Clinical Study Protocol

A single-centre, open-label, phase I study to evaluate the diagnostic performance of 89Zirconium-labelled girentuximab (89Zr-TLX250) PET in Urothelial Cancer Patients

(ZiPUP study)

*Version 5*

*21st October 2020*

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| **Short Title:**  **Sponsor:** | **89Zr-TLX250 PET in Urothelial Cancer Patients**  **South Metropolitan Health Service**  **14 Barry Marshall Parade**  **Murdoch WA 6150** |
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**Study Synopsis**

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| **Study title** | **A single-centre, open-label, phase I study to evaluate the diagnostic performance of 89Zirconium-labelled girentuximab (89Zr-TLX250) PET in Urothelial Cancer Patients (ZiPUP study)** |
| **Clinical phase** | Phase I |
| **Study duration** | 18 months |
| **Hypothesis** | 89Zirconium (Zr)-girentuximab (89Zr-TLX250) Position Emission Tomography / Computed Tomography (PET/CT) is a practical tool for the staging and detection of urothelial carcinoma and bladder cancer. |
| **Rationale** | Current urothelial cancer staging is sub-optimal. Fluorodeoxyglucose (FDG) PET/CT relies on the metabolic activity of the tumour and thus may have limited utility in low grade urothelial tumours. Urinary excretion of FDG PET/CT is also intrinsically problematic when imaging urothelial malignancies.  Girentuximab is a chimeric monoclonal antibody targeting the protein carbonic anhydrase IX (CAIX). CAIX is overexpressed in hypoxic cells, and on a range of solid tumours including bladder, renal, colon, cervical, and lung cancer.  89Zr-TLX250 PET/CT has efficacy in the assessment of renal cell carcinoma (RCC) however has not been evaluated as an imaging modality for urothelial carcinoma and bladder cancer. Hepatic clearance of 89Zr-TLX250 with low urinary excretion is expected to be advantageous for the local and distant staging of urothelial carcinoma and bladder cancer. |
| **Objectives** | **Primary objective:**  To evaluate the feasibility of using 89Zr-TLX250 PET/CT in the detection of localized and metastatic urothelial carcinoma or bladder cancer  **Secondary objectives:**   1. To evaluate the safety and tolerability of 89Zr-TLX250 PET/CT. 2. To determine the effectiveness of 89Zr-TLX250 PET/CT in detecting metastatic urothelial carcinoma or bladder cancer compared to FDG PET/CT by comparing tracer uptake ratios in mediastinum against tumour. 3. To evaluate the correlation between positive 89Zr-TLX250 PET/CT and pelvic lymphadenectomy histopathological findings in those undergoing radical cystectomy. 4. To evaluate the effectiveness of 89Zr-TLX250 PET/CT in detecting primary bladder cancer. 5. To evaluate the effectiveness of 89Zr-TLX250 PET/CT in detecting upper tract urothelial carcinoma. |
| **Investigational medicinal product (IMP)** | 89Zr-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 89Zr-DFO-TFP-GTX. |
| **Name of active ingredients** | 89Zr-TLX250 (synonyms: 89Zr-girentuximab, 89Zr-DFO-TFP-GTX) |
| **Doses** | A single slow intravenous administration of 37 mBq (± 10%) 89Zr-TLX250, containing a mass dose of 10 mg of girentuximab. |
| **Route of Administration** | A slow intravenous injection over 3 minutes. |
| **Duration of treatment** | Single diagnostic administration, followed by a diagnostic scan on Day 5 ± 2 days. |
| **Study design** | Non-randomized, non-blinded comparison of 89Zr-TLX250 PET/CT with FDG PET/CT |
| **Number of patients** | 20 (10 patients with known metastatic urothelial carcinoma or bladder cancer and 10 patients who require primary staging of localized urothelial carcinoma or bladder cancer) |
| **Study population** | Patients with histopathologically diagnosed bladder cancer or urothelial carcinoma already being staged with FDG PET/CT or those with known FDG positive metastatic disease, who are willing to undergo an additional 89Zr-TLX250 PET/CT |
| **Inclusion criteria** | 1. Patients aged 18 or older with bladder cancer or urothelial carcinoma who are able to provide informed consent 2. Negative serum pregnancy test in female patients of childbearing potential at screening. Confirmation of negative pregnancy test result from urine within 24 hours prior to receiving investigational product. 3. Consent to practise double-barrier contraception until a minimum of 42 days after 89Zr-TLX250 administration. |
| **Exclusion criteria** | 1. Active malignancy other than urothelial carcinoma or bladder cancer 2. Administration of a radioisotope within 10 physical half-lives prior to study enrolment. 3. Administration of chemotherapy, radiotherapy, or immunotherapy within 4 weeks prior to planned administration of 89Zr-TLX250 or continuing adverse effects from such therapy 4. Planned antineoplastic therapies for the period between administration of 89Zr-TLX250 and imaging 5. Serious non-malignant disease that may interfere with the objectives of the study 6. Renal insufficiency with glomerular filtration rate ≤45 mL/min/1.73m2 7. Pregnancy or lactation 8. Exposure to murine or chimeric antibodies within the last 5 years 9. Known hypersensitivity or human anti-chimeric antibodies against girentuximab 10. Exposure to any experimental diagnostic or therapeutic drug 30 days prior to the date of planned administration of 89Zr-TLX250 11. Contraindications to FDG PET/CT |
| **Endpoints** | Primary endpoint:  The feasibility of using 89Zr-TLX250 PET/CT as a diagnostic and staging tool in urothelial carcinoma and bladder cancer will be defined by the ability to recruit to the target sample size within the study duration. This reflects a willingness of clinicians to refer patients for this study and a willingness of patients to undergo 89Zr-TLX250 PET/CT as for diagnosis or staging.  Secondary endpoints:   1. Safety and tolerability  * Baseline safety evaluations will be made within 28 days prior to 89Zr-TLX250 administration. This would include vital signs, standard laboratory (full blood count, renal function, basic electrolytes and liver function test), 12-lead ECG and concomitant medication recording. * Vital signs will be recorded before and after administration of 89Zr-TLX250. 12-lead ECG and adverse event recording (NCI-CTC v 5.0) will be performed post administration. * Safety evaluations will also be made at follow-up phone consult post PET/CT 14 days (or prior to commencement of chemotherapy or surgery) post administration of 89Zr-TLX250. Safety evaluations would include enquiring about any current symptom, concomitant medication recording and adverse event recording (NCI-CTC v 5.0).  1. Effectiveness of 89Zr-TLX250 PET/CT vs FDG PET/CT in detecting metastatic or localized urothelial carcinoma and bladder cancer  * Qualitative 89Zr-TLX250 vs FDG tumour targeting   + 89Zr-TLX250 tumour uptake will be qualitatively assessed (yes/no), considering whether or not 89Zr-TLX250 binding is seen in lymph nodes or distant visceral organs.   + FDG tumour uptake will be qualitatively assessed (yes/no), considering whether or not FDG binding is seen in lymph nodes or distant visceral organs. * Quantitative 89Zr-TLX250 vs FDG tumour targeting   Tumour vs mediastinal uptake ratio for 89Zr-TLX250 PET/CT and FDG PET/CT will be calculated and compared.   1. Sensitivity and specificity of 89Zr-TLX250 PET/CT vs FDG PET/CT in detecting lymph node metastases in urothelial carcinoma or bladder cancer.  * PET/CT results will be correlated with pelvic lymphadenectomy histopathological findings in those undergoing radical cystectomy  1. Evidence for 89Zr-TLX250 PET/CT vs FDG PET/CT in detecting primary bladder cancer  * 89Zr-TLX250 uptake in the bladder will be correlated to CT urogram/cystoscopy results. 89Zr-TLX250 uptake in the bladder would be considered positive for those with residual bladder tumour. These would be in patients undergoing cystectomy.  1. Evidence for 89Zr-TLX250 PET/CT vs FDG PET/CT in detecting previously unrecognised upper tract urothelial carcinoma.  * 89Zr-girentuxumab uptake in the upper tracts will be correlated to CT urogram/ureteroscopy results to determine 89Zr-girentuximab PET’s utility in detecting upper tract urothelial carcinoma. |
| **Study Participation Duration** | * Screening period: 28 days (Day -28 to Day -1) * Study period:   + Treatment: IMP administered on Day 0   + Imaging period: Day 5 ± 2   EOS: Day 14 |
| **Sample size determination** | It is planned to include 20 patients in the study. The total number of patients planned is not based on statistical sample size estimation but has been chosen based on clinical context. |

