**	**Phone: +30 / 21099 60971** **Fax: +30 / 21099 49485** **Mobile/emergency number: +30 / 6970804545** **Email: pharmacovigilance@medwork.gr**

Study Synopsis

Study title	A confirmatory, prospective, open-label, multi-centre phase 3 study to evaluate diagnostic performance of ^{89}Zirconium-labelled girentuximab (^{89}Zr-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)
Short title	^{89}Zr-TLX250 for PET/CT imaging of ccRCC
Clinical study phase	3
Study objective(s)	**Primary objective** 1. To evaluate sensitivity and specificity of qualitative assessment of PET/CT imaging with ^{89}Zr-TLX250 to non-invasively detect ccRCC in patients with indeterminate renal masses, using histology as standard of truth. **Secondary objectives** Key secondary objectives of this study will be: 1. To determine sensitivity of ^{89}Zr-TLX250 PET/CT imaging to detect ccRCC in the subgroup of patients with indeterminate renal masses of ≤ 4 cm in largest diameter (cT1a) 2. To determine specificity of ^{89}Zr-TLX250 PET/CT imaging to detect ccRCC in the subgroup of patients with indeterminate renal masses of ≤ 4 cm in largest diameter (cT1a) Other secondary objectives of this study will be: 3. To determine positive predictive value (PPV), negative predictive value (NPV), and accuracy of ^{89}Zr-TLX250 PET/CT imaging to detect ccRCC in patients with

	indeterminate solid renal masses, and in patients with indeterminate renal masses of ≤ 4 cm (cT1a) 4. To identify a standardized uptake value (SUV) cut-off for ^{89}Zr-TLX250, suitable to discriminate ccRCC from non-ccRCC 5. To determine inter-reader variability of diagnostic assessments of ^{89}Zr-TLX250 PET/CT images, when performed by multiple readers 6. To determine intra-reader variability of diagnostic assessment of ^{89}Zr-TLX250 PET/CT images 7. To establish safety and tolerability of ^{89}Zr-TLX250 in patients with indeterminate renal masses. 8. To evaluate sensitivity and specificity of ^{89}Zr-TLX250 PET/CT imaging to detect ccRCC in patients with IRMs ≤ 3 cm, IRMs ≤ 2 cm, and Bosniak 3 and 4 lesions **Exploratory objectives** 1. To quantitatively estimate achievable tumour uptake, retention and radiation absorbed doses (Gy) for therapeutic ^{177}Lu-girentuximab, based on single time point ^{89}Zr-girentuximab PET/CT images, a general model of average girentuximab tumour kinetics, derived from serial ^{89}Zr-girentuximab imaging, and an assumed specific activity of ^{177}Lu-girentuximab. 2. To evaluate the correlation between ^{89}Zr-TLX250 SUVs and degree of histological CAIX expression. 3. To evaluate distant masses outside the kidney identified on ^{89}Zr-TLX250 whole body PET/CT in patients who present with unexpected evidence of disseminated disease
Project code	**^{89}Zr-TLX250-003**
Investigational medicinal product (IMP)	^{89}Zr-TLX250, a chimeric monoclonal antibody (INN name: girentuximab (GTX), synonyms: cG250, TLX250) with specificity for the CAIX (carbonic anhydrase 9) antigen, radiolabelled with the positron emitting radio-metal zirconium-89 via a NSuc-DFO-TFP-ester (DFO-TFP), linked to lysine residues of GTX, to yield ^{89}Zr-DFO-TFP-GTX.
Name of active ingredients	^{89}Zr-TLX250 (synonyms: ^{89}Zr-girentuximab, ^{89}Zr-DFO-TFP-GTX)
Doses	A single administration of 37 MBq (±10%) ^{89}Zr-TLX250, containing a mass dose of 10 mg of girentuximab.
Route of administration	Slow intravenous administration (IV)
Duration of treatment	Single diagnostic administration, followed by a diagnostic scan on Day 5 ± 2 days
Reference product (RP)	Not applicable

Indication	^{89}Zr-TLX250 is being developed as a PET/CT imaging agent for the characterisation, as ccRCC or non-ccRCC, of indeterminate renal masses (IRM).
Diagnosis and main criteria for inclusion	All patients must meet all of the following criteria: 1. Written and voluntarily given informed consent 2. Male or female ≥ 18 years of age 3. Imaging evidence of a single indeterminate renal mass of ≤ 7 cm in largest diameter (tumour stage cT1) on standard of care imaging, based on national standards, not older than 90 days on Day 0, but performed before any screening procedure. 4. Scheduled for lesion resection as part of regular diagnostic work-up within 90 days from planned ^{89}Zr-TLX250 administration. 5. Negative serum pregnancy tests in female patients of childbearing potential at screening. Confirmation of negative pregnancy test result from urine within 24 hours prior to receiving investigational product. 6. For patients included in France only, verification and confirmation of their affiliation with a social security 7. Sufficient life expectancy to justify nephrectomy. 8. Consent to practise highly effective contraception until a minimum of 42 days after ^{89}Zr-TLX250 administration.
Exclusion Criteria	A patient will be excluded from participation in the trial if one or more of the following criteria are met: 1. A biopsy procedure only (rather than partial or total nephrectomy) planned for histological species delineation of IRM 2. Renal mass known to be a metastasis of another primary tumour. 3. Active non-renal malignancy requiring therapy during the time frame of the study participation. 4. Chemotherapy, radiotherapy, or immunotherapy within 4 weeks prior to the planned administration of ^{89}Zr -TLX250 or continuing adverse effects (> grade 1) from such therapy (Common Terminology Criteria for Adverse Events [CTCAE] version 5.0). 5. Planned antineoplastic therapies (for the period between administration of ^{89}Zr-TLX250 and imaging). 6. Exposure to murine or chimeric antibodies within the last 5 years. 7. Previous administration of any radionuclide within 10 half-lives of the same 8. Serious non-malignant disease (e.g. psychiatric, infectious, autoimmune or metabolic), that may interfere with the objectives of the study or with the safety or compliance of the subject, as judged by the investigator 9. Mental impairment that may compromise the ability to give informed consent and comply with the requirements of the study. 10. Exposure to any experimental diagnostic or therapeutic drug within 30 days from the date of planned administration of ^{89}Zr-TLX250

	11. Women who are pregnant or breastfeeding. 12. Known hypersensitivity to girentuximab or DFO (desferoxamine) 13. Renal insufficiency with GFR ≤ 45 mL/min/ 1.73 m² 14. Vulnerable patients (e.g. being in detention)
Study design	This will be a confirmatory, prospective, open-label, multi-centre phase 3 study to evaluate sensitivity and specificity of ^{89}Zr-TLX250 PET/CT imaging to non-invasively detect clear cell renal cell cancer (ccRCC) in adult patients with indeterminate renal masses (IRM), scheduled for partial or total nephrectomy. Histological confirmation will serve as standard of truth, to assess sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), as well as accuracy of ^{89}Zr-TLX250 PET/CT imaging. According to current clinical practice in most specialist centres, patients with an IRM of ≤ 7 cm in largest diameter (stage cT1, encompassing the subgroups cT1a ≤ 4 cm, and cT1b > 4 cm to ≤ 7cm), restricted to the kidneys are routinely subjected to partial or total nephrectomy, as this intervention has curative potential in most cases. For that reason this study will be conducted in patients with IRM of stage cT1, and histological material will be obtained as part of routine nephrectomy, circumventing the need for study-specific invasive procedures. Given a reported high rate of non-diagnostic kidney biopsies, patients scheduled to undergo kidney biopsy only, rather than nephrectomy are not eligible for this study. The proportion of patients with a stage cT1 IRM, who actually do not have ccRCC (non-ccRCC patients, i.e. those in whom following surgical removal, ccRCC can be histologically ruled out) has been reported to range between 20–40%. This proportion appears to be higher in smaller (cT1a), compared with larger (cT1b) lesions. For a total study population of cT1 patients composed of 70% of the cT1a subgroup (IRM ≤ 4 cm), and assuming 34% non-ccRCC in the cT1a subgroup, a total sample size of 252 patients provides 90% power to confirm both a sensitivity and specificity of 83%, as previously reported for cT1a lesions for prior GTX-based imaging agents (^{124}I-girentuximab, ^{111}In-girentuximab). The total sample size of 252 gives 90% power to distinguish a 68% specificity threshold, assuming a non-ccRCC rate in the cT1b subset of at least 17%. In order to ensure that a sufficient number of patients with cT1a tumour stage and sufficient patients with non-ccRCC histopathology will be included into the total study population, patient accrual and histological results will be centrally evaluated and monitored by an Independent Data Monitoring Committee (IDMC); recruitment into the study will continue until the minimum required number of patients has been recruited. The IDMC members will not have access to ^{89}Zr-TLX250 PET/CT images, nor will they have access to the PET/CT results from the independent image reviewers.

	Patients who are enrolled, but are then either not administered with study drug, or who do not undergo PET/CT imaging after administration of study drug, in whom PET/CT images can not be analysed due to technical failure, or in whom surgical material can not be assessed for presence or absence of ccRCC, are defined as drop-outs. Drop-out patients will be replaced for the primary analysis and study sample size. Missing data are not expected for efficacy outcomes involving the standard of truth (i.e., sensitivity, specificity, PPV, NPV, accuracy, inter-reader and intra-reader variability). Patients will be recruited in 35–40 renal cancer care specialist centres, who have access to state-of-the-art PET/CT imaging. Following informed consent, a screening visit will be performed during which baseline examinations will be made. The study schedule will be planned considering a delivery timeline for ^{89}Zr-TLX250 of 7 – 10 days from the central study radiopharmacy, the day of administration, a PET/CT scan of the kidneys at 5 ± 2 days post administration, and the nephrectomy to be performed any time after the PET/CT imaging visit, but no later than 90 days post administration of ^{89}Zr-TLX250. On Day 0, all successfully screened patients will undergo a slow intravenous administration over a minimum of 3 minutes with ^{89}Zr-girentuximab, at the nuclear medicine service of the respective study site. Before and after administration, safety evaluations will be made. Female patients of childbearing potential will need to have their negative pregnancy test result from screening confirmed by a negative urine pregnancy test performed within 24 hours prior to dosing. Patients, in whom unexpected evidence for disseminated disease is observed, PET/CT imaging may be extended to whole body imaging (skull base to mid-thigh) at the discretion of the investigator. Patients will be informed as part of the consent procedure that any PET imaging result will not be disclosed to them until the scheduled nephrectomy has actually been performed or until surgery has been cancelled in case metastatic disease going beyond the kidney is present. A histological tumour sample from nephrectomy (15 paraffin embedded slides) will be prepared by the local institutional pathology service, and sent to the central laboratory which will determine the histological diagnosis of the renal mass – the standard of truth - (ccRCC or non-ccRCC), and determine the degree of CAIX expression. For patients in whom unexpected evidence of disseminated disease is observed, any available tissue samples from biopsies of extrarenal lesions will also be analysed centrally. On Day 42 ± 7 days p.a., a visit will be performed for all patients, during which the potential formation of anti-drug antibodies (HACA) and safety parameters will be investigated. At the final study visit, testing for HACA will be repeated, where feasible, and all necessary safety assessment will be performed. For patients who were nephrectomised within 28 days p.a., the final

	study visit will be conducted on Day 42 (± 7 days). For patients with nephrectomy between 28 and 90 days p.a., the final study visit will be performed 35 days (± 7 days) after surgery. Image data analyses will be performed by a central image core lab. Qualitative visual analysis (presence or absence of localised ^{89}Zr-TLX250 uptake inside or in vicinity of renal lesion, as seen on contrast-enhanced pre-BL MRI or equivalent standard of care imaging with contrast agent), will be used to assess test performance of ^{89}Zr-TLX250 PET/CT imaging to detect ccRCC, using histological results from the central histological reference laboratory as standard of truth. Lesions of interest will be spatially localised by the site, and independently by the image readers. The readers of the central lab will not have access to the spatial localisation determined by the site. Reading of the images will be conducted centrally and independently by three trained readers, blinded to patient medical history and any previous histology results. ^{89}Zr-TLX250 SUVs will be determined for each tumour lesion. Receiver operating characteristics (ROC) will be analysed to identify a SUV cut-off value, most appropriate to discriminate between ccRCC or non-ccRCC (ccRCC^{negative}) as evidenced by central histology results. ^{89}Zr-TLX250 activity and antibody mass concentrations in tumour at the time of imaging (MBq/cm³, mg/cm³) will be determined, considering the absolute activity bound to the tumour, lesion volume as determined by CT/MRI, and the decay-corrected specific activity. Image-derived non-primary variables will be exploratively compared to histological and clinical parameters, where merited.
Study Participation Duration	• Screening period: 30 days (Day -30 to Day -1) • Experimental part of the study: - Treatment: IMP administered on Day 0 - Imaging visit: Day 5 ± 2 days - Surgery: any time after imaging visit, but no later than Day 90 p.a. • Day 42 ± 7 days p.a., HACA testing • Final study evaluation - HACA testing and safety assessments: either Day 42 p.a., or 35 ± 7 days after nephrectomy, depending on day of surgery
Methodology	**Pre-screen morphological image for identification of an indeterminate solid renal mass** Availability of a recent contrast-enhanced abdominal MRI or equivalent imaging modality with contrast agent as part of standard of care, not older than 90 days on Day 0, but before any screening procedure, providing evidence of a newly diagnosed, single renal mass, confined to the kidney, and

measuring ≤ 7 cm in greatest diameter (stage cT1) (inclusion criterion).

Pre-BL contrast-enhanced images will be collected for precise volumetric tumour delineation, since in the context of the study, no contrast-enhanced CT or MRI will be performed.

^{89}Zr-TLX250 PET/CT imaging

1. PET imaging

Abdominal PET/CT scans including the kidneys will be acquired over 20 minutes in a single bed position if possible at a single time point on Day 5 ± 2 post administration (p.a.) of ^{89}Zr-TLX250 using static image acquisition and low dose CT.

Patients found to have evidence of N1 or M1 disease may undergo additional whole body PET/CT imaging (skull base to mid-thigh) using 6-8 bed positions with 10 minutes acquisition time per bed position at the discretion of the treating clinician to support comprehensive staging. The additional scan if requested by the treating physician needs to be completed on Day 5 ± 2 post administration of the investigational product.

2. Qualitative ^{89}Zr-TLX250 tumour targeting

^{89}Zr-TLX250 tumour uptake will qualitatively be assessed (yes / no), considering whether or not ^{89}Zr-TLX250 binding inside or in the vicinity of the target lesion, as delineated on structural imaging (contrast-enhanced pre-BL imaging), can be detected.

3. Quantitative ^{89}Zr-TLX250 tumour targeting

Absolute activity concentrations of tracer in tumour (MBq/cm³) will be calculated using attenuation-corrected count rates, and tumour volumes, as determined by contrast-enhanced pre-BL imaging. Considering specific activity (MBq/mg), protein mass dose concentrations of tracer in tumour at the time point of imaging (mg/cm³) will be calculated.

4. Estimation of ^{177}Lu-girentuximab tumour targeting

Protein mass dose concentrations of tracer in tumour (mg/cm³) at the single time point of imaging, and a general model of average girentuximab kinetics in tumour over time (derived from sequential ^{89}Zr-TLX250 biodistribution data), will be used, to estimate possible girentuximab protein kinetics in tumour lesions over a period of one week, assuming the kinetics of diagnostic ^{89}Zr-TLX250 and therapeutic ^{177}Lu-girentuximab are essentially similar. Such protein kinetic data can be used, to generate simulated time-activitiy curves for ^{177}Lu-girentuximab in tumour for different specific activity levels, to yield estimates of achievable therapeutic absorbed doses to tumour (Gy).

Determination of histological standard of truth

Surgical resection material, along with appropriate documentation of its in situ origin (to allow identification with lesion localisation on PET images) will be sent to local pathology for routine histological

	work-up (H&E staining, histological diagnosis: ccRCC vs. non-ccRCC). In addition, non-stained slides of the indeterminate mass removed during surgery will be sent to a central histology lab, for independent determination of histological diagnosis and detection of CAIX. In addition, where available, histological diagnosis of ccRCC and the detection of CAIX will be conducted on available tissue samples from biopsies of extrarenal lesions from patients in whom unexpected evidence of disseminated disease has been observed. **Diagnostic performance** Test performance parameters (sensitivity, specificity, positive and negative predictive values, accuracy), will be determined considering visually determined qualitative ^{89}Zr-TLX250 tumour uptake (yes/no), and histology (ccRCC+/ ccRCC-) as standard of truth. **Safety** The following safety evaluations will be made: 1. Standard laboratory (haematology, biochemistry) 2. Adverse event recording (NCI-CTC v 5.0) 3. Concomitant medication recording 4. 12-lead ECG 5. Vital signs 6. HACA (human anti-chimeric antibodies)	
Type of control	Not applicable	
Planned study dates	**Start of study recruitment** Q1/2019	**End of recruitment** Q3/2022 **End of study** Q4/2022
Planned number of study centres/countries	35-40 centres in the EU (Belgium, France, Spain, the Netherlands), UK, Turkey, Australia, Canada and USA.	