**Table 1.** **Schedule of Assessments**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Visit Name** | **Screening** | **IMP Administration** | **Imaging** | **Follow up** |
| **Time point** | **Within 28 days of selection** | **Day 0** | **Day 5 ± 2** | **Day 14**  **(or before starting chemotherapy or undergoing surgery)** |
| **Informed consent** | **X** |  |  |  |
| **Eligibility criteria** | **X** |  |  |  |
| **18F-FDG-PET/CT** | **X** |  |  |  |
| **Physical exam** | **X** |  |  |  |
| **ECOG status** | **X** |  |  |  |
| **Vital signs** | **X** | **X**  **Pre and post injection** | **X** |  |
| **12 lead ECG** | **X** | **X**  **Post injection** |  |  |
| **Haematology**  **Biochemistry** | **X** |  |  |  |
| **Liver function tests** | **X** |  |  |  |
| **Serum β-HCG** | **X** |  |  |  |
| **Urine analysis** | **X** |  |  |  |
| **Urine pregnancy test** |  | **X** |  |  |
| **PET/CT** |  |  | **X** |  |
| **Adverse events** |  | **X** | **X** | **X** |
| **Concomitant Medications** | **X** | **X** | **X** | **X** |

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1. **Background**
   1. **Bladder cancer and predictive biomarkers**

Bladder cancer is a deadly disease with a rising incidence worldwide. There remain no good prognostic factors for recurrence, progression, and survival beyond T classification, grade, associated carcinoma in situ, and lymph node involvement. There have been concerted global research efforts directed towards identification of biomarkers that could enhance early detection of bladder cancer. Numerous biomarkers have been investigated, though none are currently adopted in routine clinical practice.

* 1. **Carbonic anhydrase IX (CAIX)**

CAIX is an enzyme that functions as a regulator of intracellular pH, cell proliferation, and cell adhesion in response to hypoxia (Ivanov). CAIX is expressed abundantly in response to hypoxia in a wide range of cancer cell lines including renal, bladder, head and neck, lung, and colon cancer (Ivanov). Previous studies have shown that greater than 90% of clear cell renal cell carcinomas (ccRCC) express CAIX (Steffens *et al*., 1997).

Previous data has demonstrated sensitivity and specificity of urinary CAIX of 86.2% and 95.1% respectively, for detection of urothelial bladder cancer (area under the curve 90.5%) (de Martino). A significant association between CAIX expression in paired urine and tumour specimens has also been established (de Martino). Notably, CAIX was shown to have significantly higher predictive accuracy compared to urinary cytology (90.5% vs 71.7%), especially in low-grade tumours (90% vs 61.8%).