<table>
<tr><td>Number of patients</td><td>Total: approximately 252 patients scheduled for partial or total nephrectomy</td></tr>
<tr><td></td><td>Sample Size:
The total number of patients expected to be enrolled is n=252: it is expected that these will include 194 patients with cT1a tumours and 58 patients with cT1b tumours
With 194 patients with cT1a tumours it is expected that these will include at least the required number of 128 patients that are ccRCC positive and 66 patients that are ccRCC negative. Based on the actual number of patients observed during trial enrolment with cT1a tumours that are ccRCC positive and ccRCC negative, the total sample size might need to be increased to ensure the minimum of at least 128 and 66, respectively. Therefore, the distribution of enrolled patients will be centrally monitored (reviewing of staging and histology (without imaging results).</td></tr>
<tr><td>Co-primary variables</td><td>Sensitivity and Specificity of ^{89}Zr-TLX250 PET/CT imaging to detect ccRCC
These will be determined, considering the histological diagnosis (ccRCC+ or ccRCC-) as determined by the central study pathology as standard of truth, and the qualitative ^{89}Zr-TLX250 tumour targeting (tracer uptake in target lesion: yes/no), as determined by visual reading, to yield a 2 x 2 table as follows:
<table>
<tr><th></th><th>ccRCC+</th><th>ccRCC-</th></tr>
<tr><td>PET+</td><td>TP</td><td>FP</td></tr>
<tr><td>PET-</td><td>FN</td><td>TN</td></tr>
</table>
Abbreviations: FN=false negative; FP=false positive; TN=true negative; TP=true positive
a) Sensitivity will be the proportion of study patients with a true positive (TP) PET scan, out of those with positive histology for ccRCC
Sensitivity (%) = TP / (TP + FN)
b) Specificity will be the proportion of study subjects with a true negative (TN) PET scan, out of those with negative histology for ccRCC
Specificity (%) = TN / (TN + FP)</td></tr>
<tr><td>Secondary variables</td><td><u>Further test performance parameters</u>
a) Positive predictive value (PPV)
PPV (%) = TP / (TP + FP)
b) Negative predictive value (PPV)
NPV (%) = TN / (TN + FN)
c) Accuracy
Accuracy (%) = TP + TN / (TP + FP + TN + FP)
<u>Standardised uptake value (SUV)</u></td></tr>
</table>

	SUV = C_{image} / (injected dose / body weight) **Inter-reader variability** Fleiss´ kappa statistics will be used to determine the agreement between the qualitative visual assessment of ^{89}Zr-TLX250 tumour targeting (tracer uptake in target lesion: yes/no), as assessed by three independent blinded readers. An intra-class kappa of 0.70 or higher will be considered as an acceptable value. Note that both sensitivity and specificity will be determined for each of three independent readers. The study will be successful if the lower bounds of the 95% confidence intervals (CIs) for sensitivity (>70%) and specificity (>68%) in at least the same 2 out of 3 independent readers. **Intra-reader variability** Cohen´s kappa statistics will be used to determine the reproducibility of the qualitative visual assessment by individual readers when analysing the same data repeatedly. **Safety** a) General safety parameters: Frequency of occurrence and severity of abnormal findings in safety investigations (physical examination, vital signs, 12-lead ECG, clinical laboratory, AEs, concomitant medication) b) HACA **Exploratory Variables** a) In situ biological half-life of girentuximab; achievable therapeutic absorbed dose to tumour (Gy) for several specific activities and hypothetical activity doses of ^{177}Lu. b) Sub group analysis based on tumour characteristics. c) Correlation between ^{89}Zr-TLX250 SUVs and degree of histological CAIX expression. d) Qualitative ^{89}Zr-TLX250 tumour targeting (tracer uptake in extrarenal lesion: yes/no), as determined by visual reading.
Plan for statistical analysis	To take multiple testing for the two co-primary endpoints into account, testing will occur in a strictly sequential order. Firstly, the observed sensitivity will be compared against a predefined minimum expected threshold for sensitivity, using a binominal confidence interval. If the null hypothesis for sensitivity testing can be rejected, the test for specificity is performed using the same methodology, applying a predefined threshold for specificity. This strategy ensures a global level of significance of $p < 0.05$. Reader variability, as the most important secondary objectives will be determined using Kappa statistics. All other secondary variables will be analysed descriptively using exploratory statistics.

Table 1 Schedule of Study Assessments

^{89}Zr-girentuximab (^{89}Zr-TLX-250) for PET/CT Imaging of ccRCC (ZIRCON Study)

	Pre-screening	Screening	Study Period								Final Study Visit	
Examination/Evaluation			Treatment					Imaging	Surgery	Post-imaging Study Visit	If surgery within 28 days p.a.	If surgery 28 to 90 days p.a.
Time point	Pre-BL	BL	0									
Days	-90 to -1	-30 to -1	0					5±2**	90***	42±7	42±7	35±7 post surgery
Hours*			Pre-dose	dosing	0.5	1	2					
Abdo MRI with contrast or equivalent imaging[A]	x											
Informed consent		x										
Review Inclusion/Exclusion criteria		x										
General												
Medical history / Interim history		x	x									
Physical Exam		x									x	x
Vital Signs		x	x		x	x	x			x		x
Haematology & Serum Chemistry[H]		x	x					x			x	x
Urinalysis (Dipstick)[H]		x	x					x			x	x
Pregnancy Test[B]		x	x							X		
12 lead ECG		x	x				x					
^{89}Zr - girentuximab PET/CT imaging												
^{89}Zr girentuximab administration				x								
Abdominal PET/CT[C]								x				
Whole Body PET/CT[D]								x[D]				
Standard of truth determination												
Pre-scheduled nephrectomy (SoC)[E]								←	→ x			
Central histology								←	→ x			
Safety												
Concomitant medications		x	x ←					→ x	x	x		x
Baseline findings / adverse events		x	x ←					→ x	x	x		x
Anti-drug antibody / HACA blood draw[G]		x								x		x

*) hours post administration (p.a.)
**) not sooner than 72 hours p.a.
***) any time after imaging visit, but no later than 90 days p.a.

(A) Evidence of an indeterminate renal mass (IRM). MRI or equivalent standard of care imaging with contrast agent from within 3 months (90 days) of D0 is acceptable; ultrasound is not acceptable.
(B) Pregnancy test for pre-menopausal female patients at baseline, and re-test with urine pregnancy test pre-dose (within 24 hours before dosing) and on day 42 ±7.
(C) Abdominal PET + low dose CT to be conducted for all patients
(D) In case of unexpected evidence of disseminated disease (N1, M1) on imaging, patients may receive an additional whole body PET/CT from skull base to mid-thigh for complete staging at the descretion of the investigator.
(E) Standard of care (SoC): partial or total nephrectomy, open or laparoscopic, as locally established
(F) Histology to characterise ccRCC and degree of CAIX expression
(G) HACA: Human anti-chimeric antibody
(H) Safety laboratory up to 10 days before surgery including day of surgery

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List of Abbreviations

AE	Adverse event
ADR	Adverse drug reaction
BP	Blood pressure
BT	Body temperature
CAIX	Carbonic anhydrase IX
ccRCC	Clear cell renal cell carcinoma
CRA	Clinical research associate
CRO	Contract research organisation
CT	Computed tomography
CTCAE	Common criteria for adverse events
DFO	Desferoxamine
eCRF	Electronic case report form
ECG	Electrocardiogram
EDC	Electronic data capture
EOS	End of study
FAS	Full analysis set
FDA	Food and Drug Administration
FN	False negative
FP	False positive
F/U	Follow-up
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GMP	Good Manufacturing Practice
GTX	Girentuximab
HACA	Human anti-chimeric antibody
HR	Heart rate
ICH	International Conference on Harmonisation
IDMC	Independent data monitoring committee
IEC	Independent ethics committee

IMP	Investigational medicinal product
INR	International normalised ratio
IRB	Institutional review board
IRM	Indeterminate renal mass
ISF	Investigator´s site file
IV	Intravenous
mAb	Monoclonal antibody
MBq	Megabecquerel
MIRD	Medical Internal Radiation Dose
mSv	Millisievert
mGy	Milligray
MRI	Magnetic resonance imaging
NPV	Negative predictive value
p.a.	Post administration
PET	Positron-emission tomography
PI	Principal Investigator
PPV	Positive predictive value
Pre-BL	Pre-baseline
RCC	Renal cell carcinoma
ROC	Receiver operating characteristics
RP	Reference product
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SPECT	Single photon emission computed tomography
SRM	Small renal masses
SUV	Standardized uptake value
TMF	Trial master file
TN	True negative
TP	True positive

WB	Whole body

Glossary

Equivalent imaging modality as part of the standard of care	In the context of this study, “equivalent imaging” means tomographic anatomical imaging, preferably with contrast media, of the abdominal region and/or any other clinically indicated anatomical region

Study Administrative Structure

Responsibility	Name	Affiliation / Address
Sponsor	Telix International Pty Ltd	Main Office, Suite 401, 55 Flemington Road North Melbourne VIC 3051 Australia
Coordinating CRO (for imaging and data management as well as monitoring of European sites)	ABX-CRO	ABX-CRO advanced pharmaceutical services Forschungsgesellschaft m.b.H. Schössergasse 19 D-01067 Dresden – Germany Tel: +49-351-214 44-0 Fax: +49-351-214 44-15 http://www.abx-cro.com
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1 Introduction

Small renal masses (SRM) of unknown origin are frequently detected due to more frequent radiologic evaluations of the abdomen. Conventional imaging methods cannot reliably distinguish benign solid lesions from renal cell carcinoma (RCC) (Kutikov et al., 2006, Snyder et al., 2006, Schachter et al., 2007). This frequently leads to the difficult decision for urologists whether to perform a (partial) nephrectomy on a potentially benign mass or to refrain from surgery and enter patients with a potentially aggressive malignancy into a follow-up protocol until disease progression occurs. Specimens obtained by ultrasound- or computed tomography (CT)–guided biopsies have a relatively high sensitivity and specificity, but the procedures are invasive and require close follow-up of the patient (Lebret et al., 2007, Volpe et al., 2008). In addition, pooled sensitivity of fluorine-18-fluorodeoxyglucose positron-emission tomography (^{18}F-FDG-PET) imaging for detecting primary RCC was found to be only 62% (Wang et al., 2012). Post-operative benign disease was found in 15% to 30% of clinical T1a lesions in patients with a presurgical diagnosis of suspected renal cancer (Kutikov et al., 2006, Snyder et al., 2006, Schachter et al., 2007). In consequence, more advanced imaging methods are needed to prevent invasive biopsies or unnecessary surgeries, and to improve the detection of lesions suspected for metastatic and local recurrence RCC.

1.1 Background

Zirconium-89 (^{89}Zr) is coupled safely to the monoclonal antibody (mAb) using a succinylated derivative of desferrioxamine B (DFO-TFP) as bifunctional chelate. After intracellular catabolism of the radio-conjugate, ^{89}Zr stays in the target cells.

^{89}Zr-TLX250 is under clinical development as a tracer for renal tumour masses and metastases using PET imaging.

Preclinical studies suggest that labelling girentuximab with the residualizing positron emitter ^{89}Zr leads to higher tumour uptake and more sensitive detection of ccRCC lesions than the non-residualizing ^{124}I (Cheal et al., 2014) and that it is able to detect very small tumours and metastases down to 100 mg (Brouwers et al., 2004), or 7 mm^3 (Stillebroer et al., 2013).

The clinical potential of ^{89}ZrPET and PET/CT for tumour detection was initially demonstrated in head-and-neck cancer patients (Börjesson et al., 2009), and has since emerged as a promising imaging method for tumour targeting mAbs (Dijkers et al., 2010; Rizvi et al., 2012; Gaykema et al., 2013; van Asselt et al., 2014; Oosting et al., 2015).

Also for the diagnostic work-up of patients with either newly diagnosed renal lesions of unknown biological dignity, or for patients with an established diagnosis of ccRCC and a suspected progression or recurrence, the non-invasive detection of CAIX-expressing viable tumour tissue by molecular imaging with ^{89}Zr-TLX250 PET, may contribute to an improved clinical decision making in RCC patients. The existing experience from the proof-of-principle study (No. 08121986, ZIRDEE) suggests, that ^{89}Zr-TLX250 has the potential to (a) avoid unnecessary surgical interventions in

benign disease, (b) support minimal invasive treatment options such a partial nephrectomy, (c) improve staging of metastatic disease by whole body imaging, and (d) provide a functional imaging tool, allowing to non-invasively monitor the biological behaviour of indeterminate lesions following a conservative active surveillance strategy (Hekman et al., 2018).

Currently, SPECT/CT imaging using ^{111}In-labeled girentuximab is frequently used for the diagnosis of RCC. Girentuximab is a monoclonal antibody that recognises carbonic anhydrase IX (CAIX), a cell surface antigen abundantly expressed in renal cancer (Steffens et al., 1997). More than 95% of clear cell renal cancers express CAIX and the antigen is not found in normal renal tissue or in benign cysts. In an extensive analysis, the binding of girentuximab to normal human tissues was found to be restricted to the gastric and intestinal epithelium, the large biliary ducts in the liver, and some pancreatic acini (Oosterwijk et al., 1986). An IgG1 chimeric version of monoclonal antibody girentuximab (cG250) was constructed by Centocor (Malvern, PA). When girentuximab is labelled with a radionuclide it can be used as an imaging probe for SPECT or PET. After intravenous administration of this probe, both primary tumour, lymph nodes, and distant metastases can be assessed by non-invasive whole-body PET or SPECT imaging. Because of its specific and high level of expression, CAIX is an excellent target for imaging clear-cell renal cell cancer (ccRCC) lesions. The advantages of girentuximab imaging are that it is non-invasive and does not require the use of intravenous iodine contrast agents, which makes it suitable for patients with an impaired renal function.

Numerous studies were performed using radiolabelled girentuximab in ccRCC patients in the past 20 years, and more than 2,500 girentuximab administrations have been performed worldwide in several clinical trials since its discovery (Muselaers et al., 2013, 2014, Steffens et al., 1997, 1998, 1999; Brouwers et al., 2002, 2003, 2004, 2005; Oosterwijk et al., 2003; Stillebroer et al., 2013; Divgi et al., 1998, 2004). No severe side effects or allergic reactions to the antibody infusions have been reported to date. In these studies, the pharmacokinetics, toxicity, immunogenicity, and imaging characteristics of radiolabelled girentuximab in ccRCC patients were determined, and the feasibility to detect ccRCC lesions using radiolabelled girentuximab was demonstrated. Clear cell RCC is the most common subtype of renal cancer (80%), and has a higher metastatic potential than e.g., papillary or chromophobe RCCs. It is therefore especially important to detect ccRCC with high accuracy.

There is extensive experience with the ability of girentuximab radiolabelled with ^{131}I, ^{111}In, ^{177}Lu, ^{90}Y and ^{124}I to target ccRCC lesions in animals as well as in patients (Muselaers et al., 2013, 2014, Steffens et al., 1997, 1998, 1999; Brouwers et al., 2002, 2003, 2004, 2005; Oosterwijk et al., 2003; Stillebroer et al., 2013; Divgi et al., 1998, 2004). In 2007, Divgi et al. reported the possibility of specifically detecting ccRCC preoperatively with PET using ^{124}I-labeled girentuximab in 16 patients with renal masses. 15 of 16 clear-cell carcinomas were identified accurately by PET, and all nine non-clear-cell renal masses were negative for the tracer. The false negative PET in one patient with ccRCC was probably because of extensive necrosis. The sensitivity of ^{124}I-cG250 PET for ccRCC in this trial was 94%; the negative predictive value was 90%, and specificity and positive predictive accuracy were both 100% (Divgi et al., 2007). In 2012 Divgi et al. confirmed the high accuracy of

^{124}I-girentuximab PET/CT in the preoperative, non-invasive identification of ccRCC in 195 patients. They showed that the sensitivity (86%; 95%-confidence interval [CI], 75–97) and specificity (86%; 95%-CI, 69–100) of ^{124}I-girentuximab were markedly higher than those of conventional CT (Divgi et al., 2012). At Radboud UMC, girentuximab labelled with the gamma-emitting radionuclide indium-111 (^{111}In-grientuximab) is used to detect ccRCC lesions. In 2013 a retrospective analysis was performed with 22 patients with a SRM to assess the diagnostic value of ^{111}In-girentuximab SPECT/CT (Muselaers et al., 2013). Uptake of ^{111}In-girentuximab in the lesion was seen in 15/15 patients with ccRCC and in 1 patient with a papillary type II RCC. No uptake was reported in 6 patients, and they either did not have a ccRCC or showed no progression on long-term follow-up. Furthermore ^{111}In-girentuximab imaging proved to be valuable in 7 patients suspected of relapse or metastatic ccRCC. In four of these patients, the lesions showed preferential uptake of ^{111}In-girentuximab and local or systemic treatment was initiated. In three other cases, no ^{111}In-girentuximab targeting was observed. During follow-up of these three patients, one showed progression, for which systemic treatment was started. In the two other patients, no progression occurred, suggesting a benign nature of the lesions.

Distinct advantages of PET and PET/CT as compared to SPECT are the superior resolution, the short acquisition time for whole-body 3D images, and the potential for quantitative analysis of tumour targeting. Clinical PET trials with ^{89}Zr-labeled mAbs have been performed or are ongoing with at least 15 mAbs, including most of the FDA approved mAbs. ^{89}Zr-PET has become an integrated part of the mAb development programs of several of the world-leading pharmaceutical and biotech companies. Girentuximab can be stably labelled with the PET radionuclide ^{89}Zr (^{89}Zr-girentuximab) and in preclinical studies the in vivo distribution of ^{89}Zr-girentuximab was shown to be identical to that of ^{111}In-girentuximab (Brouwers et al. 2004). In addition, due to prolonged trapping of the radiolabel in the tumour and simultaneous washout from normal tissues, PET imaging with ^{89}Zr-girentuximab was shown to be superior to ^{124}I-girentuximab (Cheal et al., 2014). Combining the superior characteristics of PET with the use of the residualizing ^{89}Zr radionuclide are major steps forward in the development of this imaging biomarker.

1.2 Rationale of the Study

The early identification of ccRCC is crucial for planning possible surgery and treatment. Radiolabelled girentuximab has been shown in several studies, that it has useful targeting properties to detect ccRCC in PET/CT imaging. The tumour cell specificity of ^{89}Zr-girentuximab using PET is able to differentiate between ccRCC and tumour or metastases from other origin, as well as differentiating from non-malignant renal masses, and thus avoid repeated biopsy or unnecessary surgery. It is anticipated to develop ^{89}Zr-girentuximab (^{89}Zr-TLX250) as an improved imaging agent for ccRCC.

In a single-centre, single-arm and open label proof-of-concept study No. 08121986 (Phase 2b – ZIRDEE study), conducted and recently completed by Radboud, 30 patients suspected of primary, recurrent or metastatic ccRCC and in whom conventional diagnostics were inconclusive, were included. A PET/CT was acquired 4 to 5 days after single intravenous administration of 5 mg

^{89}Zr-TLX250 (37 MBq). Preliminary results of this study suggest that ^{89}Zr-TLX250 PET imaging can have a positive impact on clinical decision-making management of ccRCC. The extent of the tumour disease can be evaluated, the number of metastatic sites can be identified, and the imaging distinguishes solitary and oligometastatic ccRCC from more extensive metastatic ccRCC. The results of the study also demonstrated the capability of ^{89}Zr-TLX250 to differentiate between ccRCC and non-malignant tumours of the kidneys based on histology results.

Results of a bridging study (ZIRDOSE), investigating the safety and tolerability and the impact of two different mass doses (5 mg and 10 mg) of the antibody on biodistribution and tracer uptake has been completed. The study showed a safety profile similar to that of other radiolabelled monoclonal antibodies, and favourable imaging properties of the 10 mg mass dose compared to the 5 mg mass dose.

According to current clinical practice in most specialist centres, patients with an IRM of ≤ 7 cm in largest diameter (stage cT1, encompassing the subgroups cT1a ≤ 4 cm, and cT1b > 4 cm to ≤ 7 cm), restricted to the kidneys are routinely subjected to partial or total nephrectomy, as this diagnostic intervention has curative potential in most cases.

The aim of this phase 3 study (ZIRCON) is to investigate the potential of ^{89}Zr-TLX250 to determine whether an IRM of ≤ 7 cm (stage cT1) has the aggressive ccRCC phenotype verified by histopathology as standard of truth.

1.3 Benefit-Risk Assessment

Girentuximab is a monoclonal antibody against carbonic anhydrase IX (CAIX), a cell surface antigen that is expressed abundantly in renal cancer (Steffens et al., 1997). More than 95% of clear cell renal cancers express CAIX. In an extensive analysis, the binding of girentuximab to normal human tissues was found to be restricted to the gastric and intestinal epithelium, the large biliary ducts in the liver, and some pancreatic acini.

There is more than 20 years of experience in humans with SPECT or PET imaging using girentuximab labelled with various radioligands including ^{124}I and ^{111}In. These studies investigated the pharmacokinetics, toxicity, immunogenicity, and imaging characteristics of radiolabelled girentuximab in ccRCC patients, and demonstrated the feasibility to detect ccRCC lesions using radiolabelled girentuximab. Although never observed in previous trials, allergic-type reactions are possible during and immediately following the administration of girentuximab. There are extensive safety data in numerous studies, more than 2500 administrations of girentuximab have been performed in several clinical studies, unlabelled girentuximab has been administered to 545 patients across 5 studies and radiolabelled girentuximab has been administered to >500 patients. In clinical studies administration of Zirconium-89 (^{89}Zr) labelled monoclonal antibodies were proven to be safe (Börjesson et al., 2009, Oosting et al., 2015).

In preclinical studies imaging using ^{89}Zr-girentuximab was proven to be safe and feasible. No local or systemic side effects were observed. Girentuximab can be stably labelled with the PET radionuclide ^{89}Zr the in-vivo biodistribution of ^{89}Zr-TLX250 was shown to be identical to that of ^{111}In-girentuximab (Brouwers et al., 2004). ^{89}Zr-TLX250 was shown to have higher diagnostic resolution ^{124}I-girentuximab in animal studies due to prolonged trapping of the radiolabel in the tumour and simultaneous washout from normal tissues (Cheal et al., 2014).

The pharmacokinetics and pharmacodynamics of ^{131}I-girentuximab were studied by Steffens et al. (1997). For large kidney tumours overall tumour uptake ranges from 2.4% to 9.0%. The mean blood clearance curves of girentuximab fitted a two-compartment model: a distribution phase and an elimination phase. The half-life of the distribution phase was 3.8 hours (SD 2.0 hours). The half-life of the elimination phase was dependent on the protein dose level. At the 2 mg protein dose level, $t_{1/2}$, was significantly lower ($t_{1/2}$ = 39.6 ± 9.6 hours), compared with the other, higher protein dose levels ($t_{1/2}$ = 68.5 ± 13.5 hours). Loh et al. showed in 1998 that there is a wide variability in pharmacokinetic parameters among patients. This reflects the differences in individual patient clearance and exchange kinetics of girentuximab (Loh et al., 1998).

In a clinical phase 1 study investigating safety, tolerability, imaging characteristics, biodistribution and dosimetry, ^{89}Zr-TLX250 was found to be safe, and to provide improved imaging characteristics, compared to ^{124}I-girentuximab, in line with preclinical findings (Cheal et al., 2014).

In the present phase 3 ZIRCON trial, ^{89}Zr-TLX250 will be administered as a single dose with 37 MBq of ^{89}Zr as an imaging agent. The total girentuximab dose will be adjusted to 10 mg in 0.9% saline. This is a radioactivity dose which is established in mAb imaging with ^{89}Zr.

Radiation dosimetry was evaluated in a bridging dosimetry study ZIRDOSE investigating the safety and tolerability of ^{89}Zr-girentuximab. The whole body effective dose for administration of ^{89}Zr-girentuximab in this phase 1 study was 0.487 ± 0.014 mSv/MBq using the FDA-approved dose calculation tool OLINDA 1.1 and the ICRP 60 standard (Stabin et al., 2005). The absorbed/effective dose was calculated accordingly and resulted in a total whole body effective dose of 18.0 ± 0.5 mSv for 37 MBq. When a newer software IDAC-Dose 2.1 and the ICRP 103 standard (Andersson et al., 2017) is used, the resulting effective dose will be 0.551 ± 0.030 mSv/MBq or 20.5 ± 1.1 mSv for 37 MBq.

Preliminary safety data in the bridging study (ZIRDOSE) with ^{89}Zr-girentuximab administered to 5 patients per 5 mg and 10 mg girentuximab mass dose, each, did not prompt any safety concern over the treatment. In the course of the study, no treatment-related SAEs or SUSARs were reported from any of the 10 patients. The severe SAE of postoperational bleeding was considered by the investigator as not related to the study treatment. A total of 7 AEs were experienced by 4 patients. An unlikely or no relationship to treatment was assessed by the investigator for 6 AEs. Mild nausea in one patient was considered by the investigator as possibly related to the study treatment.

All patients within the present phase 3 ZIRCON trial will undergo an abdominal PET/CT scan. The CT scan will be a low-dose CT for the purpose of attenuation correction of the PET data only. In

order to keep the effective dose of this abdominal low-dose CT within a specified limit of 1 mSv, or less, the acquisition parameters for the low-dose CT will be restricted. These parameters for imaging will be defined in a separate subject imaging manual.

The combined whole body effective dose of ^{89}Zr-girentuximab administration and abdominal low-dose CT is expected to be below 20 mSv based on the accepted standard OLINDA 1.1 and ICRP 60, or below 23 mSv based on IDAC-Dose 2.1 and ICRP 103, for all patients. The lifetime attributable risk for incidence of radiation-induced cancer for an effective dose of 23 mSv is 0.4% (ICRP 103, 2007), which is comparable to the risk from a diagnostic CT of chest, abdomen and pelvis (Smith-Bindman et al., 2009).

In the context of this phase 3 trial, no additional diagnostic CT will be performed. Patients with suspected metastatic disease may undergo an optional additional whole body PET/CT scan, which would result in an additional radiation dose from the low-dose CT of approx. 3 mSv applying the same restrictions on the CT acquisition protocol as mentioned above.

Given the well-known safety and tolerability of radiolabelled girentuximab, confirmed for ^{89}Zr-TLX250 in the context of a phase I safety study, and further considering the low antibody doses used in this study, no harmful effects exceeding the risk of established diagnostic imaging procedures are to be expected. The results of this study may contribute to the development of ^{89}Zr-TLX250 as an improved imaging agent for ccRCC, allowing to avoid or delay the need for partial or total nephrectomy - a procedure associated with up to 20% overall complication, and 0.5% – 1.0% lethality rate (Lowrance et al., 2010) – in patients with renal lesions of indeterminate dignity. Although, highly unlikely, ^{89}Zr-TLX250 may cause allergic-type reactions. The study centres are well equipped to treat allergic/anaphylactic reactions.

2 Study Objectives

2.1 Primary Objective

The primary objective of this study will be:

To evaluate sensitivity and specificity of qualitative assessment of PET/CT imaging with ^{89}Zr-TLX250 to non-invasively detect ccRCC in patients with indeterminate renal masses, using histology as standard of truth.

2.2 Secondary Objectives

Key Secondary objectives of this study will be:

1. To determine sensitivity of ^{89}Zr-TLX250 PET/CT imaging to detect ccRCC in the subgroup of patients with indeterminate renal masses of ≤ 4 cm in largest diameter (cT1a)
2. To determine specificity of ^{89}Zr-TLX250 PET/CT imaging to detect ccRCC in the subgroup of patients with indeterminate renal masses of ≤ 4 cm in largest diameter (cT1a)

Other Secondary objectives of this study will be:

3. To determine positive predictive value (PPV), negative predictive value (NPV), and accuracy of ^{89}Zr-TLX250 PET/CT imaging to detect ccRCC in patients with indeterminate solid renal masses, and in patients with indeterminate renal masses of ≤ 4 cm (cT1a)
4. To identify a standardized uptake value (SUV) cut-off for ^{89}Zr-TLX250, suitable to discriminate ccRCC from non-ccRCC
5. To determine inter-reader variability of diagnostic assessments of ^{89}Zr-TLX250 PET/CT images, when performed by multiple readers
6. To determine intra-reader variability of diagnostic assessment of ^{89}Zr-TLX250 PET/CT images
7. To establish safety and tolerability of ^{89}Zr-TLX250 in patients with indeterminate renal masses.
8. To evaluate sensitivity and specificity of ^{89}Zr-TLX250 PET/CT imaging to detect ccRCC in patients with IRMs ≤ 3 cm, IRMs ≤ 2 cm, and Bosniak 3 and 4 lesions.

2.3 Exploratory Objectives

Exploratory objectives will be:

1. To quantitatively estimate achievable tumour uptake, retention and radiation absorbed doses (Gy) from therapeutic ^{177}Lu-girentuximab, based on single time point ^{89}Zr-TLX250 PET/CT images, a general model of average girentuximab tumour kinetics, derived from serial ^{89}Zr-girentuximab imaging, and an assumed specific activity of ^{177}Lu-girentuximab.

2. To evaluate the correlation between ^{89}Zr-TLX250 SUVs and degree of histological CAIX expression

3. To evaluate the distant masses outside the kidney identified on ^{89}Zr-TLX250 whole body PET/CT in patients who present with unexpected evidence of disseminated disease

3 Overview of Methodology and Design

3.1 Study Design

This will be a confirmatory, prospective, open-label, multi-centre phase 3 study (ZIRCON) in adult patients with pre-study imaging evidence of indeterminate renal masses (IRM) of ≤ 7 cm in largest diameter, and scheduled for partial or total nephrectomy as part of their standard of care. The study is designed to evaluate sensitivity and specificity of ^{89}Zr-TLX250 PET/CT imaging to non-invasively detect clear cell renal cell cancer (ccRCC).

Histological confirmation will serve as standard of truth, to assess sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), as well as accuracy of ^{89}Zr-TLX250 PET/CT imaging.

Consequently, this study will be conducted in patients with IRM of stage cT1, in which histological material is obtained as part of routine nephrectomy, circumventing the need for study-specific invasive procedures. Given a reported high rate of non-diagnostic kidney biopsies, patients scheduled to undergo kidney biopsy only, rather than nephrectomy are not eligible for this study.

Approximately 252 adult patients will be recruited in 35 – 40 renal cancer care specialist centres in Europe (Belgium, France, Spain, the Netherlands), UK, Turkey, Australia, Canada and USA, who have access to state-of-the-art PET/CT imaging. The number of enrolled patients may be increased to ensure adequate precision in measuring both sensitivity and specificity of ^{89}Zr-TLX250 PET/CT imaging.

Study Conduct

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

On Day 0, all successfully screened patients will undergo a slow intravenous administration of the study drug over a minimum of 3 minutes with ^{89}Zr-TLX250, at the nuclear medicine service of the respective study site. Before and after the administration, safety evaluations will be made.

In patients, in whom unexpected evidence for disseminated disease is observed, PET/CT imaging may be extended to complete whole body imaging (skull base to mid-thigh) using 6-8 bed positions with 10 minute acquisition time per bed position at the discretion of the investigator. The additional scan if requested by the treating physician needs to be completed on Day 5 ± 2 post administration of the investigational product.

Patients will be informed as part of the consent procedure, that any PET imaging result will not be disclosed to them, until the scheduled nephrectomy has actually been performed or until surgery has been cancelled in case metastatic disease going beyond the kidney is present.

A histological tumour sample from nephrectomy (15 paraffin embedded slides) will be prepared by the local institutional pathology service, and sent to the central histological reference laboratory, which will determine the histological diagnosis of the renal mass (ccRCC or non-ccRCC), and determine the degree of CAIX expression. For patients in whom unexpected evidence of disseminated disease is observed, any available tissue samples from biopsies of extrarenal lesions will also be analysed centrally for the histological diagnosis of ccRCC and CAIX expression.

Patients who do not have an evaluable PET/CT imaging post study drug administration and do not have a confirmed histopathology diagnosis are defined as drop-outs. To ensure credibility in the assessment of sensitivity and specificity, drop-out patients will be replaced to achieve the desired sample size and power for the primary analysis.

On Day 42 ± 7 days, a post-imaging visit will be performed in all patients, during which the potential formation of anti-drug antibodies (HACA) and some safety parameters will be investigated.

A final study visit will be performed either on Day 42 ± 7 days p.a. for patients with nephrectomy within 28 days after administration of ^{89}Zr-TLX250, and 35 ± 7 days after surgery for patients with nephrectomy between 28 and 90 days p.a.

Image data analyses will be performed by a central image core lab. Qualitative visual analysis (presence or absence of localised ^{89}Zr-TLX250 uptake inside or in vicinity of the target lesion, as seen on contrast-enhanced CT or MRI), will be used to assess test performance of ^{89}Zr-TLX250 PET/CT imaging to non-invasively detect ccRCC, using histological results from the central histological reference laboratory as standard of truth.

Reading for the co-primary endpoints (sensitivity and specificity) will be conducted independently by three trained readers, blind to history, and histology results. Inter-reader concordance will be assessed using kappa statistics. Similarly, kappa statistics will be used to assess intra-reader variability, using a subset of 10% of randomly selected cases read twice by individual readers.

^{89}Zr-TLX250 SUVs will be determined for each tumour lesion. Receiver operating characteristics (ROC) will be analysed, to identify a SUV cut-off value, most appropriate to discriminate between ccRCC or non-ccRCC as evidenced by central histology results.

^{89}Zr-TLX250 activity and antibody mass concentrations in tumour at the time of imaging (MBq/cm³, mg/cm³) will be determined, considering the absolute activity bound to the tumour, lesion volume as determined by CT/MRI, and the decay-corrected specific activity.

Image-derived non-primary variables will be exploratively compared to histological and clinical parameters, where merited.

No interim analysis is planned.

The duration for the study itself including recruitment phase is estimated to be 12 months.

The study duration for a single patient will be approximately between 4 - 6 months.

3.2 Study Endpoints

The co-primary endpoints of this study are the sensitivity and specificity of ^{89}Zr-TLX250 PET/CT imaging to detect ccRCC in patients with IRM of tumour stage cT1, i.e. ≤ 7 cm in largest diameter and scheduled nephrectomy. PET/CT scans will be determined as true positive (TP) and true negative (TN) by visual reading (among 3 independent readers) and comparison to histopathological diagnosis for ccRCC. Image data analyses will be performed by a central image core lab. Qualitative visual analysis (presence or absence of localised ^{89}Zr-TLX250 uptake inside or in vicinity of lesions, as seen on contrast-enhanced pre-baseline (pre-BL) imaging), will be used to assess test performance of ^{89}Zr-TLX250 PET/CT imaging to non-invasively detect ccRCC, using histological results from the central histological reference laboratory as standard of truth.

Secondary endpoints include the determination of the study drug's potential to detect ccRCC in IRMs ≤ 4 cm in largest diameter (tumour stage cT1a), as well as determination of predictive values (standard uptake values (SUVs)) of PET signals in the kidney. Moreover, the reproducibility of the qualitative visual assessment of tumour targeting will be determined and safety and tolerability will be assessed.

Reading for the co-primary endpoints (sensitivity and specificity) will be conducted independently by three trained readers, blind to history, and histology results. Inter-reader concordance will be assessed using kappa statistics. Similarly, kappa statistics will be used to assess intra-reader variability, using a subset of 10% of randomly selected cases read twice by individual readers.

^{89}Zr-TLX250 SUVs will be determined for each tumour lesion. Receiver operating characteristics (ROC) will be analysed to identify a SUV cut-off value most appropriate to discriminate between ccRCC or non-ccRCC as evidenced by central histology results.

^{89}Zr-TLX250 activity and antibody mass concentrations in tumour at the time of imaging (MBq/cm³, mg/cm³) will be determined, considering the absolute activity bound to the tumour, lesion volume as determined by CT/MRI, and the decay-corrected specific activity, using a general model of average girentuximab kinetics in tumour over time (derived from sequential ^{89}Zr-TLX250 biodistribution data from earlier studies).

A sub-group analysis will evaluate sensitivity and specificity of ^{89}Zr-TLX250 PET/CT imaging to detect ccRCC in patients with IRMs ≤ 3 cm, IRMs ≤ 2 cm, and Bosniak 3 and 4 lesions.

3.3 Justification of the Study Design

This open-label phase 3 study is designed to confirm the sensitivity and specificity of PET/CT imaging with ^{89}Zr-TLX250 to non-invasively detect ccRCC in patients with a pre-study diagnosed IRM of ≤ 7 cm (stage cT1) who are scheduled for partial or total nephrectomy.

For the evaluation of specificity of a diagnostic imaging agent, study patients with histologically confirmed absence of the target disease (non-ccRCC) are required.

An estimated total of 252 patients with an IRM of ≤ 7 cm and scheduled partial or radical nephrectomy will be included in the study. However, this number may be increased depending on the proportion of eligible patients with stage cT1a tumours, and the proportion considered non-ccRCC patients after surgery and histological verification, in order to maintain the planned statistical robustness of the study.

In this phase 3 study, a protein mass dose of the mAb girentuximab of 10 mg is chosen. From a small clinical dose-escalation study (Steffens et al., 1997) with five protein dose levels (2, 5, 10, 25 and 50 mg) of girentuximab it can be assumed that higher doses of girentuximab (10 mg and above) result in a lower hepatic uptake and a lower bowel activity, providing a lower physiological background signal. Additionally, a mass dose of 10 mg of girentuximab is in current clinical use in the USA.

In a clinical bridging study (ZIRDOSE) investigating safety, tolerability, imaging characteristics, biodistribution and dosimetry, ^{89}Zr-TLX250 was found to be safe, and to provide improved imaging characteristics, compared to ^{124}I-girentuximab, in line with preclinical findings (Cheal et al., 2014).

In the present phase 3 trial, ^{89}Zr-TLX250 will be administered as a single dose with 37 MBq of ^{89}Zr as an imaging agent. The total girentuximab dose will be adjusted to 10 mg in 0.9% saline. This is a radioactivity dose which is established in mAb imaging with ^{89}Zr. Radiation dosimetry was evaluated in the now completed bridging dosimetry trial (ZIRDOSE) investigating the safety and tolerability of ^{89}Zr-girentuximab.

The whole body effective dose for administration of ^{89}Zr-girentuximab in this phase 1 study was 0.487 ± 0.014 mSv/MBq using the most widely established dose calculation tool OLINDA 1.1 and the ICRP 60 standard (Stabin et al., 2005). The absorbed/effective dose was calculated accordingly and resulted in a total whole body effective dose of 18.0 ± 0.5 mSv for 37 MBq.