A seminal study by Klatte *et al*., (2009) confirmed differential expression of CAIX in non-invasive versus invasive bladder tumours, and in low grade versus high grade bladder cancers. Importantly, Klatte and team confirmed that CAIX was distinctly expressed in >70% of urothelial carcinomas, but was not expressed in normal urothelial tissue. CAIX was also found to perform well as a prognostic marker, and is predictive of 3 endpoints in bladder cancer: recurrence, progression, and overall survival. These findings provide strong rationale for investigating the potential use of CAIX as a targeted imaging agent for the identification and diagnosis of bladder cancer. By the same token, the utility of CAIX as a therapeutic target also merits further investigation.

**1.3 Immuno-Positron Emission Tomography / Computed Tomography (PET/CT) and Zirconium-89-girentuximab (89Zr-TLX250)**

Immuno-PET” is a novel imaging modality that enables the tracking of targeted vehicles and carriers through the use of isotope-labelled monoclonal antibodies. Many ligand-target combinations have been studied for both diagnostic and therapeutic use. A notable example in the field of theranostics with an established therapeutic role is 177Lu-PSMA-617, a radionuclide agent that has garnered success in the treatment of castrate-resistant prostate cancer (Hofman *et al*., 2018).

Due to its intrinsic chemical properties, 89Zr has been identified as a suitable ligand candidate for this approach (Van Dongen *et al*., 2015). Girentuximab (used interchangeably with TLX-250) is an antibody directed against CAIX that has been widely studied in the setting of renal cell carcinoma (RCC). Since its introduction in the 1980s, over 2000 girentuximab injections have been administered worldwide in several clinical trials. To date, there have been no reports of serious side effects or allergic reactions to girentuximab.

There are a wide range of potential clinical applications for 89Zr-TLX250PET/CT (Van Dongen *et al*., 2015) including: 1. Disease diagnosis and staging, 2. Patient stratification, 3. Monitoring of treatment response, and 4. Planning of radioimmunotherapy.

To date, 89Zr-TLX250has been most widely evaluated as a diagnostic imaging agent for ccRCC. Hekman *et al*., (2018) studied the use of 89Zr-TLX250 PET/CT in the two cohorts of patients; 1. Patients with an indistinct renal mass and 2. Patients suspected of recurrent/metastatic ccRCC. The use of 89Zr-TLX250 PET/CT as a means of identifying ccRCC was found to have a significant impact on clinical decision making. In patients with an indeterminate renal mass, 5 out of 6 masses that internalised the 89Zr-TLX250 imaging agent were histologically confirmed as ccRCC after surgical removal of the tumours. The 6th patient with Von Hippel Lindau syndrome received additional cryoablation for PET positive lesions that were not detected using MRI. No progression was observed in the 9 patients with 89Zr-TLX250 negative tumours (mean duration of follow up 13 months ± 4.9 months).

In patients suspected of recurrent/metastatic ccRCC, 89Zr-TLX250PET/CT imaging was able to assist with the treatment and patient care decision making process, including defining the extent of metastatic disease, distinguishing cccRCC from other cancers, and providing further diagnostic interpretation where biopsies were not feasible. Urinary excretion of FDG PET/CT is intrinsically problematic when imaging urinary tract malignancies. Hepatic clearance of 89Zr-TLX250 with low urinary excretion is expected to be advantageous for the local and distant staging of urothelial carcinoma and bladder cancer.

In the setting of breast cancer, 89Zr-labelled antibodies have been investigated as a means of selecting the best candidates to receive the antibody-drug conjugate, ado-trastuzumab-emtansine (T-DM1) (Dijkers *et al*., 2010). T-DM1 combines the antitumour properties of the HER2 antibody, trastuzumab, with a cytotoxic agent, DM1. 89Zr-trastuzumab PET enables quantification of monoclonal antibody uptake in HER2 positive lesions, which may in turn, be used to predict therapeutic efficacy with T-DM1.

Early-phase studies have also explored the use of 89Zr-immuno-PET as a potential tool in monitoring response to breast cancer therapy (Gaykema *et al*., 2013) and radiotherapy (Holland *et al*., 2010). HSP90 are implicated in the key hallmarks of breast cancer progression. Gaykema and colleagues were able to demonstrate change in the size of tumour lesions on 89Zr-trastuzumab PET following administration of HSP90 inhibitor NVP-AUY922 in patients with advanced HER2 or ER-positive breast cancer.

Collectively these studies highlight the potential diagnostic and therapeutic applications of 89Zr-girentiximab (89Zr-TLX250) where this Phase I study aims to investigate the extension of its application into metastatic urothelial carcinoma or bladder cancer.

1. **Aims and objectives**

The aim of this study is to determine if it is practical to use 89Zr-TLX250PET/CT in the staging and detection of localized and metastatic urothelial carcinoma or bladder cancer.

The primary objective is to evaluate the feasibility of using 89Zr-TLX250PET/CT as a new diagnostic and staging modality to detect urothelial carcinoma or bladder cancer.

Secondary objectives are as follows:

1. To evaluate the safety and tolerability of 89Zr-TLX250PET/CT
2. To determine the effectiveness of 89Zr-TLX250PET/CT in detecting metastatic urothelial carcinoma or bladder cancer compared to FDG PET/CT by comparing tracer uptake ratios in mediastinum against tumour. To evaluate the correlation between positive 89Zr-TLX250PET/CT and pelvic lymphadenectomy histopathological findings in those undergoing radical cystectomy.
3. To evaluate the effectiveness of 89Zr-TLX250PET/CT in detecting primary bladder cancer.
4. To evaluate the effectiveness of 89Zr-TLX250PET/CT in detecting upper tract urothelial carcinoma.