When a newer software IDAC-Dose 2.1 and the ICRP 103 standard (Andersson et al., 2017) is used, the resulting effective dose will be 0.551 ± 0.030 mSv/MBq or 20.5 ± 1.1 mSv for 37 MBq.

All patients within the present phase 3 trial will undergo an abdominal PET/CT scan. The CT scan will be a low-dose CT for the purpose of attenuation correction of the PET data only. In order to keep the effective dose of this abdominal low-dose CT within a specified limit of 1 mSv, or less, the

acquisition parameters for the low-dose CT will be restricted. These parameters for imaging will be defined in a separate subject imaging manual.

The combined whole body effective dose of ^{89}Zr-girentuximab administration and abdominal low-dose CT is expected to be below 20 mSv based on the accepted standard OLINDA 1.1 and ICRP 60, or below 23 mSv based on IDAC-Dose 2.1 and ICRP 103, for all patients. The lifetime attributable risk for incidence of radiation-induced cancer for an effective dose of 23 mSv is 0.4% (ICRP 103, 2007), which is comparable to the risk from a diagnostic CT of chest, abdomen and pelvis (Smith-Bindman, 2009).

In the context of this phase 3 trial, no additional diagnostic CT will be performed. Patients with suspected metastatic disease may undergo an optional additional whole body PET/CT scan, which would result in an additional radiation dose from the low-dose CT of approximately 3 mSv applying the same restrictions on the CT acquisition protocol as mentioned above.

Given the well-known safety and tolerability of radiolabelled girentuximab, confirmed for ^{89}Zr-TLX250 in the context of a phase I safety study, and further considering the low antibody doses used in this study, no harmful effects exceeding the risk of established diagnostic imaging procedures are to be expected. The results of this study may contribute to the development of ^{89}Zr-TLX250 as an improved imaging agent for ccRCC, allowing to avoid or delay the need for partial or total nephrectomy - a procedure associated with up to 20% overall complication, and 0.5 – 1.0% letality rate (Lowrance et al., 2010) – in patients with renal lesions of indeterminate dignity. Although, highly unlikely, ^{89}Zr-TLX250 may cause allergic-type reactions. The study centres are well equipped to treat allergic/anaphylactic reactions.

This study does not offer any treatment for patients with ccRCC; therefore, patients will be offered state of the art therapeutic options after imaging with the study drug ^{89}Zr-TLX250. Cancer treatment will not be delayed by study participation.

3.4 Protocol Adherence

Strict adherence to all specifications laid down in this protocol is required for all aspects of the study conduct; the investigator may not modify or alter the procedures described in this protocol. If protocol modifications are necessary, all alterations that are not solely of an administrative nature will require a formal protocol amendment (see Section 13.1 for the involvement of Independent Ethics Committee(s) IEC(s) / Institutional Review Board(s) IRB(s)).

If an investigator has deviated from the protocol in order to eliminate an immediate hazard to patients, or for other inevitable medical reasons, the investigator has to document all such deviations, including the reasons thereof, and submit the document to the sponsor and the head of the medical institution as applicable.

4 Study Population

4.1 Patient Population

It is planned to have 252 adult patients with an indeterminate renal mass (IRM) on standard of care imaging, obtained at pre-study, and who are clinically suspicious for renal cell carcinoma and scheduled for partial or total nephrectomy as part of their regular diagnostic work-up/clinical care.

4.2 Eligibility

4.2.1 Inclusion Criteria

All patients must meet all of the following criteria:

1. Written and voluntarily given informed consent
2. Male or female ≥ 18 years of age
3. Imaging evidence of a single indeterminate renal mass of ≤ 7 cm in largest diameter (tumour stage cT1), on standard of care imaging based on national standards, not older than 90 days on Day 0, but performed before any screening procedure.
4. Scheduled for lesion resection as part of regular diagnostic work-up within 90 days from planned IV ^{89}Zr-TLX250 administration.
5. Negative serum pregnancy tests in female patients of childbearing potential at screening. Confirmation of negative pregnancy test result from urine within 24 hours prior to receiving investigational product.
6. For patients included in France only, verification and confirmation of their affiliation with a social security.
7. Sufficient life expectancy to justify nephrectomy.
8. Consent to practise highly effective contraception until a minimum of 42 days after IV ^{89}Zr-TLX250 administration.

4.2.2 Exclusion Criteria

A patient will be excluded from participation in the trial if one or more of the following criteria are met:

1. A biopsy procedure only (rather than partial or total nephrectomy) planned for histological species delineation of IRM.

2. Renal mass known to be a metastasis of another primary tumour.
3. Active non-renal malignancy requiring therapy during the time frame of the study participation.
4. Chemotherapy, radiotherapy, or immunotherapy within 4 weeks prior to the planned administration of ^{89}Zr -TLX250 or continuing adverse effects (> grade 1) from such therapy (Common Terminology Criteria for Adverse Events [CTCAE] version 5.0).
5. Planned antineoplastic therapies (for the period between IV administration of ^{89}Zr-TLX250 and imaging).
6. Exposure to murine or chimeric antibodies within the last 5 years.
7. Previous administration of any radionuclide within 10 half-lives of the same.
8. Serious non-malignant disease (e.g. psychiatric, infectious, autoimmune or metabolic), that may interfere with the objectives of the study or with the safety or compliance of the subject, as judged by the investigator
9. Mental impairment that may compromise the ability to give informed consent and comply with the requirements of the study
10. Exposure to any experimental diagnostic or therapeutic drug within 30 days from the date of planned administration of ^{89}Zr-TLX250
11. Women who are pregnant or breastfeeding.
12. Known hypersensitivity to girentuximab or DFO (desferoxamine)
13. Renal insufficiency with GFR ≤ 45 mL/min/ 1.73 m²
14. Vulnerable patients (e.g. being in detention)

4.2.3 Recruitment

Potential patients of this study will be recruited by the urological service of the study centre and undergo a formal screening visit. Patients will be approached to find out whether they would be interested in participating in the study. Interested patients will be provided with an information sheet and will undergo an informed consent procedure prior to any study procedures (see Section 13.2). Should the patient consent to the study, a schedule will be planned. Administration of ^{89}Zr-TLX250 on Day 0 will be performed.

Recruitment may be stopped at the sponsor's discretion. An estimated total of 252 patients with an IRM of ≤ 7 cm and scheduled partial or radical nephrectomy will be included in the study. However,

in order to maintain adequate study power, this number may be increased depending on the proportion of non-ccRCC patients after surgery and histological verification.

4.3 Withdrawal of Patients from Study Participation or Medication

4.3.1 Withdrawal

Patients may decide to withdraw from the study at any time for any reason without prejudice to their further medical care. The investigator may withdraw a patient for any of the following reasons:

- Adverse event (AE): if patient is unwilling to continue because of an AE or if continued participation of the patient would be an unnecessary risk to the patient's health, in the opinion of the investigator.
- Non-compliance
- Protocol violation
- Pregnancy
- Lost to follow-up

4.3.2 Withdrawal Procedures

Although patients are not obliged to give their reason(s) for withdrawing prematurely from a trial, the investigator should make every effort to ascertain the reason(s) for withdrawal while fully respecting the patient's rights. The investigator will make every effort to contact the patient and complete the termination page on the case report form (CRF) and, if possible, the assessments outlined for early withdrawal.

A termination eCRF page is to be completed for every patient, whether or not the patient completed the study. The reason for any early discontinuation should be indicated on this form. The primary reason for a patient withdrawing prematurely should be selected from the following standard categories of early termination:

- Safety Reason/AE: Clinical or laboratory events occurred that in the medical judgment of the investigator, for the best interest of the patient, are reasons for discontinuation. This includes serious and non-serious AEs regardless of relation to study medication.
- Protocol Violation: The patient's findings or conduct failed to meet at least one protocol entry criterion, met at least one exclusion criterion, or failed to adhere to the protocol requirements (e.g., drug non-compliance, failure to return for defined number of visits) as judged by the investigator or sponsor. The violation necessitated premature termination from the study.
- Withdrawal of Consent: The patient desired to withdraw from further participation in the study in the absence of an investigator-determined medical need to withdraw. If the patient gave a reason for withdrawing, it should be recorded in the eCRF.

- Lost to Follow-Up: The patient stopped coming for visits, patient did not undergo surgery within the specified protocol timelines, and/or study personnel were unable to contact the patient.
- Incorrect Enrolment: The patient did not meet the required inclusion/exclusion criteria for the study.

The date of study drug administration must be documented.

Appropriate follow-up of withdrawn patients will be performed, as required.

Attempts to contact a patient who withdraws from a study must be documented.

4.3.3 Replacement

A number of patients enrolled in the study may have incomplete data. Their study dispensation is as follows in Table 2 (see also Section 9.2.2).

Table 2 Study Disposition of Enrolled Patients with Incomplete Data for Primary Analysis

Reason study data are incomplete	FullAnalysis Set?	Safety Analysis Set?	Notes
Withdrawal prior to administration of IV ^{89}Zr-TLX250	No	No	Replace (All subsequent categories assume administration of IV ^{89}Zr-TLX250 occurred)
Withdrawal before PET/CT imaging	No	Yes	
PET/CT images cannot be analysed due to technical failure	No	Yes	eCRF to document technical failures
Incorrect enrolment (did not meet the required inclusion/exclusion criteria)	No	Yes	
Patient withdrawal for reasons not related to disease (pregnancy, noncompliance, etc.)	No	Yes	See section 4.3.2
Evidence of N1 or M1 disease on ^{89}Zr-TLX250 PET/CT imaging, leading to additional staging and/or change in treatment strategy.	Yes	Yes	Histopathologic determination of any lesion (primary renal or metastatic) will be taken as standard of truth
No evidence of N1 or M1 disease, and nephrectomy material not available for evaluation of presence or absence of ccRCC - for example if surgery is performed and no tissue is removed for assessment.	No	Yes	eCRF to document reasons

Sample size determination is based on the Full Analysis Set.

All patients in the Safety Analysis Set will complete final study visit procedures following withdrawal or study completion.

Patients who have received study drug and are withdrawn due to an AE related to the study drug will be included in the safety analysis.

Patients who received study PET imaging, but do not have adequate surgical material to analyse may be followed-up by further imaging at the discretion of the investigator, in the best interest of the patient.

4.4 Patient Identification

All patients who attend a screening visit will be identified by a unique identification number ("Patient Number") that consists of 5 digits in two parts:

- The site number is a 2-digit number that is provided by the sponsor or the ABX-CRO project manager prior to the start of recruitment.
- The screening number is a 3-digit number that is consecutively assigned by the site to each patient after informed consent.

Example: The first patient screened by site "01" will receive patient number 01-001.

Example: The third patient at site "12" will receive patient number 12-003.

The screening number will be assigned at the screening visit by the responsible nuclear medicine service of the study centre, if the initial review of the patient's history/patient interview indicates possible eligibility, and if the informed consent form has been signed by the patient.

Investigational sites are required to keep a patient identification list in the trial master file (TMF) (see also Section 10.4.1), identifying their patients by name, date of birth, patient number and status (screen failure/completed study/withdrawn). This list will be reviewed by assigned monitors, but has to stay on site and will not be collected, in order to protect confidentiality.

5 Study Treatment

5.1 Study Drug ^{89}Zr-TLX250

5.1.1 Chemical Properties

^{89}Zr-TLX250, is a chimeric monoclonal antibody (INN name: girentuximab) with specificity for the CAIX (carbonic anhydrase 9) antigen, radiolabelled with the positron emitting radio-metal zirconium-89. Girentuximab has a CAS number of 916138-87-9.

The chemical formula, without the ^{89}Zr and the desferrioxamine, is $C_{6460}H_{1006}N_{1718}O_{2018}S_{48}$ with a molecular mass of 146.5 kg/mol.

5.1.2 Pharmaceutical Properties

^{89}Zr-TLX250 is formulated as a solution for intravenous administration in glass vials (Europe, Australia, Turkey and Canada) or in a syringe (USA) at the nominal dosage strength 37 MBq (±10%) for single intravenous use. The ^{89}Zr-TLX250 drug product is manufactured as “ready-to-use”. The composition of ^{89}Zr-TLX250 solution for IV administration includes the active pharmaceutical ingredient in a buffered solution without other excipients, as described in the investigator’s brochure.

A complete record of batch numbers and expiry dates of all study medication will be maintained in the trial master file (TMF).

5.1.3 Storage and Handling

The product is to be shipped and stored at room temperature (15°C to 30°C) inside the lead-shielded container provided and protected from light.

The product must be handled within a hospital environment only, by an accredited radiopharmacist and/or nuclear medicine physician according to international and local radiation protection guidelines.

5.1.4 Dosage and Administration

The mass dose of ^{89}Zr-TLX250 to be used in this phase 3 study will be 10 mg, labelled with 37 MBq (±10%) ^{89}Zr per dose.

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

No dietary restrictions prior to dosing are necessary.

Please refer to the IMP Handling Manual for a detailed description. In brief, prior to administration, an indwelling intravenous catheter has to be placed into the antecubital vein or an equivalent venous access. Please refer to Figure 1.

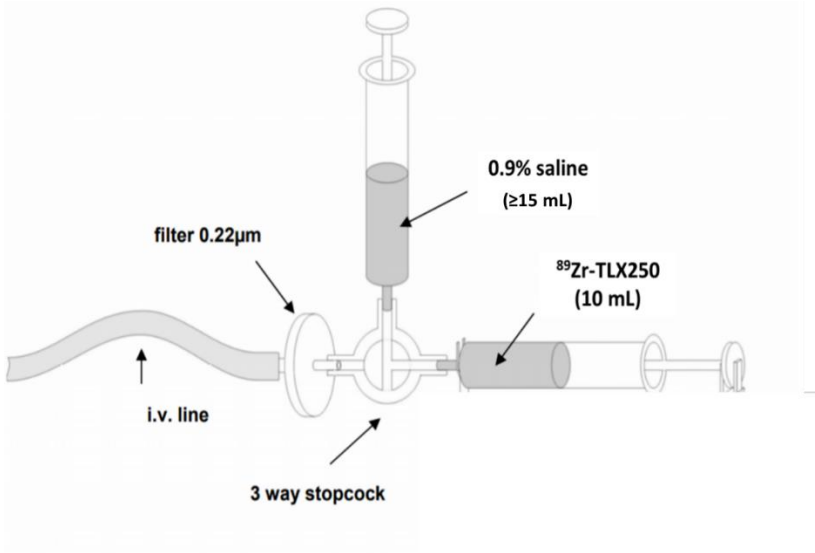

Figure 1 Infusion set with filter

Intravenous infusion set-up showing 0.22 micrometer filter in-line between syringe and infusion port (for reference only).

The radiopharmaceutical will be slowly administered through the indwelling catheter and followed with a ≥15 mL saline flush. The syringe will be assayed prior and after administration to assess the injected radioactive dose (MBq).

The dose that will be administered to the individual patient will be assessed using a dosing calibrator as outlined in the IMP Handling Manual.

5.1.5 Packaging and Labelling

^{89}Zr-TLX250 solution for IV administration will be supplied in glass vials (Europe, Australia, Turkey and Canada) or in a syringe (USA) in appropriate packaging (lead-shielded containers bearing a radioactive warning symbol in accordance with radioactive pharmaceutical requirements). The labels of the packaging supplied by the sponsor will include the following information as a minimum:

- Name and address of sponsor
- Study number
- Name of study drug and formulation
- Dose strength
- Batch number

- Expiry date
- Storage instructions
- Radioactive warning symbol
- “For Clinical Trial Use only”.

All manufacturing, formulation and labelling will be done in accordance with applicable current GMP and local guidelines and laws.

5.1.5.1 Medication Numbering

A system of medication numbering in accordance with all requirements of Good Manufacturing Practice (GMP) and any applicable regulatory requirement will be used for all study drugs. This will ensure that, for each patient, any dosing of study drug can be identified and traced back to the original bulk ware of the active ingredients.

Lists linking all numbering levels will be maintained by the institutions in charge of study drug packaging.

5.1.6 Drug Logistics and Accountability

5.1.6.1 Supply, Storage, Dispensation and Return

^{89}Zr-TLX250 solution for IV administration will be manufactured, handled and stored in accordance with GMP. ^{89}Zr-TLX250 contains radioactive material and should only be handled by personnel trained in the use of radioactive isotopes with proper shielding and monitoring. Receipt and use of ^{89}Zr-TLX250 is limited to institutions holding an appropriate handling permit by their competent national or regional authority.

All required documentation, e.g. written approval from the independent ethics committee (IEC)/institutional review board (IRB) and regulatory authority, as appropriate, needs to be provided before ordering for a site can take place. The dose order will be a direct order from the study site to the Sponsor who shall arrange appropriate supply of IMP. The coordinating CRO will also be in copy of the order (please refer to the IMP Handling Manual for details). Upon establishment of patient eligibility (see Section 4.2), the clinical site manager will order individualised doses of ^{89}Zr-TLX250 solution for IV administration, via the Sponsor for direct delivery to the study site. A dose can be cancelled at any time however if the cancellation is less than 2 days prior to administration date then the site will need to follow IMP handling manual for appropriate disposal of product. ^{89}Zr-TLX250 for IV administration will be provided by Telix International Pty Ltd and used unchanged from the original state. The treating investigator at the site will delegate ordering of ^{89}Zr-TLX250 solution for IV administration to the clinical site manager, overseeing eligibility and planned treatment dates, for direct delivery to the site to the attention of the radiopharmacist.

The IMP will be shipped at room temperature (15°C to 30°C) inside an appropriately shielded container.

Upon receipt at site, ^{89}Zr-TLX250 solution for IV administration will be kept in a secure, temperature-controlled, restricted-access location and in accordance with applicable regulatory requirements at the radiopharmacy of the site. The IMP should be stored at ambient temperature (15°C to 30°C) without freezing, and should be used by the expiration date and time printed on the label.

^{89}Zr-TLX250 doses will be accompanied by an individual certificate of analysis for each batch. Upon verification of the correct radioactive dose, as specified by the study protocol, the radiopharmacist will hand over the investigational product in a syringe, kept in a lead-shielded container, to the nuclear medicine investigator, or a designated and suitably qualified deputy for administration. This syringe will be labelled by the radiopharmacist according to institutional standards.

Storage, handling and destruction must be performed according to local guidelines regarding radioactive waste management. Details are outlined in the IMP Handling Manual.