**3. Overview of Methodology and Design**

**3.1 Study design**

This will be a non-randomised, non-blinded, single centre, phase 1 feasibility study comparing 89Zr-TLX250PET/CT with FDG PET/CT in patients with urothelial carcinoma or bladder cancer. This study will include 2 cohorts of adult patients; 1. Those with known metastatic urothelial carcinoma and bladder cancer and 2. Those undergoing primary staging for recently diagnosed urothelial carcinoma or bladder cancer.

Patients with known metastatic urothelial or bladder cancer who have FDG PET/CT scans to assess response to systemic treatment will undergo 89Zr-TLX250PET/CT within 28 days of receiving a FDG PET/CT. Patients undergoing clinical staging with FDG PET/CT as part of standard of care for recently diagnosed urothelial carcinoma or bladder cancer will undergo 89Zr-TLX250PET/CT imaging within 28 days of receiving a FDG PET. PET/CT scans will be reported by Nuclear Medicine physicians. Clinical decisions will be based on the FDG PET/CT imaging, according to the current standard practice. Any lesions presenting as positive on 89Zr-TLX250PET/CT scans but not on FDG PET/CT imaging which may be deemed as potentially clinically significant, will be arbitrated by the Uro-oncology Multidisciplinary Meeting to determine if any change in patient management is required.

Twenty patients will be recruited at a single centre which has access to PET/CT imaging. Ten patients will have known metastatic urothelial carcinoma or bladder cancer while the remaining ten patients will be undergoing primary staging for histologically diagnosed urothelial carcinoma or bladder cancer.

Histological correlation of lymph nodes with increased uptake on 89Zr-TLX250PET/CT and FDG PET/CT will be performed in patients who proceed with cystectomy and pelvic lymph node dissection. Histological correlation will also be performed on bladder specimens which demonstrate increased uptake on both 89Zr-TLX250PET/CT and FDG PET/CT scans. The location of increased FDG or 89Zr-TLX250uptake in the upper tracts of patients diagnosed with upper tract urothelial carcinoma will be compared to standard imaging such as a CT urogram, available intraoperative ureteroscopy findings, urine cytology or histopathology of upper tract lesion biopsies to determine if either PET/CT was able to detect upper tract urothelial carcinoma.

**3.2 Study conduct**

Following informed consent, a screening visit will be performed during which baseline examinations and investigations will be made. The screening visit and FDG PET scan will be within 28 days of 89Zr-TLX250administration. The study schedule will be planned, considering a delivery timeline for 89Zr-TLX250of 7-10 days the supplying pharmacy, an imaging interval of 5+/- 2 days post administration, and open radical cystectomy, in those proceeding with surgery, to be performed any time after 89Zr-TLX250PET/CT imaging.

On Day 0, all successfully screened patients will undergo a single slow intravenous administration of 37 mBq (±10%) 89Zr-TLX250, containing a mass dose of 10 mg of girentuximab, over a minimum of 3 minutes. All investigative medicinal product (IMP) administration will be performed in the nuclear medicine department of the clinical trial site. To detect any treatment or infusion-related toxicity, before and after administration of 89Zr-TLX250 the patients will have their vital signs recorded. Cardiac function will be monitored using a 12-lead ECG and adverse event recording (NCI-CTC v 5.0).

On Day 5 +/- 2 days, whole body PET/CT imaging will be performed on 4 bed positions using an acquisition time of up to 45 minutes to maximise image quality. Image data analyses will be performed by Nuclear Medicine physicians at the study site. Qualitative visual analysis (presence or absence of 89Zr-TLX250uptake in lymph nodes or distant visceral organs) and well as quantitative analysis (tumour vs mediastinal uptake ratio for 89Zr-TLX250PET/CT and FDG PET/CT) will be performed.

Histological specimens in those who proceed to cystectomy and pelvic lymphadenectomy, would be analysed by a Uro-pathologist at the study site.

Safety evaluations will also be made at a follow-up phone consult 14 days after administration of 89Zr-TLX250. Baseline and safety evaluations will include vital signs, standard laboratory (full blood count, renal function, basic electrolytes and liver function test), 12-lead ECG and concomitant medication recording and adverse event recording (NCI-CTC v 5.0).

**3.3 Endpoints**

***3.3.1 Primary endpoint***

Primary endpoint of this study is to evaluate the feasibility of using 89Zr-TLX250PET/CT as a new diagnostic and staging modality to detect urothelial carcinoma or bladder cancer. The feasibility will be ascertained by the ability to recruit to the target sample size within the study duration. This reflects a willingness of clinicians to refer patients for this study and a willingness of patients to undergo 89Zr-TLX250PET/CT for diagnosis or staging.

***3.3.2. Secondary endpoints***

1. Safety and tolerability

* Baseline safety evaluations will be made within 28 days prior to 89Zr-TLX250administration. This would include vital signs, standard laboratory (full blood count, renal function, basic electrolytes and liver function test), serum β-HCG for pre-menopausal women, urine analysis, 12-lead ECG and concomitant medication recording.
* Vital signs will be recorded before and after administration of 89Zr-girentuximab. 12-lead ECG and adverse event recording (NCI-CTC v 5.0) will be performed post administration.
* Safety evaluations will also be made at follow-up phone consult 14 days after (or before commencement of chemotherapy or surgery) 89Zr-TLX250 administration. Safety evaluations would include enquiring about any current symptom, concomitant medication recording and adverse event recording (NCI-CTC v 5.0).