5.1.6.2 Drug Accountability

The investigator (or radiopharmacist, whatever applicable in certain countries) will confirm receipt of the study drug by telefax or the method given in the IMP Handling Manual and will use the study drug only within the scope of this clinical study and in accordance with this study protocol. He / she will keep a record of the dispensed study drug.

Receipt, distribution and return of the study drug must be properly documented on the forms provided by the sponsor giving the following information: study protocol number, sender, receiver, date, mode of transport, quantity, batch number, expiration date and retest date, if applicable.

The coordinating clinical research organization (CRO) will monitor the drug accountability records at regular points during the study and will perform drug reconciliation at the end of the study.

5.2 Treatment Assignment

Once full establishment of eligibility by the site, the screening physician will confirm eligibility. Imaging day must be scheduled before the administration of the study drug after which, the individual patient number will be allocated.

Upon patient number assignment, the authorized site representative for the study can order the study drug through the "^{89}Zr-TLX250 clinical trial IMP Order Form" in the IMP Handling Manual.

More details on the procedure are given in the IMP Handling Manual.

5.3 Blinding

This is an open-label study.

5.4 Treatment Compliance

^{89}Zr-TLX250 will be administered by study personnel at the site. Details of each administration will be recorded in the eCRF.

Treatment of Overdose

^{89}Zr-TLX250 has a very favourable safety profile.

The risk of overdosing is minimal in this trial, as individual doses will be prepared centrally by a radiopharmaceutical contract manufacturer. Nevertheless, if accidental overdosing of radio-labelled product should occur, it will result in increased radioactive tissue exposure, with kidney and bone marrow as the critical organs.

In the event of an overdose of ^{89}Zr-TLX250, no specific treatments are available, and the patient should be treated at the discretion of the investigator.

5.5 Radiation Precautions

Medical administration of radioactive diagnostic tracers such as ^{89}Zr-TLX250 is guided by national radiation safety regulations, differing extensively between countries.

Excretion limits acceptable for discharge will be defined by the investigators in compliance with the local regulations. Commonly, patients will be discharged from the hospital 2 hours p.a., unless the investigator decides otherwise.

Patients will be encouraged to increase fluid intake and to void frequently through the first day after administration.

The following safety precautions apply for patients:

- Patients should be advised to observe rigorous hygiene in order to avoid risk of contamination of others using the same toilet facility.
- A double toilet flush is recommended.
- Patients should wash their hands thoroughly every time after using the toilet.
- During the first week after treatment, patients should follow detailed instructions, as given in the trial participant card, regarding their distance from and contact to other persons.

The following precautions apply for health care workers and for laboratory assessments:

Healthcare personnel are advised to limit the time of close contact with patients injected with (^{89}Zr)-labelled radiopharmaceuticals. Use appropriate shielding on the day of administration. Laboratory assessments will be performed by the central laboratory. Because of the potential for radioactivity in some blood and urine samples, the site personnel must adhere to their SOPs and/or any guidance and regulations for handling radioactive substances. It is mandatory to use protective high quality (latex/nitrile) gloves in any direct contact with the radiopharmaceutical (vial/syringe) and with the patient.

Please also refer to the IMP Handling Manual.

6 Therapies other than Study Treatment

6.1 Prior and Concomitant Therapy

Prior medications (within 30 days from planned dosing visit at Day 0) and all medications (including herbal medications) taken from Day 0 until EOS must be recorded in the patient's eCRF.

Treatment (concomitant medication or physical therapy) for AEs must be recorded in the AE section of the patient's eCRF.

The reason for treatment, generic name, administration form, strength, dose, frequency of dosing, route of administration, start date and, if applicable, stop date should also be recorded in the eCRF. All therapies and medications will be encoded according to the World Health Organization Drug Dictionary classification.

6.1.1 Prohibited Medication

The following medications and therapies are prohibited, and patients will be withdrawn from the study if one of the following is administered during study participation. However, patients can be included when the respective washout period before enrolment into the study is considered (Table 3).

Table 3 Prohibited Concomitant Medication

Drug / Therapy	Washout Period (before first administration of study drug)
Any radiopharmaceutical	10 half-lives of the radionuclide
Any other experimental diagnostic or therapeutic IMP	4 weeks
Any chemo-, radio- or immunotherapy	4 weeks
Exposure to murine or chimeric antibodies	5 years

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

6.1.2 Permitted Concomitant Medication

Vitamins, herbal preparations and other nutritional supplements are permitted during this study but must be recorded.

At each visit, the investigator will ask the patient whether any medication was taken since the previous visit.

Other therapy considered necessary for the patient's health and well-being may be given at the discretion of the investigator.

Patients are allowed to be vaccinated against COVID-19; the recommendation is for the patient to be asymptomatic and have recovered from any side effects prior to infusion. The vaccine must be listed as a concomitant medication.

Patients with co-morbidities such as hypertension and other chronic medical conditions requiring ongoing medications need to stay on their medications, unless they are part of the list of forbidden medication as listed above.

6.2 Post-Study Therapy

Following completion of this study, the patients will be treated according to clinical practice at the discretion of the investigator. This includes treatment of the tumour disease as well as any conditions that may arise during the trial. Description of these conditions and treatments will be provided in the study report as appropriate.

Patients who received study PET imaging, but do not have adequate surgical material to analyse may be followed-up by further imaging at the discretion of the investigator, in the best interest of the patient.

7 Schedule of Evaluations and Visit Description

7.1 Schedule of Evaluations

A detailed schedule of events is presented in Table 1

For time points when more than one procedure is scheduled, the assessments will be performed in an order as clinically appropriate (e.g. pre-dose schedule assessments in following order: vital signs, blood sampling for haematology and clinical chemistry, urine sampling, 12-lead ECG).

Concomitant medication and adverse events (AEs) will be recorded continuously from Day 0 until EOS.

7.2 Screening

Screening is to take place between 30 days and 1 day before (-30 days to -1 day) administration of ^{89}Zr-TLX250 on Day 0. Evidence of an IRM must be given from pre-study standard of care imaging (based on national standards), conducted within 90 days of Day 0 (Day -90 to Day -1), but before any screening procedure is performed.

After signing the informed consent form, patients will undergo the following screening investigations and procedures:

- Review of inclusion/exclusion criteria
- Medical history
- Physical exam
- Vital signs
- Haematology
- Serum chemistry
- Urinalysis (Dipstick)
- Pregnancy test from serum (for premenopausal female patients)
- 12-lead ECG
- Concomitant medications
- Baseline findings
- HACA testing

7.3 Treatment (Day 0)

The following examinations and procedures will be performed on Day 0:

7.3.1 Pre-dose

- Update of medical history
- Vital signs
- Haematology
- Serum chemistry
- Urinalysis (Dipstick)
- Pregnancy test from urine (for premenopausal female patients) within 24 hours before administration
- 12-lead ECG
- Concomitant medication
- Baseline findings

7.3.2 Administration of Study Drug (Time-point 0)

Administration of ^{89}Zr-TLX250 will be slowly conducted over a minimum of 3 minutes via the IV route (see Section 5.1.4).

7.3.3 Time-points 0.5 and 1 Hours p.a.

- Vital signs
- Concomitant medications
- Adverse event monitoring

7.3.4 Time-point 2 Hours p.a.

- Vital signs
- 12-lead ECG which can be conducted at 2h ± 5 mins after administration of the IMP.
- Concomitant medication
- Adverse event monitoring

7.4 Imaging (Day 5 ± 2 Days, but not sooner than 72 hours p.a.)

As part of PET/CT hybrid acquisition, abdominal PET static and low dose CT including the kidneys will be performed. In case of unexpected evidence of disseminated disease (N1, M1) on imaging, patients may have an additional whole body PET/CT scan from skull base to mid-thigh at the discretion of the treating clinician for complete staging.

- ^{89}Zr-TLX250 PET/CT imaging
  - Abdominal static PET/CT using low dose CT without contrast agent in a single bed position using an acquisition time of 20 minutes to maximise image quality.
  - Optional additional whole body PET/CT imaging (skull base to mid-thigh) using 6-8 bed positions with 10 minute acquisition time per bed position in case of unexpected evidence of disseminated disease (N1, M1). The additional scan if requested by the treating physician needs to be completed on Day 5 ± 2 post administration of the investigational product.
- Haematology
- Serum chemistry
- Urinalysis (Dipstick)
- Concomitant medications
- Adverse event monitoring

7.5 Surgery (Until Day 90 p.a.)

- Pre-scheduled partial or total nephrectomy as standard of care, open or laparoscopic, as locally established (to be performed any time after imaging, but no longer than 90 days p.a. and image acquisition). In patients who have foci of extra-renal radioactivity accumulation, a biopsy of the most accessible lesion may be carried out instead of the planned nephrectomy.
- Central histology of the renal mass or extra-renal lesion to characterise ccRCC/non-ccRCC and degree of CAIX expression
- Concomitant medications
- Adverse event monitoring

7.6 Post-Imaging Visit (Day 42 ± 7 days p.a.)

All patients will have a visit on Day 42 ± 7 days p.a., irrespective of their nephrectomy and if feasible, which will include the following examinations/procedures:

- Vital signs

- Concomitant medications
- Adverse event monitoring
- HACA testing
- Pregnancy test from urine (for premenopausal female patients)

7.7 Final Study Visit

The final study visit will be conducted depending on the nephrectomy date.

It is expected that most patients will have their partial or total nephrectomy scheduled between 28 and 90 days p.a. (see Section 7.7.2).

A minor proportion of patients is expected to have a scheduled nephrectomy early after administration of ^{89}Zr-TLX250, i.e. within 28 days p.a. (see Section 7.7.1).

7.7.1 Final Study Visit, if Surgery ≤ 28 Days p.a. (Day 42 ± 7 Days p.a.):

For patients who had their nephrectomy scheduled within 28 days p.a., the visit on Day 42 ± 7 days p.a. will serve as the final study visit and the following assessments will be done in addition to the ones described in Section 7.6 on the same day:

- Physical examination
- Haematology
- Serum chemistry
- Urinalysis (Dipstick)

7.7.2 Final Study Visit, if Surgery >28 Days p.a. (35 ± 7 Days after Surgery)

For patients whose nephrectomy was scheduled between 28 and no longer than 90 days p.a., the final study visit will be at 35 ± 7 days *after surgery*, and the following assessments will be performed.

- Physical examination
- Vital signs
- Haematology
- Serum chemistry
- Urinalysis (Dipstick)
- Concomitant medications

- Adverse event monitoring
- HACA testing

8 Procedures and Variables

Patients will provide written informed consent before any study-related procedures can be performed (see Section 13.2).

Patient-related events and activities including specific instructions, procedures, concomitant medications, dispensing of study drug, and descriptions of AEs are to be recorded in the appropriate source documents and eCRFs.

The schedule of assessments is provided in Table 1. Unless otherwise specified, all examinations and procedures will be performed by the investigator or other regular study personnel.

An additional visit can be scheduled at any time if the investigator considers it necessary.

8.1 Baseline Characteristics

It is anticipated to recruit 252 evaluable male or female patients ≥ 18 years with evidence of an IRM scheduled for partial or total nephrectomy (see Section 4.2).

8.1.1 Demographic Characteristics

The following demographic characteristics will be recorded:

- date of birth or age, depending on local EC requirements
- weight, height, ethnic origin

8.1.2 Medical and Surgical History, Baseline Findings

Medical/surgical history and medical conditions present before the administration of ^{89}Zr-TLX250 will be recorded at the screening visit and pre-dose on Day 0.

Detailed instructions on the differentiation between (i) medical / surgical history and (ii) baseline findings can be found in Section 8.8.1.1.

The patients should have a sufficient life-expectancy to justify nephrectomy (see Section 4.2).

8.1.3 Prior and Concomitant Medication

Prior and concomitant medication will be recorded on the eCRF from screening and throughout the study, beginning on Day 0, until the EOS visit (see Section 6).

The following concomitant medication should not be recorded on the eCRF:

- Anaesthetics, analgesics, sedatives and laxatives given in routinely used regimen and dosage in connection with nephrectomy

8.1.4 Pre-baseline Morphological Imaging

Patients with suspected ccRCC, typically receive abdominal MRI or CT with and without contrast agent as part of their initial diagnostic work-up. Contrast enhanced MRI or CT is also the standard for re-staging in patients after initial therapy. The imaging methodology will be conducted according to the institutional routine practise.

Pre-baseline images will be collected for evidence of a single indeterminate renal mass (IRM) and for precise volumetric tumour delineation.

A current contrast-enhanced abdominal MRI or equivalent standard of care imaging (based on national standards) with contrast agent, not older than 90 days on Day 0, but conducted before any screening procedure, should be available, providing evidence of a newly diagnosed, single renal mass, confined to the kidney, and measuring ≤ 7 cm in greatest diameter (stage cT1) (inclusion criterion). Ultrasound images will not be acceptable.

In the scope of this clinical study, no contrast-enhanced CT or MRI will be performed.

Lesions of interest will be spatially localised by the site and independently by the central image readers. The central image readers will not have access to the spatial localisation determined by the site. For lesions located within the kidney, spatial localisation should be conducted as follows

- Definition of the diseased kidney (left or right)
- Definition of the segment within the kidney containing the lesion. The segments are based on Figure 2
- In the event of a total nephrectomy the pathologist should specify the segment location that was used to provide the tissue samples used for central analysis

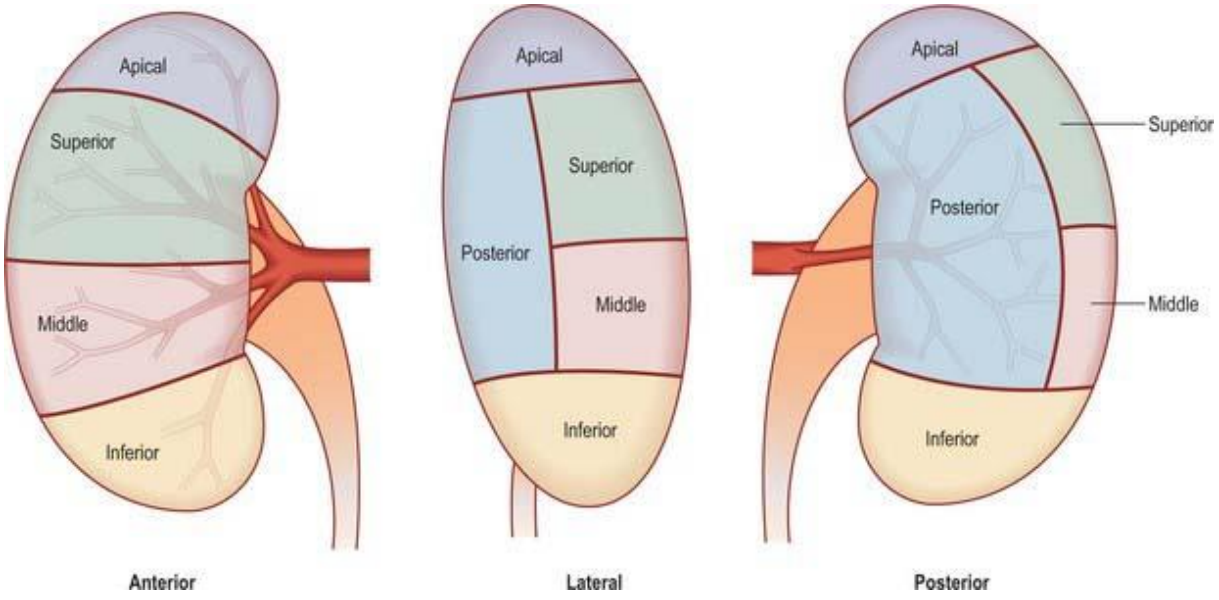

Figure 2 Overview of kidney segments for spatial localisation

From: Gray's Anatomy, 40th Edition, chapter 74, Figure 12

For patients with extra-renal disease the location of the lesion used to obtain the sample should be described by the pathologist. The independent image reviewers will define the image location of interest for extra-renal lesions in a blinded fashion.

8.1.5 Pregnancy Tests and Assessment of Postmenopausal Status

Part of the blood samples taken for the clinical laboratory tests at screening will be used to perform a serum β-HCG pregnancy test in women of childbearing potential. On Day 0, a urine pregnancy test will be performed within 24 hours before administration of study drug to confirm the negative pregnancy result from screening. Furthermore a urine pregnancy test will be performed on Day 42 ± 7 days p.a.

In postmenopausal women < 55 years a permanent postmenopausal status must be proven through history of hysterectomy or hormone analysis in serum, with estradiol < 20 pg/mL and follicle stimulating hormone FSH < 40 IU/L, or last spontaneous bleeding at least 2 years before start of the study.

8.2 Imaging during the Study

The parameters used to acquire each image in this study are outlined in the Subject Imaging Manual. The image review charter provides detailed descriptions of all imaging procedures, including baseline imaging, as well as the process used for spatial colocalisation of lesions on PET images.

8.2.1 ^{89}Zr-TLX250 PET / CT Imaging

8.2.1.1 PET/CT Imaging

Abdominal PET/CT scans including the kidneys will be acquired over 20 minutes in a single bed position at a single time point on Day 5 ± 2 post administration (p.a.) of ^{89}Zr-TLX250 using static image acquisition and low dose CT without contrast agent.

Patients found to have evidence of N1 or M1 disease may undergo additional whole body imaging (skull base to mid-thigh) using 6-8 bed positions with 10 minute acquisition time per bed position at the discretion of the treating clinician to support comprehensive staging. The additional scan if requested by the treating physician needs to be completed on Day 5 ± 2 post administration of the investigational product.

8.2.2 Imaging Analysis

Reading for the co-primary endpoints (sensitivity and specificity) will be conducted independently by 3 trained readers, blind to history, and histology results.

Details of the assessments are described in the Image Review Charter that will be provided to the central reviewer.

8.2.2.1 Qualitative ^{89}Zr-TLX250 Tumour Targeting

^{89}Zr-TLX250 tumour uptake will qualitatively be assessed (yes /no), considering whether or not ^{89}Zr-TLX250 binding inside or in the vicinity of the target lesion, as delineated on structural imaging (contrast-enhanced pre-BL imaging), can be detected.

Local and central reviewers will designate the lesions as having a status of positive (ccRCC) or negative (other than ccRCC). The interpretation of the ^{89}Zr-TLX250 PET/CT images as positive or negative for ccRCC will be made on the basis of visual examination only.

The lesion will be classified as PET-positive if:

- Radioactivity in the lesion is clearly visible, AND
- Radioactivity in the lesion is greater than that in normal tissue (for example, in ipsilateral or contralateral kidney)

If these two criteria are not met, the lesion will be classified as negative. A ^{89}Zr-TLX250 PET/CT scan is considered positive, if there is at least one positive tumour lesion.

8.2.2.2 Quantitative ^{89}Zr-girentuximab Tumour Targeting

Absolute activity concentrations of tracer in tumour (MBq/cm³) will be calculated using attenuation-corrected count rates, and tumour volumes, as determined by contrast-enhanced pre-BL MRI or equivalent imaging modality with contrast agent as part of the standard of care. Considering specific activity (MBq/mg), protein mass dose concentrations of tracer in tumour at the time point of imaging (mg/cm³) will be calculated.

8.2.2.3 Estimation of ^{177}Lu-girentuximab Tumour Targeting

Protein mass dose concentrations of tracer in tumour (mg/cm³) at the single time point of imaging, and a general model of average girentuximab kinetics in tumour over time (derived from sequential ^{89}Zr-TLX250 biodistribution data), will be used, to estimate possible girentuximab protein kinetics in tumour lesions over a period of one week, assuming the kinetics of diagnostic ^{89}Zr-girentuximab and therapeutic ^{177}Lu-girentuximab are essentially similar. Such protein kinetic data can be used, to generate simulated time-activity curves for ^{177}Lu-girentuximab in tumour for different specific activity levels, to yield estimates of achievable therapeutic absorbed doses to tumour (Gy).

8.2.2.4 Local Review of PET/CT Images

Local image review will involve qualitative assessment only and will follow the same guidelines as being used for the qualitative independent, blinded review. However, local reviewers will not be blinded with respect to patient data.

8.2.2.5 Independent Central Review of PET/CT Images

A blinded central review of the ^{89}Zr-TLX250 PET/CT images will be undertaken by an Independent Review Committee (IRC) consisting of 3 experienced reviewers not involved in the conduct of the trial. Reviewers will be independent of the study and without affiliation to the trial Sponsor. They will be blinded with regard to institution, histopathological diagnosis and clinical data. The central PET/CT reviewers will be asked to evaluate both kidneys and the link to the actually operated kidney will be done on the basis of the local pathology report retrospectively. This evaluation will be based on PET/CT images (low dose CT proportion without contrast) only.

Image sets covering extra-renal body regions will have all assessments conducted in the same way by blinded readers. The readers will localise the region within the body of the lesion of interest and then identify it as PET positive or PET negative, based on comparative regional uptake of activity. The readers will be blinded to the histology information on the tissue in question. In the event of multiple non-target lesions, the largest 2 lesions as determined by longest diameter, in each organ, will be evaluated for PET response.

Image data analyses will be performed by a central image core lab. Qualitative visual analysis (presence or absence of localised ^{89}Zr-TLX250 uptake inside or in vicinity of the target lesion, as seen on contrast-enhanced pre-BL imaging), will be used to assess test performance of ^{89}Zr-TLX250

PET/CT imaging to non-invasively detect ccRCC, using histological results from the central histological reference laboratory as standard of truth.

8.3 Determination of Histological Standard of Truth

Partial and total nephrectomy are routinely used in the management of cT1 renal tumours.

All patients enrolled in the study will already be scheduled for partial nephrectomy or total nephrectomy as part of standard work-up and management of an indeterminate renal mass.

A small number of patients may be found to have an extra-renal focus of increased radioactivity accumulation that is suspicious for metastatic disease. In these patients, the investigator may elect to undertake further diagnostic work-up including additional imaging, which may result in a change in surgical strategy. Results of the PET scans should not dictate clinical management.

If results of further standard workup confirm metastatic disease, then biopsy might be performed. Biopsy results will be considered in the exploratory analysis (See Section 9.1.2.7).

The resected lesion will be localised by the site surgeon or pathologist using the localisation scheme in 8.1.4 above. The independent image readers will not have access to this evaluation.

8.3.1 Local Pathology Assessment

Surgical resection material, along with appropriate documentation of its in situ origin, allowing identification with lesion localisation on PET images will be sent to the local pathology department for routine histological work-up (H&E staining, histological diagnosis: ccRCC vs. non-ccRCC).

If surgical material is taken from extra-renal locations then samples of this tissue should be prepared in the same way as renal samples and submitted for analysis in the same way.

The results from the local pathology assessment on diagnosis will not be part of the study.

8.3.2 Independent Central Pathologist

Representative, non-stained but paraffin-embedded slides of lesion tissue (N=15) will be sent to a central pathology service as contracted by the Sponsor. The procedures for preparation, labelling and shipment of these representative slides from the local pathologists to the central pathologist will be described in a separate Pathology Manual to be provided to the local pathologists.

The primary purpose of the independent histopathology review is the determination of the histological diagnosis of the renal mass (ccRCC or non-ccRCC) as the standard of truth for comparison with ^{89}Zr-TLX250 imaging.

For patients in whom unexpected evidence of disseminated disease has been observed, any available tissue samples from biopsies of extrarenal lesions will also be analysed centrally.

Details of the central evaluation procedure are described in a separate document prepared by the central pathology service.

8.4 Diagnostic Performance

Test performance parameters (sensitivity, specificity, positive and negative predictive values, accuracy), will be determined considering visually determined qualitative ^{89}Zr-TLX250 tumour uptake (yes/no), and histopathology (ccRCC+/ ccRCC-) as standard of truth.

8.5 Safety Evaluation

As extensive safety information on ^{89}Zr-TLX250 and on girentuximab radiolabelled with other radionuclides is already available, only the following basic standard safety evaluations will be made:

1. Standard laboratory (hematology, clinical chemistry and urinalysis)
2. Physical examination
3. 12-lead ECG
4. Vital signs
5. Adverse event recording (NCI-CTCAE v 5.0)
6. Concomitant medication recording
7. HACA testing

8.6 Sample Shipment

Study product will be shipped as requested to the site in patient specific vials (Europe, Australia, Turkey and Canada) or syringe (USA) in appropriately shielded containers. Sites should complete the "^{89}Zr-TLX250 Order Form" and submit this to the study sponsor or designated contact. Acknowledgement of order will be sent to the site. Product accountability will be monitored during the study with the appropriate study specific form.

8.7 Sample Retention / Destruction

Blood and urine samples will be immediately processed for safety reasons. No samples will be retained. Blood samples drawn for analysis will be discarded / destroyed after analysis has been completed.

8.8 Safety

8.8.1 Baseline Findings

8.8.1.1 Definition of Baseline Finding

A baseline finding is defined as any untoward medical condition in a study patient who has signed the informed consent form but not yet received the first dose of the study drug. This includes conditions stabilised by treatment. By definition, a baseline finding cannot be causally related to study drug; however, it may be causally related to the study (e.g. caused by study-conduct-related investigations).

Differentiation between medical / surgical history and baseline findings:

Conditions which started before signature of informed consent and for which no symptoms or treatment are present until the first administration of study drug (e.g., seasonal allergy without acute complaints) are recorded as medical / surgical history.

Conditions which started before signature of informed consent and for which symptoms or treatment are present between signature of informed consent and first administration of study drug (e.g. allergic pollinosis) are recorded as baseline findings.

Differentiation between baseline findings and adverse events:

Conditions (e.g., abnormal physical examination findings, symptoms, diseases, laboratory) present before the first administration of study drug will be documented as baseline findings.

Conditions which started or deteriorated after the first administration of study drug will be documented as adverse events.

Categories, assessments and documentation of baseline findings

The date and time of the first acute occurrence of the event is documented as the onset.

If the baseline finding is "continuing" into the treatment phase, no AE is to be recorded if, after start of study treatment, the event has the same or milder pattern and intensity. If the finding worsens in terms of either the pattern or intensity after study drug administration, the event must be documented as an AE.

If the event is concluded, this should be recorded in the eCRF ("resolved"). If the event vanishes but re-occurs during treatment, an AE with a start date of its re-occurrence should be entered.

All baseline findings will be assessed and documented by the investigator according to the following categories:

- Seriousness: for each baseline finding, the seriousness must be determined according to the criteria given in Section 8.8.2.2. If serious, the baseline finding has to be handled in the same way as an SAE.
- Intensity
- Specific drug treatment
- Specific non-drug treatment
- Causal relationship to study conduct
- Outcome

The intensity of an event, the causal relationship to study conduct, and the outcome of the baseline finding should be classified according to the same categories used for AEs, as specified in Section 8.8.2.2.

8.8.1.2 Serious Baseline Findings

Definition

Baseline findings will be regarded as serious if they meet the criteria used for defining serious adverse events (SAEs) and will be reported on the SAE form (see Section 8.8.2.5).

8.8.2 Adverse Events

8.8.2.1 Definition of Adverse Event

The definitions below follow International Conference on Harmonization (ICH) – Good Clinical Practice (GCP) (see also ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting):

Adverse event (AE)

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product.

By definition, for this study, all AEs are regarded as 'treatment emergent', i.e., not seen before treatment or, if already present before treatment, worsened after start of treatment.

Pre-planned or elective surgeries or therapies should be recorded in the patient's source documents but are not to be considered AEs unless there was any change to the patient's medical condition during the AE collection period.

All AEs will be assessed and documented by the investigator according to the categories detailed in Section 8.8.2.2.

8.8.2.2 Categories of Adverse Event Assessment

Seriousness

The seriousness must be determined for each AE, according to the criteria given in Section 8.8.2.5.

Intensity

The intensity of an AE is classified according to NCI-CTCAE version 5.0, taking into account the possible range of the intensity of the event:

- NCI-CTCAE Grade 1 (mild)
- NCI-CTCAE Grade 2 (moderate)
- NCI-CTCAE Grade 3 (severe)
- NCI-CTCAE Grade 4 (life-threatening)
- NCI-CTCAE Grade 5 (fatal)

Study drug action

AEs requiring any action, i.e. medication or therapy for treatment, should be treated according to recognised standards of medical care to protect the health and well-being of the patient.

Any potential study drug action to resolve the AEs is to be documented as follows

- Drug withdrawn
- Dose reduced
- Dose not changed
- Other action (stopped: definitely, temporarily with exact dates)

Any potential study drug action to resolve the AEs is to be documented in free text in the eCRF, e.g. 'dose interrupted', 'dose interrupted and re-started'.

Causal relationship to study drug

The possible causal relationship between the AE and the administration of the study drug is classified according to the following question:

“Is there a reasonable likelihood that the event was caused by the study drug?”

Possible answers are:

- Related (plausible time relationship to the administration of IMP/RP. No plausible explanation by underlying/concurrent disease or other drugs/events),
- Possible (plausible time relationship to the administration of IMP/RP, but the AE can be also plausibly explained by the underlying/concurrent disease or other medicinal products / events),
- Unlikely (unlikely temporal relationship to the administration of IMP/RP. Other medicinal products, events, and the underlying/concurrent disease provide a plausible explanation)
- Not related (clear evidence that the AE is not connected to the IMP/RP administration)
- Not assessable (no evaluation possible based on present data, additional clarification and follow-up necessary)

Causal relationship to study conduct

The possible causal relationship between the AE and any study-conduct-related procedures and activities required by the protocol is classified according to the following question:

The assessment of a possible causal relationship between the AE and the study conduct other than the relationship to study drug is based on the following question:

"*Is there a reasonable likelihood that the event was caused by the study conduct?*"

Possible answers are "related", "not related", "not assessable".

Outcome

The outcome of the AE is to be documented as follows:

- Recovered
- Recovered with sequelae
- Ongoing
- Fatal
- Unknown.

8.8.2.3 Assessment and Documentation of Adverse Events

At every assessment time point during the study until EOS, the patient will be asked a non-leading question such as "*Have you had any health problems since you were last asked / since your last visit?*". All AEs reported in response to questioning, as well as AEs reported spontaneously and

occurring at any other time, will be recorded on the 'adverse event' page(s) in the eCRF, regardless of causality.

If an AE fulfils any of the SAE criteria, both the AE pages of the eCRF and the Serious Adverse Event Form must be completed. SAEs are recorded for the entire duration of the study.

For both serious and non-serious AEs, documentation must be supported by an entry in the patient's hospital notes. Required information includes: the type of AE, seriousness of the event, start date, date of resolution, actions required, outcome and an assessment of its relationship to study drug and an estimate of its severity (using National Cancer Institute-Common Toxicity Criteria [NCI-CTCAE] criteria, version 5.0, see Appendix I). NCI-CTCAE severity will be marked in the SAE Report Form using the numeric grades: grade 1 (mild), grade 2 (moderate), grade 3 (severe), grade 4 (life-threatening) and grade 5 (fatal).

All abnormal laboratory, vital signs and 12-lead ECG results and findings from the physical examination considered to be clinically relevant by the investigator should also be recorded as AEs. If an abnormal laboratory result meets any of the SAE criteria, this must also be reported on a Serious Adverse Event Form.

All AEs that meet one criterion for "serious" require the completion of an SAE Report Form, in addition to being recorded on the AE pages of the patients' eCRF. This applies to all SAEs, whether or not they were considered to be related to study treatment.

8.8.2.4 Expected Adverse Events

Expected Conduct-related AEs

The use of an indwelling cannula for the purpose of blood sampling and administration of study drug may be accompanied by mild bruising and also, in rare cases, by transient inflammation of the vessel wall. After initial irritation, the presence of an indwelling cannula is usually painless and hardly noticeable. The same applies to single vein punctures for blood sampling.

Patients may also experience discomfort from lying in the camera, e.g. back pain.

Expected Adverse Drug Reactions

The definition below follows ICH-GCP (see also ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting):

Adverse drug reaction (ADR)

In the pre-approval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established, all noxious and unintended responses to a medicinal product related to any dose should be considered as ADR. The phrase 'responses to a

medicinal product' means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

An overview on the ADRs that were observed in clinical studies with ^{89}Zr-TLX250 or girentuximab radiolabelled with comparable radionuclides can be retrieved from the Investigator's Brochure.

Unexpected Adverse Drug Reactions

An unexpected adverse drug reaction is defined as any adverse drug experience, the nature, specificity or severity of which is not consistent with the applicable product information (e.g. investigator's brochure for an unapproved investigational product or Summary of Product Characteristics for an approved product). "Unexpected" as used in this definition refers to an adverse drug experience that has not been previously observed and included in the product information, rather than from the perspective of such experience not being anticipated from the pharmacological properties of the investigational product. Any unexpected ADR, as of formal criteria of an SAE may not be met, (see above), has to be reported by the investigator immediately after informing the sponsor, using an SAE form.

8.8.2.5 Serious Adverse Events

Definition of Serious Adverse Events

The following SAE definition is based on ICH guidelines and the final rule issued by the Food and Drug Administration (FDA) and effective 06 Apr 1998. It is to be applied to both, AEs (defined in Section 8.8.2.1) and baseline findings (defined in Section 8.8.1).

An SAE is classified as any untoward medical occurrence that at any dose

- Results in death, or
- Is life threatening, or
- Requires inpatient hospitalization or prolongation of existing hospitalization, or
- Results in persistent or significant disability / incapacity, or
- Is a congenital anomaly / birth defect.

The term 'life threatening' in the definition refers to an event in which the patient was at risk of death at the time of the event, it does not refer to an event which hypothetically might have caused death if it were more severe.

Medical and scientific judgment should be exercised in deciding whether it is appropriate to also report an AE as serious in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples of such events are intensive treatment in an

emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in inpatient hospitalization; or development of drug dependency or drug abuse.

Actions and Reporting Obligations in Case of Serious Adverse Events

All AEs that meet the criteria for serious require the completion of a SAE Report Form, in addition to being recorded on the AE pages of the patients' eCRF. This applies to all SAEs, whether or not they were considered to be related to study treatment.

SAEs must be reported within 24 hours, once the Investigator or other study site personnel are aware of the event. The reporting is delegated by the Sponsor to the coordinating CRO (see page 5). An initial written report should be prepared using the SAE Report Form and faxed to the Sponsor. This report should provide a detailed description of the SAE. Any other relevant documents such as anonymised copies of hospital records may also be attached, if available. If it is not possible to notify the Sponsor by fax within 24 hours, an initial notification by telephone should be made, to include the following information:

- Identification of the Investigator and centre.
- Patient number and initials
- Confirmation of study medication given, with date and dose.
- Concomitant medication and indication for using such medication.
- Information on the event, including date and time of onset of symptoms, severity, resolution (if applicable), date of death or other outcome (as applicable).
- Relationship with study medication in the Investigator's opinion.

All reports of death, both toxic death and death as a result of progression of disease, should be reported to the Sponsor immediately using the SAE Report Log. A detailed description of the cause of death should be provided. Autopsy reports, if available, should also be sent to the Sponsor as soon as they become available. Any additional information which becomes known to the Investigator should be provided in a follow-up report.

8.8.2.6 Other Relevant Safety Information

The following other safety relevant information must be documented in the patient medical record as well as in the AE pages of the eCRF, even if side effects (ADRs) resulting from the event were not observed.

Additionally, for all events (post-study related safety information, pregnancies, overdose, drug interaction, medication error) that fulfil the criteria for seriousness, an SAE Form must be completed by authorized staff and signed by the investigator.

a) Post-study related safety information

Any SAE (including deaths) which occurs until the final study visit should be reported by the investigator to the sponsor in case the investigator becomes aware of it.

b) Pregnancies

Every effort will be made to avoid pregnancy during the use of the IMP. Pregnancies occurring during the study (foetal exposure to the IMP) need to be reported.

In case of pregnancy during the study, the investigator should complete the Pregnancy Notification Form and send or fax it to the project manager or designee.

Follow-up information on the outcome of mother and foetus will be requested by a sponsor representative.

Overdose, interaction, and medication error

The following safety relevant information should be reported as AE or, if the reaction fulfils one of the criteria for seriousness, as SAE.

c) Drug overdose

An overdose is a deliberate or inadvertent administration of a treatment at a dose higher than specified in the protocol and higher than the known therapeutic dose that is of clinical relevance. The reaction must be clearly identified as an overdose and reported accordingly using the Adverse Event reporting form.

d) Drug interaction

A drug interaction is a situation in which a substance or medicinal product affects the activity of an IMP, i.e. increases or decreases its effects, or produces as effect that none of the products would exhibit on its own. The reaction must be clearly identified as a drug interaction.

e) Medication error

A medication error involves the inadvertent administration or unintended use of a medicinal product which may be caused by the naming, presentation of pharmaceutical form/packaging, or instructions for use/labelling. The reaction must be clearly identified as a medication error.

8.8.3 Clinical Laboratory Tests

Blood and urine samples will be taken for measurement of haematology and biochemistry parameters and dip stick urinalysis at the following time points:

- Screening Visit

- Day 0 pre-dose
- Day 5 ± 2 days
- Final study visit: Day 42 ± 7 days p.a. (for patients with nephrectomy ≤ 28 days p.a.)
- Final study visit: 35 ± 7 days after surgery (for patients with nephrectomy > 28 days p.a.)