1. Effectiveness of 89Zr-TLX250PET/CT vs FDG PET/CT in detecting metastatic urothelial carcinoma or bladder cancer.

* Qualitative 89Zr-TLX250vs FDG tumour targeting
  + 89Zr-TLX250tumour uptake will be qualitatively assessed (yes / no), considering whether or not 89Zr-TLX250binding is seen in lymph nodes or distant visceral organs.
  + FDG tumour uptake will be qualitatively assessed (yes / no), considering whether or not FDG binding is seen in lymph nodes or distant visceral organs.
* Quantitative 89Zr-TLX250vs FDG tumour targeting

Tumour vs mediastinal uptake ratio for 89Zr-TLX250PET/CT and FDG PET/CT will be calculated and compared. Sensitivity and specificity of 89Zr-TLX250PET/CT vs FDG PET/CT in detecting lymph node metastases in urothelial carcinoma or bladder cancer

* PET/CT results will be correlated with pelvic lymphadenectomy histopathological findings in those undergoing radical cystectomy

3. Evidence for 89Zr-TLX250PET/CT vs FDG PET/CT in detecting primary bladder cancer

* 89Zr-TLX250uptake in the bladder would be considered positive for those with residual bladder tumour. These would be in patients undergoing cystectomy.

4. Evidence for 89Zr-TLX250PET/CT vs FDG PET/CT in detecting previously unrecognised upper tract urothelial carcinoma

* 89Zr-TLX250uptake in the upper tracts will be correlated to CT urogram/ureteroscopy results to determine 89Zr-TLX250PET/CT’s utility in detecting upper tract urothelial carcinoma

**4. Study population**

**4.1 Target population**

A sample size of 20 adult patients has been selected, of which 10 patients would have known metastatic urothelial carcinoma or bladder cancer while the other 10 would be undergoing primary staging for histologically diagnosed urothelial carcinoma or bladder cancer. The total number of patients planned is not based on statistical sample size estimation but has been chosen based on clinical context.

**4.2 Eligibility**

***4.2.1 Inclusion criteria***

Patients must meet the following criteria for study entry:

1. Aged ≥18
2. Able to provide informed consent
3. Histologically diagnosed with urothelial carcinoma or bladder cancer (or upper tract urothelial carcinoma diagnosed based on standard imaging and malignant urine cytology or direct visualisation on ureteroscopy) or known metastatic urothelial carcinoma or bladder cancer (based on previous imaging and /or histopathology)
4. Negative serum pregnancy test in female patients of childbearing potential at screening. Confirmation of negative pregnancy test result from urine within 24 hours prior to receiving investigational product.
5. Consent to practise double-barrier contraception until a minimum of 42 days after 89Zr-TLX250administration.

**4.2.2 *Exclusion criteria***

Patients must not meet any of the following criteria for study entry:

1. Active malignancy other than urothelial carcinoma or bladder cancer
2. Administration of a radioisotope within 10 physical half-lives of 89Zr prior to study enrolment.
3. Administration of chemotherapy, radiotherapy, or immunotherapy within 4 weeks prior to planned administration of 89Zr-TLX250or continuing adverse effects from such therapy
4. Planned antineoplastic therapies for the period between administration of 89Zr-TLX250and imaging
5. Serious non-malignant disease that may interfere with the objectives of the study
6. Renal insufficiency with glomerular filtration rate ≤45 mL/min/1.73m2
7. Pregnancy or lactation
8. Exposure to murine or chimeric antibodies within the last 5 years
9. Known hypersensitivity or human anti-chimeric antibodies against girentuximab
10. Exposure to any experimental diagnostic or therapeutic drug 30 days prior to the date of planned administration of 89Zr-TLX250
11. Contraindications to FDG PET/CT

***4.2.3 Recruitment***

Potential patients of this study will be recruited by the urological and the medical oncology service at the study site and undergo a formal screening visit. Patients will be approached to determine if they would be interested in participating in the ZiPUP study. Interested patients will be provided with an information sheet and will undergo an informed consent procedure prior to any study procedures. Should the patient consent to the study, a study schedule will be planned. Administration of 89Zr-TLX250on Day 0 will be performed. Recruitment would be stopped after 10 metastatic urothelial carcinoma or bladder cancer patients and 10 primary staging urothelial carcinoma or bladder cancer patients have been recruited.

**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 Replacement***

A patient who is included in the study, but then fulfils any one of the following, will be considered to have dropped-out:

* Has not received an administration of intravenous 89Zr-TLX250
* Did not undergo PET/CT imaging after IV administration of study drug
* Whose PET/CT images cannot be analysed due to technical failure

Patients who drop-out of the study will be replaced. All patients who drop-out after receiving IV 89Zr-TLX250 will need to undergo all study assessments (as set out by the schedule of evaluation in Table 3) until the final follow-up phone call.

Patients who have received study drug and are withdrawn due to an AE will not be replaced.

**4.4 Patient Identification**

All patients who provide informed consent for the study will be assigned a unique identification number (“Patient Number”) that consists of 5 digits. Each patient’s patient number will be assigned at the time of recruitment. The study site is required to keep a patient identification list in the trial master file (TMF), identifying their patients by name, date of birth, patient number and status (screen failure/completed stud /withdrawn). This list will remain on site to protect confidentiality.

**5. Study Treatment**

**5.1 Study drug 89Zr-TLX250**

**5.1.1 Chemical Properties**

89Zr-TLX250 is a chimeric monoclonal antibody with specificity for the CAIX antigen, radiolabeled with the positron emitting radio-metal zirconium-89. Girentuximab has a CAS number of 916128-87-9.

The chemical formula, without the 89Zr, is C6460H1006N1718O2018S48 with a molecular mass of 146.5 kg/mol.