Laboratory assessments will be performed by a central laboratory. Because of the potential for radioactivity in some blood samples, the laboratory must adhere to their SOPs and/or any guidance and regulations for handling radioactive substances.

Samples will be tested for the following parameters:

Haematology: haemoglobin, haematocrit, mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), white blood cell count (total and differential: leukocytes, neutrophils, eosinophils, basophils, lymphocytes, monocytes), red blood cells, platelets

Biochemistry: sodium, potassium, chloride, calcium, glucose, creatinine, urea, albumin, total bilirubin, aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase, gamma-glutamyl transferase (GGT), lipase, amylase, total protein

Clotting status: prothrombin time (quick), reagent-independent prothrombin ratio (international normalised ratio; INR), activated partial thromboplastin time (aPTT).

Immunogenicity: HACA.

Urinalysis: density, pH, protein, glucose, blood, urobilinogen, erythrocytes, leukocytes, ketones, bilirubin, nitrite.

A serum β-HCG pregnancy test will be performed only in premenopausal women at screening. Confirmation of the negative result will be done with a urine pregnancy test within 24 hours before administration of the study drug on Day 0 and at the Day 42 (± 7 days) time point (see Section 8.1.5).

The investigator will sign each laboratory assessment to confirm review of the results. Clinically relevant values have to be highlighted as “c.s.” (“clinically significant”). The results will be sent back to the investigational sites and be included in the patient’s eCRF.

8.8.4 Vital Signs

Body temperature and supine blood pressure and heart rate will be measured on the non-dominant arm after 5 minutes of supine rest at the following time points:

- Screening Visit
- Day 0, pre-dose, 0.5, 1 and 2 hours p.a.

- Post-Imaging Study visit Day 42 ± 7 days (for all patients)
- 35 ± 7 days after surgery (for patients with nephrectomy 28 to 90 days p.a.)

Results will be recorded in the eCRF and in the medical records.

8.8.5 12-Lead ECG

12-Lead ECGs will be recorded after 5 minutes supine rest at the following time points:

- Screening Visit
- Day 0, pre-dose and 2 hours p.a.

ECG-results will be classified by the local investigator into normal or abnormal, respectively, at baseline. Follow-up ECGs will be assessed with regard to clinically relevant changes, relative to baseline by the investigator. Relevant changes will be categorically (e.g., arrhythmia, ischemic signs, other) documented in the patient's file, and pseudonymised copies of the pertaining ECG will be collected as part of the eCRF.

8.8.6 Physical Examination

Physical examinations will be performed at the following time-points:

- Screening Visit
- Day 42 ± 7 days (for patients with nephrectomy within 28 days p.a.)
- 35 ± 7 days after surgery (for patients with nephrectomy from 28 to 90 days p.a.)

The physical examination will consist of general appearance, orientation to time, space and person, cardio-pulmonary auscultation, manual abdominal examination, and further investigation of any abnormal system, as appropriate.

8.8.7 HACA Determination in Serum

In order to detect possible formation of antibodies against girentuximab, serum samples will be collected at Screening, on Day 42 ± 7 days p.a. and at the final study visit.

The final study visit will be conducted in relation to the scheduled nephrectomy.

i) If the scheduled nephrectomy occurs > 28 day p.a. (i.e., between 28 and 90 days p.a.), the final study visit and the blood draw for HACA serum sample will be on Day 35 ± 7 days *after surgery*.

ii) If the scheduled nephrectomy occurs ≤ 28 days p.a. (i.e. within 28 days p.a.), the final study visit and the blood draw for HACA serum sample will be on Day 42 ± 7 days *after administration.*

Blood sampling will be ≤ 3 mL per sample.

An approximately 2 mL blood sample will be collected in an unheparinized (clotted) tube, stored overnight at 2-8°C and centrifuged at 1000-2000 rpm for 10 minutes. Three 200 µL serum aliquots will be transferred into three separately labelled 2 mL cryo-vial and stored at –20°C. Please refer to the central laboratory manual for details on shipping.

The presence of HACA in sera of patients will be tested quantitatively and qualitatively using validated ELISAs in the Bioanalytics Department of Agilex Biolabs Pty Ltd, South Australia, Australia.

8.9 Total Volume of Blood

A summary of the blood to be collected from each patient in this study is presented in Table 4. The maximum total volume of blood to be collected from patients over the study period will be 115 mL. For patients who will have their final study visit at Day 42 ± 7 days, 18 mL of blood less will be drawn amounting to a total of 97 mL.

Table 4 Summary of Blood Volumes Collected for Each Patient

Sample	Volume per sample	Number of samples	Total volume
Clinical laboratory tests:			
Screening (incl. β-HCG)	23 mL	1	23 mL
Day 0, pre-dose	20 mL	1	20 mL
Day 5 ± 2 days	18 mL	1	18 mL
Day 42 ± 7 days	18 mL	1	18 mL
Up to 10 days before surgery, including the day of surgery	18 mL	1	18 mL
Final visit (on Day 35 ± 7 days after surgery, if not Day 42 ± 7 days)	18 mL	1	18 mL
Overall TOTAL	-	-	115 mL

8.10 Total Radiation Exposure

The ^{89}Zr-TLX250 related radiation exposure will be 37 MBq (+/-10%) per single administration.

The combined whole body effective dose of ^{89}Zr-girentuximab administration and abdominal low-dose CT is expected to be below 20 mSv based on the accepted standard OLINDA 1.1 and ICRP 60, or below 23 mSv based on IDAC-Dose 2.1 and ICRP 103, for all patients (Section 1.3).

Patients with suspected metastatic disease may undergo an additional whole body PET/low dose CT at the discretion of the Principal Investigator. The additional radiation of this optional imaging is approx. 3 mSv.

9 Statistical Methods and Determination of Sample Size

The study design, statistical hypotheses, sample size calculations, and statistical methods selected for this study are based on previous scientific advice granted by the US Food and Drug Administration (FDA) for a planned confirmatory study with girentuximab as an imaging agent.

9.1 List of Variables and Population Characteristics

9.1.1 Co-Primary Variables

The primary study objective is to evaluate the diagnostic efficacy in all patients by comparing the sensitivity and specificity of ^{89}Zr-TLX250 PET/CT imaging to thresholds of 0.70 (sensitivity) and 0.68 (specificity), using histology as standard of truth.

The co-primary variables of this study will be the sensitivity and specificity of ^{89}Zr-TLX250 PET/CT imaging to detect ccRCC.

a) Sensitivity is defined as the proportion of study patients with a true positive (TP) ^{89}Zr-TLX250 PET/CT scan (detection of clear cell carcinoma), relative to those with positive histopathological diagnosis for ccRCC:

   Sensitivity (%) = TP / (TP + FN)

b) Specificity is defined as the proportion of study patients with a true negative (TN) ^{89}Zr-TLX250 PET/CT imaging result (no ccRCC), relative to those with a negative histopathological diagnosis of non-ccRCC (histological result:= TN + FP):

   Specificity (%) = TN / (TN + FP)

The sensitivity and specificity of ^{89}Zr-TLX250 PET/CT imaging will be compared separately to their respective prespecified thresholds. The comparison of sensitivity/specificity data will be based on data from the following 2x2 table (Table 5) which summarises the results of the qualitative ^{89}Zr-TLX250 tumour targeting (tracer uptake in target lesion: yes/no) as determined by visual reading and the central study pathology as standard of truth.

Table 5 Probability Calculated on All Cases with Positive Histopathology

		Reference Standard Histopathology (standard of Truth)		
		positive (ccRCC)	**negative (no ccRCC)**	**Total**
Outcome ^{89}Zr-TLX250 PET/CT scan	**positive (ccRCC)**	TP	FP	# of cases with positive PET/CT: TP+FP
	negative (no ccRCC)	FN	TN	# of cases with negative PET/CT: FN+TN
total		# of cases with ccRCC TP+FN	# of cases without ccRCC FP+TN	N

Abbreviations: FN = false negative; FP = false positive; TN = true negative; TP = true positive;

The point estimate of sensitivity of PET/CT is TP/(TP+FN) and the point estimate of specificity is TN/(TN+FP). Wilson's binomial (score) confidence intervals will be used to compare the 95% confidence interval lower boundary of each quantity to the threshold of 0.70 (sensitivity) and 0.68 (specificity).

Note that both sensitivity and specificity will be determined for each of three independent readers. The study will be successful if the lower bounds of the 95% confidence intervals (CIs) for sensitivity (>70%) and specificity (>68%) in at least the same 2 out of 3 independent readers.

9.1.2 Secondary Variables and Exploratory Analyses

To investigate diagnostic performance in the subgroup of patients with small lesions (cT1a, dimension ≤ 4 cm in longest diameter), sensitivity and specificity with corresponding Wilson (score) 95% CIs will be calculated for such patients.

In addition to the primary efficacy parameters (sensitivity, specificity), the positive predictive value, the negative predictive value and the accuracy will also be calculated as secondary efficacy parameters using data from patients in the subgroup of tumours ≤ 4 cm in largest diameter. Sensitivity and specificity in the cT1a group will be the key secondary endpoints; while positive predictive value, the negative predictive value and the accuracy in the cT1a group will be additional secondary endpoints.

9.1.2.1 Predictive Values and Accuracy

a) Positive predictive value (PPV)
The positive predictive value is defined as the probability that a positive histopathology diagnosis was obtained given that the result of the ^{89}Zr-TLX PET/CT scan is positive (detection of ccRCC).

$$PPV\ (\%) = TP / (TP + FP)$$

b) Negative predictive value (PPV)

The negative predictive value is defined as the probability that a negative histopathology diagnosis was obtained given that the result of the ^{89}Zr-TLX250 PET/CT scan is negative (no detection of ccRCC).

NPV (%) = TN / (TN + FN)

c) Accuracy
The accuracy or probability of a correct test result is defined as the probability that the ^{89}Zr-TLX250 PET/CT scan result is correct, i.e. the probability that the PET/CT scan is positive if the histopathological diagnosis for ccRCC is positive or that the PET/CT scan is negative if the histopathological diagnosis for ccRCC is negative.

Accuracy (%) = TP + TN / (TP + FP + TN + FP)

9.1.2.2 Standardized Uptake Value (SUV)

^{89}Zr-TLX250 SUVs will be determined for each tumour lesion. Receiver operating characteristics (ROC) will be analysed, to identify a SUV cut-off value, most appropriate to discriminate between ccRCC or non-ccRCC as evidenced by central histology results.

SUV = C_{image} / (injected dose / body weight)

9.1.2.3 Inter-reader Variability

Fleiss´ kappa statistics will be used to determine the agreement between the qualitative visual assessment of ^{89}Zr-TLX250 tumour targeting (tracer uptake in target lesion: yes/no), as assessed by three independent blinded readers (section 8.2.2.4). An intra-class kappa of 0.70 or higher will be considered as an acceptable value. Note that both sensitivity and specificity will be determined for each of three independent readers. The study will be successful if the lower bounds of the 95% confidence intervals (CIs) for sensitivity (>70%) and specificity (>68%) in at least the same 2 out of 3 independent readers.

9.1.2.4 Intra-reader Variability

Intra-reader variability will be assessed by having each of the 3 independent blinded readers perform 2 image evaluations on a randomly selected set of 10% cases. A washout period will be introduced between the two interpretations to minimize recall bias. The percent of agreement between the two interpretations will be computed for each reader. Cohen´s kappa statistics will be used to determine the reproducibility of the qualitative visual assessment by individual readers when analysing the same data repeatedly.

9.1.2.5 Sub group Analysis

Evaluation of sensitivity and specificity of ^{89}Zr-TLX250 PET/CT imaging to detect ccRCC in patients with IRMs ≤ 3 cm, IRMs ≤ 2 cm, and Bosniak 3 and 4 lesions, as follows:

1) Bosniak 3 and 4 lesions (as determined by the independent central readers)
2) Indeterminate renal masses ≤ 3 cm in largest diameter (as determined by the independent central readers)
3) Indeterminate renal masses ≤ 2 cm in largest diameter (as determined by the independent central readers)

9.1.2.6 Safety

a) General safety parameters:

Frequency of occurrence and severity of abnormal findings in safety investigations (physical examination, vital signs, 12-lead ECG, clinical laboratory, urinalysis, adverse events, concomitant medication)

b) HACA testing

9.1.2.7 Exploratory Variables

In situ biological half life of girentuximab protein in tumour lesions will be estimated, using a general model of average girentuximab kinetics in tumour tissue, derived from serial ^{89}Zr-TLX250 imaging. Based on (a) protein residence times in the lesions, (b) an assumed specific activity of therapeutic labelling with Lutetium-177 (^{177}Lu), and (c) the measured tumour lesion volume (CT dimensions), an achievable therapeutic absorbed dose to tumour (Gy), will be determined for several specific activities and hypothetical activity doses of ^{177}Lu.

Exploratory analyses will be delineated in more detail in the Statistical Analysis Plan (SAP) prior to analysis including extra-renal lesions used as a histology standard of truth (when N1 or M1 disseminated disease is suspected)

Additional exploratory investigations correlating the ^{89}Zr-TLX250 tumour lesion SUVs, semi-quantitation of CAIX expression as determined by immunohistochemisty, and evaluation of the distant masses outside the kidney identified on ^{89}Zr-TLX250 whole body PET/CT in patients with unexpected evidence of disseminated disease will be conducted.

9.1.3 Population Characteristics

Population characteristics will include:

- Clinical suspicion of ccRCC due to imaging evidence of indeterminate renal mass of ≤ 7 cm (stage cT1)
- Scheduled for total or partial nephrectomy as part of regular diagnostic work-up at a given date

Summary tables and listings will be provided for demographics and other baseline characteristics, including:

- Age, ethnic origin, sex, physical exam
- Medical/surgical history and baseline findings
- Prior and concomitant medication

9.2 Statistical and Analytical Plans

A detailed description of the study analyses and statistical methods will be presented in the Statistical Analysis Plan (SAP). The SAP will be finalized by the study physician and approved by the sponsor prior to the start of the statistical analysis.

9.2.1 General Considerations

The aim of this study is to evaluate sensitivity, specificity, PPV, NPV, as well as accuracy of ^{89}Zr-TLX250 PET/CT imaging using a 37 MBq (1 mCi) activity dose to detect ccRCC in patients with IRM of stage cT1, and who are scheduled for partial or total nephrectomy.

Histological confirmation from nephrectomy (or biopsies of extrarenal lesions from patients in whom unexpected evidence of disseminated disease is observed) will serve as standard of truth. The qualitative ^{89}Zr-TLX250 PET/CT imaging assessments of 3 independent readers will be the primary imaging result.

All data will be listed and trial summary tables will be provided. Descriptive statistics will be presented. Secondary variables will be summarized. The statistical evaluation will be performed by using SAS® statistical software (version 9.4, or higher).

9.2.2 Analysis Sets

The Full Analysis Set (FAS) will consist of all enrolled patients who have evaluable PET/CT imaging and have a confirmed histopathology diagnosis (Table 2).

The Safety Analysis Set (SAF) will consist of all patients who received ^{89}Zr-TLX250.

The Screening Analysis Set (for CONSORT-style accounting of subject disposition) will consist of all patients assigned a Patient Number (section 4.4).

All primary and secondary efficacy analyses will be carried out using the FAS.

9.2.3 Statistical Analyses

Statistical analyses will be performed after database lock, after all study data including the final study visit have been collected and cleaned.

For all variables (primary and secondary), the statistical analyses in this study will be descriptively using exploratory statistics.

Descriptive analyses will include:

- Mean, standard derivation, median and range for continuous variables,
- Median, range and frequency distribution for discrete (ordinal) variables,
- Frequency distribution for nominal variables

9.2.3.1 Analysis of Primary and Key Secondary Objectives

Within this trial, two co-primary endpoints (sensitivity and specificity) shall be analysed.

The analysis for sensitivity uses only those patients with a positive histopathological diagnosis of clear cell carcinoma. These are expected to be about 70% of the included patient population. Sensitivity of ^{89}Zr-TLX250 will be considered adequate if the **lower boundary of a 95% Wilson (score) confidence interval for sensitivity is higher than 0.7** for at least the same two of three independent readers.

The analysis for specificity uses only those patients with a negative histopathological diagnosis of clear cell carcinoma. These are expected to be about 30% of the included patient population. Specificity of ^{89}Zr-TLX250 will be considered adequate if the **lower boundary of a 95% Wilson (score) confidence interval for specificity is higher than 0.68** for at least the same two of three independent readers. Two-sided tests will be consistently used in the evaluation.

To account for multiplicity and to control Type I error under the paradigm of two co-primary endpoints, sensitivity and specificity will each be estimated at the 5% significance level. For the study to be deemed successful, the lower limit of the 95% Wilson confidence interval for both sensitivity and specifity must exceed their respective pre-specified thresholds.

Assuming the null hypothesis is rejected for both co-primary endpoints, formal statistical testing will proceed to the family of Key Secondary Endpoints (i.e., sensitivity and specificity in the cT1a group). Within this family, the fixed-sequence method will first assess sensitivity, followed by specificity. Results pertaining to specificity will only be considered formal evidence if the null hypothesis pertaining to sensitivity is rejected.

Additional details will be provided in the SAP.

9.3 Determination of Sample Size

It is planned to include approximately 252 evaluable patients in the study.

9.3.1 Sample Size Estimation

The study sample size for the population of patients with indeterminate renal mass (i.e., patients with cT1 tumors) has 2 components: Sensitivity and Specificity. Sample size is estimated for Sensitivity and Specificity, respectively, and the larger of the two estimates will represent the final study sample size. The basic assumptions underlying sample size estimation are the following:

- In the population of patients with indeterminate renal mass (i.e. cT1 patient population), approximately 70% are cT1a and 30% are cT1b patients.
- In the cT1a subpopulation, approximately a third (34%) are expected to show no signs of renal cell carcinoma following histopathology assessment (i.e. ccRCC negative).
- It is expected from a clinical standpoint that the subpopulation of cT1b patients would show a much lower rate of negative histopathologies than the cT1a subpopulation. For the purpose of powering this trial, it is assumed that the rate of non-ccRCC histopathologies in the cT1b subpopulation would be at least 17%, half the rate in the cT1a subpopulation.

Sensitivity: to ensure the study has 90% power to show that the lower limit of the 2-sided 95% confidence interval (Wilson) for sensitivity is above the critical limit (or non-inferiority limit) of 70%, the minimum sample size required for the population of cT1 patients under above assumptions is 125, when assuming a true sensitivity of 83%.