**5.1.2 Pharmaceutical Properties**

89Zr-TLX250 is formulated as a solution for intravenous administration in glass vials at the nominal dosage strength 37 MBq (±10%) for single intravenous use. The 89Zr-TLX250 is manufactured as “ready-to-use”. The composition of 89Zr-TLX250 solution for IV administration includes the active pharmaceutical ingredient in a buffered solution without other excipients. Table 2 provides a detailed listing of the specifications of the 89Zr-TLX250 IMP.

**Table 2: Specifications of 89Zr-TLX250 Solution for Intravenous Administration**

|  |  |
| --- | --- |
| Active component: | 37 MBq 89Zr-TLX250 |
| Batch volume: | ≤ 10 mL |
| Mass dose girentuximab | 10 mg |
| Other ingredients: | Girentuximab, 89Zr-DFO-girentuximab |
| Solvent: | NaCl 0.9% |
| Appearance: | Clear, colourless to light yellow and free from visible particles |
| pH: | 5.0 – 8.0 |
| Radiochemical purity: (ITLC after purification) | 89Zr-TLX250 ≥ 90% |
| Radiochemical purity (SE-HPLC after purification) | 89Zr-DFO-girentuximab ≥ 90%  89Zr / 89Zr-DFO ≤ 10%  Aggregates ≤ 5% |
| Identity: | Rtsample = Rtreference ± 10% |
| Sterility | No growth |
| Endotoxins | ≤ 17.5 EU/mL |
| Expiry time | 96 hours at 15°C - 30°C in bulk vial |
| Primary packaging | Type 1 glass vials |

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 89Zr-TLX250 to be used in this phase 1 study will be 10 mg, labelled with 37 MBq (±10%) 89Zr 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 study site.

No dietary constrictions prior to dosing are necessary.

Prior to administration, an indwelling intravenous catheter has to be placed into the antecubital vein or an equivalent venous access. The radiopharmaceutical will be slowly administered through the indwelling catheter and followed with a saline flush.

**5.1.5 Packaging and Labelling**

89Zr-TLX250 solution for IV administration will be supplied in glass vials in appropriate packaging (lead-shielded containers bearing a radioactive warning symbol in accordance with radioactive pharmaceutical requirements). The labels of the packaging supplied by Telix International Pty Ltd 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**

89Zr-TLX250 solution for IV administration will be manufactured, handled and stored in accordance with GMP. 89Zr-TLX250 contains radioactive material and should only be handled by personnel trained in the use of radioactive isotopes with proper shielding and monitoring.

The dose order will be a direct order from the study site to Telix International Pty Ltd who shall arrange appropriate supply of 89Zr-TLX250. Upon establishment of patient eligibility (see Section 4.2), the clinical site manager will order individualized doses of 89Zr-TLX250 solution for IV administration, via Telix International Pty Ltd, 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 dispose of the product appropriately. 89Zr-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 89Zr-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, 89Zr-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 study 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.

89Zr-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.

**5.1.6.2 Drug Accountability**

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.

**5.2 Treatment Assignment**

After fully establishing the eligibility of the patient by the clinical trial site staff, the screening physician will confirm eligibility and an imaging day will be scheduled before the administration of the study drug. When the imaging day has been confirmed, the individual patient number will be allocated.

**5.3 Treatment Compliance**

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

**5.4 Treatment of Overdose**

89Zr-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 89Zr-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 89Zr-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 (89Zr)-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.

**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 CRF.

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

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 CRF. 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 forbidden, and patients will be withdrawn from the study, if one of the following will be administered during study participation. However, patients can be included when the respective washout period before enrolment into the study is considered (refer to Table 3)

**Table 3: Forbidden 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 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 standard 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.

**7. Schedule of Evaluations and Visit Description**

**7.1 Schedule of Evaluations**

A detailed schedule of events is presented in Table **4**.

**Table 4: The schedule of study assessments is set out as follows:**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Visit Name** | **Screening** | **IMP Administration** | **Imaging** | **Follow Up** |
| **Time point** | **Within 28 days of selection** | **Day 0** | **Day 5 ± 2** | **Day 14**  **(or before starting chemotherapy or undergoing surgery)** |
| **Informed consent** | **X** |  |  |  |
| **Eligibility criteria** | **X** |  |  |  |
| **18F-FDG-PET/CT** | **X** |  |  |  |
| **Physical exam** | **X** |  |  |  |
| **ECOG status** | **X** |  |  |  |
| **Vital signs** | **X** | **X**  **Pre and post injection** | **X** |  |
| **12 lead ECG** | **X** | **X**  **Post injection** |  |  |
| **Haematology**  **Biochemistry** | **X** |  |  |  |
| **Liver function tests** | **X** |  |  |  |
| **Serum β-HCG** | **X** |  |  |  |
| **Urine analysis** | **X** |  |  |  |
| **Urine pregnancy test** |  | **X** |  |  |
| **PET/CT** |  |  | **X** |  |
| **Adverse events** |  | **X** | **X** | **X** |
| **Concomitant Medications** | **X** | **X** | **X** | **X** |

For time points when more than one procedure is scheduled, the assessments will be performed in an order as clinically appropriate.

**7.2 Screening and FDG PET/CT**

Screening is to take place between 28 days and 1 day before administration of 89Zr-TLX250 on Day 0. Evidence of histologically diagnosed with urothelial carcinoma or bladder cancer (or upper tract urothelial carcinoma diagnosed based on standard imaging and malignant urine cytology or direct visualisation on ureteroscopy) or known metastatic urothelial carcinoma or bladder cancer (based on previous imaging and /or histopathology) must be given 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
* Basic electrolytes and renal function
* Liver function tests
* Urinalysis (Dipstick)
* Pregnancy test from serum (for premenopausal female patients)
* 12-lead ECG
* Concomitant medications
* Baseline findings

FDG PET/CT would be performed between 28 days and 1 day before the administration of 89Zr-TLX250 on Day 0 in line with routine site protocols as part of standard of care.