Specificity: to ensure the study has 90% power to show that the lower limit of the 2-sided 95% confidence interval (Wilson) for the specificity is above the critical limit (or non-inferiority limit) of 68%, the minimum sample size required for the population of cT1 patients under above assumptions is 252, when assuming a true specificity of 83%.

An estimated total of 252 patients with an IRM of ≤ 7 cm and scheduled partial or radical nephrectomy will be included in the study. However, in order to maintain adequate study power, this number may be increased depending on the proportion of non-ccRCC patients after surgery and histological verification.

Table 6 provides an example of the expected sample size required with different observed non-ccRCC rates.

Table 6: Planned sample size estimates*

	Outcome	Null	Alt.	Non-ccRCC Rate in CT1a Group	Non-ccRCC Rate in CT1b Group	Alpha	Power	N Total
Scenario (1)	Specificity	0.68	0.83	0.34	0.17	0.05	0.90	**252**
	Sensitivity	0.70	0.83	0.34	0.17	0.05	0.90	125
Scenario (2)	Specificity	0.68	0.83	0.25	0.20	0.05	0.90	**284**
	Sensitivity	0.70	0.83	0.25	0.20	0.05	0.90	116
Scenario (3)	Specificity	0.68	0.83	0.25	0.15	0.05	0.90	**317**
	Sensitivity	0.70	0.83	0.25	0.15	0.05	0.90	114

* Sample size estimates to achieve 90% power based on rates of non-ccRCC in both CT1a and CT1b groups. Scenario (1) represents the originally planned sample size; while Scenario (2) and Scenario (3) provide potential sample size updates based on different non-ccRCC rates.

Note that both sensitivity and specificity will be determined for each of three independent readers. The study will be successful if the lower bounds of the 95% confidence intervals (CIs) for sensitivity (>70%) and specificity (>68%) in at least the same 2 out of 3 independent readers.

9.3.2 Independent Data Monitoring Committee

An independent data monitoring committee (IDMC) will be established by the sponsor and will monitor the number of evaluable patients cT1a and cT1b tumors, and with ccRCC^{positive} ccRCC^{negative} tumors and give feedback to the sponsor on whether the planned sample size is appropriate or not.

The IDMC will evaluate patient accrual and histological results at 50% (126) and 75% (189) of evaluable cases. Counts of evaluable cases (excluding cases where ^{89}Zr-TLX250 PET/CT imaging and/or tissue collection were either not performed or are pending) in 4 categories based on initial tumour size (cT1a, cT1b) and IRM histology (ccRCC, non-ccRCC). The IDMC will provide feedback to the sponsor of whether the proposed sample size will be likely to be sufficient or not. Based upon this feedback the sponsor may consider an amendment to the protocol that could modify inclusion criteria to include only cT1a patients subsequently or to increase the sample size to ensure sufficient power.

Enrollment will not be halted during the data review procedure.

The IDMC members will not review ^{89}Zr-TLX250 PET/CT images or imaging data, nor will they have access to the results generated by either the independent image readers or the local reader.

The committee will be composed of at least three members, specialised in biostatistics, pathology and/or oncology. The committee will have the above described responsibility only that will be detailed in an IDMC charter.

10 Data Handling and Quality Assurance

10.1 Data Recording

10.1.1 Source Data and Records

Source data are defined as all information related to clinical findings, observations, or other activities in the study, written down in original records or certified copies of original records, allowing reconstruction and evaluation of the clinical study.

The investigator will maintain adequate source records (e.g. case histories or patient files for each patient enrolled). Source records should be preserved for the maximum period of time required by local regulations.

For each patient enrolled, the investigator will indicate in the source record(s) that the patient participates in this study.

All data entered in the eCRF must be supported by source data in the patient records.

10.1.2 Electronic Case Report Form (eCRF)

For this study, patient data will be entered into a sponsor defined electronic case report form (eCRF) within the Electronic Data Capture (EDC) system, transmitted electronically to the sponsor or designee and combined with data provided from other sources in a validated data system. The case report form will be supplied for recording all study data from each patient. It is the responsibility of the investigator to ensure that the eCRFs are completed in full. All data therein must be supported by source documentation at the study centre.

The investigator may authorize site staff (e.g. sub-investigators, nurses) to enter study data into the validated EDC system. This must be documented in the Delegation of Authority Log signed by the investigator.

All site personnel will be trained on the EDC system and study specific eCRFs prior to receiving access to the live database for data entry.

The site will also receive approved eCRF Completion Guidelines which will assist data entry and data issues/questions. Once the data base is active, the site will be notified to begin data entry. Additional site training may be provided as refreshers throughout the study, if needed.

The completion of study page of the eCRF must be signed by the principal investigator at the end of the study confirming that he/she is satisfied with its completion and accuracy. An eCRF must be completed for every patient who signed an informed consent. The eCRFs must be kept up-to-date so that they always reflect the latest observations on the patient.

Study monitors will perform source data verification as defined for the study.

If any errors or discrepancies in the eCRFs are found during data entry or review, discrepancies will be generated within the EDC system, and 'manual' queries will be generated by either a monitor or data management.

Discrepancies and queries can only be corrected by the investigator(s) or other authorised site personnel. Study monitors must never enter or correct date in the eCRF. An audit trail in the EDC documents all changes to the data over the entire study period.

In all cases, patient initials or personal data will not be collected by or transmitted to the sponsor or the coordinating CRO.

10.1.3 Missing Data

If any information is not available, and it is considered by the Investigator that it will never be available (e.g. the weight at a particular visit was not recorded), the Investigator will score out the question box in the eCRF and, if appropriate, explain, on the eCRF, why the investigation was missed out (e.g. the patient was not well enough to undergo the procedure).

Since patients who do not have evaluable PET/CT or do not have a confirmed histopathology diagnosis are considered drop-outs and replaced (Section **Error! Reference source not found.**); missing data are not expected for efficacy outcomes which involve the standard of truth (i.e., sensitivity, specificity, PPV, NPV, accuracy, inter-reader and intra-reader variability).

10.1.4 Storage of Study Records

It will be the responsibility of the Investigator to guarantee adequate storage for all study records, including the hospital notes during the study and for a minimum of 15 years following the end of the study, or as per current national regulations. If he/she leaves the employ of the hospital he/she will inform the sponsor and nominate a contact person who will have access to the study documents.

The investigator should take measures to prevent accidental or premature destruction of these documents.

Essential documents shall be archived in such a way that ensures that they are readily available upon authorities' request.

The investigator's site file (ISF) is not to be destroyed without the sponsor's approval. The investigator's contract will contain all regulations relevant for the study centre.

Archiving is described in Section 10.6.

10.2 Monitoring

This study will be monitored at all stages of its development by Accredited Study Monitors appointed by the Sponsor / CRO. Monitoring will include personal visits and telephone communication to ensure that the investigation is conducted according to the protocol and in order to comply with guidelines of GCP and applicable regulatory requirements. On-site review of eCRFs will include a review of data entries in the EDC for completeness and clarity, and consistency with source documents available for each patient. Additionally, remote checks of eCRF entries by monitors may take place, if required.

Each eCRF will be reviewed on site and checks will be made against source documents to ensure accurate, authentic and complete data that reflects the actual experience of the patient in the study (see Section 10.1.2). In addition, monitoring must ensure that the safety and rights of subjects are being protected. The Investigator must ensure that the hospital notes will be available for direct verification of source data. The Sponsor will not keep any records of patients' full identity.

To this end, the Investigator agrees to allow regular visits (frequency depending on recruitment, but estimated at monthly) by the study monitors and to ensure they have a suitable area in which to work (e.g. a desk) and adequate access to study personnel and documents.

Medical monitors and clinical research associates (CRAs) or assistants may request to witness patient evaluations occurring as part of this protocol. The investigator and appropriate personnel will be periodically requested to attend meetings or trainings organised by the sponsor to ensure acceptable protocol execution.

10.3 Data Processing

The coordinating CRO (ABX-CRO) will be responsible for the processing and quality control of data. Data management will be carried out as described in the CRO's standard operating procedures (SOPs) for clinical studies to ensure the integrity of the data, e.g. removing errors and inconsistencies of the data. This includes double data entry into the electronic database, generation and resolution of data queries.

Data entry into database will be carried out by trained persons according to SOPs for clinical studies at ABX-CRO, Dresden, Germany. Data entry and correction will be tracked by a validated audit trail. All systems are validated and compliant to FDA's ordinance 21 CFR part 11.

The FDA-validated medical dictionary MedDRA will be used for data coding (e.g., AEs, baseline findings, medication, medical/surgical history). The processes used for coding will be specified in the SAP.

10.4 Data Confidentiality

10.4.1 Documentation of Patient´s Participation

For all patients who give informed consent, regardless of whether they receive any study medication, the Investigator must record patient identification data in the "Patient Identification List" (full name, initials, date of birth, patient identification code). The patient identification list must allow for the definite identification of any patient that takes part in the study. In addition, study participation must be documented in the patient's regular medical records. For details about patient identification, see Section 4.4.

10.4.2 Data Protection

To protect the patient's identity, a unique patient identification code will be assigned by the Investigator to each trial patient and used in lieu of the patient's name when the Investigator reports adverse events and/or other trial related data. Thus, this number, rather than the patient's name, will appear on all documents and will be cross-referenced by the patient's date of birth. Personal information will be treated as confidential, but may need to be reviewed by the PIs, the ethics committee and regulatory authorities.

In order to be compliant with any country-specific laws, all relevant submissions to the respective authorities will be done and the corresponding approvals will be obtained before collection of any data considered to be sensitive, such as: ethnic origin, race, full date of birth etc.

10.5 Auditing

A member of the sponsor's (or the coordinating CRO´s) quality assurance unit may arrange to visit the investigator in order to audit the performance of the study at the study site and the study documents originating there. The auditor(s) will usually be accompanied by a CRA or the study team lead. The investigator will be informed about the outcome of the audit.

In addition, inspections by health authority representatives - including foreign authorities - and IEC(s) / IRB(s) are possible at any time. The investigator is to notify the sponsor of any such inspection immediately.

10.6 Archiving

The sponsor and the investigator / medical institution shall, in every case, retain the essential documents relating to this study for at least 15 years after its completion or as per current national regulations. They shall retain the documents for a longer period if required by other applicable regulatory requirements or by a separate agreement between the sponsor and the investigator. Essential documents shall be archived in such a way that ensures that they are readily available upon authorities' request.

Electronic CRFs (including queries and audit trails) will be retained by the sponsor, and copies will be sent to the investigator to maintain as the investigator copy.

Patient (hospital) files will be archived according to local regulations and in accordance with the maximum period of time permitted by the hospital, institution or private practice. The ISF is not to be destroyed without the sponsor's approval. The investigator's contract will contain all regulations relevant for the study centre.

Storage is described in Section 10.1.4.

11 Premature Termination of the Study

At the discretion of the PI, the entire study may be cancelled for medical reasons. In addition, Sponsor retains the right to end the study for medical-scientific or GCP-relevant reasons. In case of premature termination, the investigators, IECs and Regulatory Authorities will be informed by the project manager / study manager. As required by local law, current safety-relevant information will be provided to the IEC and the regulatory authorities by the sponsor. The sponsor will also inform all investigators about relevant safety events according to the applicable regulations.

If a trial is prematurely terminated or suspended for any reason, the investigator should promptly inform the trial patients and should assure appropriate therapy and follow-up. Should the study be terminated and/or the site closed for whatever reason, all documentation will be stored at the institution for the legally required period. Access will be granted to the coordinating CRO during this period. All radioactive study medication pertaining to the study must be discarded in compliance to the applicable local regulations.

12 Investigator's Obligations and Regulatory Aspects

12.1 Investigator's Commitment

By signing this protocol, the investigator accepts to carry out all procedures related to this study according to the laws and guidelines of their respective countries and the European Union related to

the conduct of clinical research. All investigators must allow access to all documents pertinent to the study.

The study may be subject to inspection or audit by Regulatory Authorities and will be monitored by authorized company personnel to ensure adherence to these guidelines.

The protocol must be read thoroughly and the instructions herein must be followed exactly. Any deviations should be agreed between the sponsor and the investigator, with appropriate written protocol amendments made to reflect the changes agreed upon. Substantial amendments to the protocol will not be implemented until after approval by the appropriate IEC / IRB / regulatory authority according to national legislation. Where the deviation occurs for the well-being of the patient, the monitor must be informed and a course of action agreed. Subsequently all such deviations, including the reasons thereof, will be submitted to the sponsor and the IEC(s) / IRB(s) as well as the relevant Competent Regulatory Agencies/Authorities if applicable and according to national regulations.

If an Investigator moves, withdraws from the study or retires, the responsibility for conducting the study and maintaining the records may be transferred to another investigator at the same centre who will accept responsibility for taking over the study. Notice of transfer must be made to and agreed by the sponsor.

12.2 Documentation

12.2.1 Approvals and Agreements

The following documents must be made available to the Sponsor prior to enrolling patients into the study:

- Signed final protocol Investigator's agreement page
- Completed and signed Investigator agreement, where applicable.
- *Curriculum Vitae* and *Financial disclosure* of the principal investigator together with co-investigators at his/her centre, where appropriate. Each should be up-to-date, signed and dated, confirming their accuracy.
- Copy of the Ethics Committee/Investigational Review Board's and Regulatory Agencies' approval.
- List of members of the Ethics Committee / Investigational Review Board and their affiliations.
- Sample of the consent form and patient information leaflet to be used (if different from the ones provided by the Sponsor).

12.2.2 Hospital Case Notes

The investigator should maintain individual patient records, usually hospital notes. The records should include a note about the participation in the study, date and time of patient's signature of informed consent, patient visit dates, records of vital signs, medical history, examinations, any adverse event, and other notes as appropriate. Source documents containing key data relevant to the patient's condition, procedures and outcome must be kept by the Investigator and will be reviewed by the study monitor. All main entries on the eCRF must be backed up by source data.

12.3 Insurance

Patients and investigators taking part in the study will be supplied with insurance cover according to the requirements of their country.

13 Ethical and Legal Aspects

13.1 Ethical and Legal Conduct of the Study

The planning and conduct of this clinical study are subject to national laws. Only when all of the requirements of the appropriate regulatory authority have been fulfilled will the study begin. The Guidelines of the World Medical Association Declaration of Helsinki, the Guidelines of GCP as well as the demands of national drug and data protection laws and other applicable regulatory requirements will be strictly followed.

The investigator is responsible for ensuring that no patient is subject to any study-related examination or activity before that patient and/or legal guardian has given informed consent. The patient or the parents/guardians of the patient must give written consent, after the receipt of detailed information. The verbal explanation will cover all the elements specified in the written information provided for the patient.

The investigator will inform the patient of the aims, methods, anticipated benefits and potential hazards of the study including any discomfort it may entail. The investigator will inform patients that in providing informed consent, they are giving permission for representatives of the study centre PIs, ethics committees, or regulatory authorities to inspect their medical records to verify the information is collected. Patients will be informed that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws. The patient must be given every opportunity to clarify any points he/she does not understand and if necessary, ask for more information. At the end of the interview the patient may be given time to reflect if this is required, or if the patient requests more time. Patients and/or legal guardian will be required to sign and date the informed consent form. After completion, the consent forms will be kept and archived by the investigator in the investigator's study file (ISF).

It should be emphasized that the patient has the liberty to withdraw their consent to participate at any time, without penalty or loss of benefits to which the patient is otherwise entitled. Patients who refuse to give or withdraw written informed consent must not be included or continued in the study.

13.2 Patient Information and Consent

All relevant information on the study will be summarized in an integrated patient information and consent sheet provided by the sponsor or the study centre. A sample patient information and informed consent form is provided as a document separate to this protocol.

Based on this patient information sheet, the investigator will explain all relevant aspects of the study to each patient, before his / her entry into the study (i.e., before examinations and procedures associated with selection for the study are performed).

The investigator will also mention that written approval of the IRB / IEC has been obtained.

Each patient will have ample time and opportunity to ask questions and will be informed about the right to withdraw from the study at any time without any disadvantage and without having to provide reasons for this decision.

Following this informative discussion, the patient will be asked if he / she is willing to sign and personally date a statement of informed consent, which includes consenting to the processing of his / her data as explained in the patient information sheet. Only if the patient voluntarily agrees to sign the informed consent form and has done so, may he / she enter the study. Additionally, the investigator will personally sign and date the form, too. The patient will receive a duplicate of the signed and dated form.

The signed informed consent statement is to remain in the ISF or, if locally required, in the patient's file of the medical institution. In addition, the consent process will be documented in the source documents with an independent entry.

The investigator will document in the eCRF the time and date of obtaining informed consent. In the event that informed consent is obtained on the date that baseline study procedures are performed, the study record or patient's clinical record must clearly show that informed consent was obtained prior to these procedures.

The informed consent form and any other written information provided to patients will be revised whenever important new information becomes available that may be relevant to the patient's consent, or there is an amendment to the protocol which necessitates a change to the content of the patient information and/or the written informed consent form. The investigator will inform the patient of changes in a timely manner and will ask the patient to confirm his/her participation in the study by signing the revised informed consent form. Any revised written informed consent form and written information must receive the IRB / IEC's approval in advance of use.

13.3 Financial Disclosure

Each investigator (including principal and/or any sub-investigators; as well as their spouses and dependent children) who is directly involved in the treatment or evaluation of research patients has to provide a financial disclosure according to all applicable legal requirements. All relevant documentation will be filed in the TMF and/or ISF, as appropriate.

13.4 Publication Policy

The sponsor may be interested in the publication of the results of this study. As some of the information concerning the study drug and the sponsor's development activities may be strictly confidential, any publication manuscript (including conference contributions, etc.) must first be reviewed by the sponsor and the coordinating CRO before its submission or presentation.

Publication of subgroup data and single centre data shall not be performed until the complete study has been published. All relevant aspects regarding publication will be part of the contract between the coordinating CRO and the investigator / institution.

The sponsor has committed to the global industry position on disclosure of information about clinical trials. The information regarding the study protocol is made publicly available on the internet at www.clinicaltrials.gov. This derives from the standards that international medical journal editors have established requiring protocol registration at the outset of the study as a prerequisite of consideration for publication.

13.5 Compensation for Health Damage of Patients / Insurance

Where required by the laws and regulations of the country in which the study is performed, insurance of patients against health impairment occurring as a result of participation in the study will be set up in accordance with said laws and regulations. All relevant documentation regarding such insurance will be filed in the TMF and/or ISF, as appropriate.

14 Appendices

Appendix I – NCI CTCAE

Version 5.0 of the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), dated 27 November 2017, may be viewed and/or downloaded by accessing the following website:

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

A printed version will be provided to the Investigators.

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