**7.3 Treatment (Day 0)**

Urine pregnancy tests would be performed for pre-menopausal women. Vital signs will be recorded before and after administration of 89Zr-TLX250. 12-lead ECG and adverse event recording (NCI-CTC v 5.0) will be performed post administration

**7.4 Imaging (Day 5 ± 2 Days, but no sooner than 72 hours post administration)**

As part of PET/CT hybrid acquisition, whole body PET static and low dose CT including brain to mid-thigh will be performed. Vital signs will be recorded. Those who have potentially significant lesions with increased uptake on 89Zr-TLX250 PET/CT but not on FDG PET/CT would have their imaging discussed at the next available Uro-Oncology MDT to determine if further investigation or a deviation in management plan is required. Adverse event recording (NCI-CTC v 5.0) will be performed.

**7.5 Surgery**

Those who are deemed suitable for surgery would undergo their radical cystectomy and pelvic lymph node dissection any time after imaging.

Histopathology specimens will be sent to the study site pathology service to be reported by a specialist Uro-pathologist.

**7.6 Follow-up phone consult (Day 14 or before commencement of chemotherapy or surgery) / Final visit**

All patients will have a phone consult on Day 14 post administration (or before commencement of chemotherapy or surgery), which will include the following:

* Current symptoms enquiry
* Concomitant medications
* Adverse event recording (NCI-CTC v 5.0)

**8. Procedures and Variables**

Patients will provide written informed consent before any study-related procedures can be performed.

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

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

**8.1 Baseline Characteristics**

**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/oncological/surgical history and medical conditions present before the administration of 89Zr-TLX250 will be recorded at the screening visit.

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

**8.1.3 Prior and Concomitant Medication**

Prior and concomitant medication will be recorded on the CRF from screening.

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

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

**8.1.4 Pre-baseline Morphological Imaging**

**8.1.5 Tumour Histology**

A detailed tumour histology at the time of diagnosis will be recorded on the CRF.

**8.1.6 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.

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.

**8.2.1 FDG PET/CT Imaging**

Whole body PET/CT scans will be acquired over a maximum of 45 minutes in 4 bed positions at a single time point between 28 days and 1 day before the administration of 89Zr-TLX250 on Day 0 in line with routine site protocols.

**8.2.2 89Zr-TLX250** **PET / CT Imaging**

Whole body PET/CT scans will be acquired over a maximum of 45 minutes in 4 bed positions at a single time point on Day 5 ± 2 post administration (p.a.) of 89Zr-TLX250 using static image acquisition and low dose CT without contrast agent.

**8.2.3 Imaging Analysis**

Reading for the secondary endpoints (effectiveness of 89Zr-TLX250 PET/CT in detecting metastatic urothelial carcinoma or bladder cancer) will be conducted by two trained readers and in the event that the trained readers do not reach the same conclusion, a third adjudicator reader will review the patient images and the majority rule will apply.

**8.2.3.1 Qualitative 89Zr-TLX250** **Tumour Targeting**

89Zr-TLX250 tumour uptake will qualitatively be assessed (yes /no), considering whether or not 89Zr-TLX250 binding is noted inside or in the vicinity of lymph nodes or distant visceral organs.

The lesion will be classified as PET-positive if:

* Radioactivity in the lesion is clearly visible

A 89Zr-TLX250 PET/CT scan is considered positive, if there is at least one positive lymph node or distant metastasis.

**8.2.3.2 Quantitative 89Zr-TLX250** **Tumour Targeting**

Tumour vs mediastinal uptake ratio for 89Zr-TLX250 PET/CT will be calculated. Results will be reported as 0, 1, 2, or 3 for no, low, intermediate, or high 89Zr-TLX250 uptake. Scores 2 and 3 are empirically considered typical for metastatic lesions.

**8.2.3.3 Qualitative FDG** **Tumour Targeting**

FDG tumour uptake will qualitatively be assessed (yes/no), considering whether or not FDG binding is noted inside or in the vicinity of lymph nodes or distant visceral organs.

The lesion will be classified as PET-positive if:

* Radioactivity in the lesion is clearly visible

An FDG PET/CT scan is considered positive, if there is at least one positive lymph node or distant metastasis.

**8.2.2.4 Quantitative FDG** **Tumour Targeting**

Tumour vs mediastinal uptake ratio for FDG PET/CT will be calculated. Results will be reported as 0, 1, 2, or 3 for no, low, intermediate, or high FDG uptake. Scores 2 and 3 are empirically considered typical for metastatic lesions.

**8.3 Determination of Histological Standard of Truth**

Newly diagnosed urothelial carcinoma or bladder cancer patients who do not have distant metastasis on FDG PET imaging will proceed with cystectomy and pelvic lymphadenectomy as part of standard of care.

**8.3.1 Pathology Assessment**

Surgical resection material, along with appropriate documentation of its *in-situ* origin, allowing identification with lesion localisation on PET/CT images will be sent to the local pathology department for routine histological work-up (H&E staining, histological diagnosis). The determination of pelvic lymph node histology would be used as standard of truth for comparison with 89Zr-TLX250 and FDG PET/CT imaging. Bladder histology will be compared to 89Zr-TLX250 and FDG PET/CT imaging to determine if primary tumour was detected.

**8.4 Diagnostic Performance**

Test performance parameters (sensitivity, specificity, positive and negative predictive values, accuracy), will be determined considering visually determined qualitatitive 89Zr-TLX250 tumour uptake (yes/no), qualitative FDG tumour uptake (yes/no), and histopathology (lymph nodes positive / negative for tumour).

**8.5 Safety Evaluation**

Clinical experience in 40 patients administered with 89Zr-TLX250 as a single dose, reported mild nausea, which is an expected side effect of girentuximab.

The following side effects have also been observed with 89Zr-TLX250 but, the study doctor considered these unlikely or not related to the study treatment:

* Diarrhoea
* Urinary tract infection
* Common cold
* Monoclonal gammopathy (condition where abnormal proteins (antibodies) are found in the blood)
* Headache
* Flank pain (discomfort in your upper abdomen or back and sides)

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

* Standard laboratory (hematology, clinical chemistry and urinalysis)
* Physical examination
* 12-lead ECG
* Vital signs
* Adverse event recording (NCI-CTCAE v 5.0)
* Concomitant medication recording

**8.6 Sample Shipment**

Study product will be shipped as requested to the site in patient specific vials in appropriately shielded containers. Product accountability will be monitored during the study with the appropriate study specific form.

**8.7 Sample Retention/Destruction**

Baseline blood and urine samples will be processed routinely and no samples will be retained. If the patient consents, PET/CT images may be used in future research for which there is no defined plan as yet.

**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 CRF ("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 recognized 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 CRF, 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 CRF, regardless of causality.

If an AE fulfils any of the SAE criteria, both the AE pages of the CRF 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’ CRF. 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.

***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. “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’ CRF. 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. 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. 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 CRF, 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.

Participants will contact the Clinical Trials Nurse if they develop any AEs or have any questions regarding any symptoms they may be experiencing.

***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.

**c) 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.

***d) 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.

***e) 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.

***f) 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 (urine only)

Laboratory assessments will be performed the study site 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

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 (see Section 8.1.6).

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 included in the patient’s CRF.

**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 and 1-hour p.a.

Results will be recorded in the CRF 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, 1-hour p.a.

ECG-results will be classified by the 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 CRF.

**8.8.6 Physical Examination**

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

* Screening Visit

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.

**8.9 Total Radiation Exposure**

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

The combined whole-body effective dose of 89Zr-TLX250 administration and whole-body low-dose CT was calculated to be approximately 28mSv for all patients.

**9. Determination of sample size and statistical methods**

A pragmatic target sample size of 20 patients has been chosen for this phase 1 feasibility study, based on clinical context and logistical factors. Descriptive statistics will be used in the reporting of the primary and secondary endpoints for this pilot study.

**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 CRF must be supported by source data in the patient records.

**10.1.2 Case Report Form (CRF)**

For this study, patient data will be entered into case report form (CRF). 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 CRFs 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 CRF. This must be documented in the Delegation of Authority Log signed by the investigator.

All site personnel will be trained on the study specific CRFs prior to receiving access to data entry.

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

If any errors or discrepancies in the CRFs are found during data entry or review, “manual” queries will be generated.

Discrepancies and queries can only be corrected by the investigator(s) or other authorised site personnel.

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

**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 CRF and, if appropriate, explain, on the CRF, why the investigation was missed out (e.g. the patient was not well enough to undergo the procedure).

**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 10.5.

**10.2 Monitoring**

To enable monitoring and audits, records will be kept of the following:

* Identity of participants
* Original signed consent forms
* Copies of all CRFs
* Safety reporting forms
* Source documents
* Operation reports and medical notes
* Correspondence

**10.3 Data Management**

Enrolled patients will have clinical data collected on hardcopy case report forms and electronic Microsoft Excel spreadsheets.

**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, and only the study team at the hospital may access information collected as part of this study.

**10.5 Archiving**

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.

CRFs (including queries and audit trails) will be retained by the study site.

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.

Storage is described in Section 10.1.4.

**11 Ethical and Regulatory requirements**

## 11.1 Ethical conduct of the study

There will be a clinical relationship between the investigators and the participants as the investigators will be part of the treating team.

This study will be conducted according to the Guidance for Good Clinical Practice E6 (R2) and in compliance with applicable laws and regulations. The study will be performed in accordance with the NHMRC Statement on Ethical Conduct in Research Involving Humans 2007 (updated 2018), the Australian Code for the Responsible Conduct of Research, 2018, and the principles laid down by the World Medical Assembly in the Declaration of Helsinki 2013.

## 11.2 Ethics and regulatory review

Human research ethics committee (HREC) approval will be sought for the trial protocol, protocol amendments, informed consent documents, and relevant study documents.

The ‘Radiological Council’ approval for the study is currently being sought and will be submitted to HREC when obtained.

## 11.3 Protocol amendments

Approval of amendments by the Institutional HREC and/or Research Governance is required prior to changes to the protocol. In some instances, an amendment may require a change of consent form. The Investigator must receive approval/advice of the revised consent form prior to implementation of the change. In addition, changes to the data collected or trial activities, if required, will be incorporated in the amendment.

The investigator should not implement any changes to, or deviations from, the protocol except where necessary to eliminate immediate hazard(s) to trial participant(s).

## 11.4 Informed consent

Eligible patients will only be enrolled after providing written informed consent. Patients will be given a full explanation, in lay terms, of the aims of the study and potential risks. It will be explained that they may refuse to take part in, or withdraw from the study without prejudice to their future care and treatment. In the case where the patient is not fluent in English an interpreter will be present during the consenting process. Patients will be issued with a copy of the information provided and their consent to participate in the study.

1. **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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