Phase I Safety and Biodistribution Study of ^{124}I-PEG-AVP0458 Diabody in Patients with TAG-72 Positive Ovarian and Prostate Cancer

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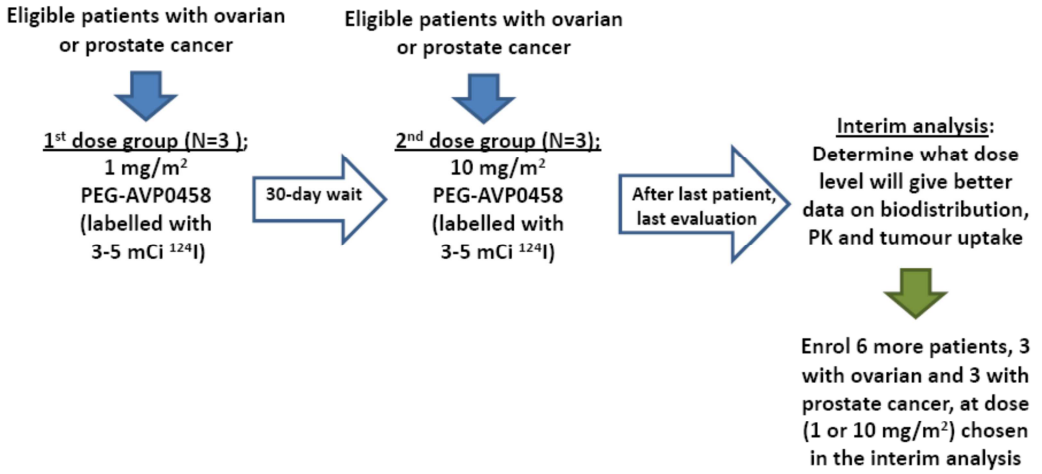
Protocol Synopsis

Title	Phase I Safety and Biodistribution Study of ^{124}I-PEG-AVP0458 Diabody in Patients with TAG-72 Positive Ovarian and Prostate Cancer
Study Design	Phase I, open-label, single-dose escalation cohort study
Clinical Sites	1. Austin Health, Heidelberg, VIC 2. Peter MacCallum Cancer Centre, Melbourne, VIC
Investigators	Andrew Scott, Ian Davis, Arun Azad, Linda Mileshkin, Tim Akhurst, Scott Williams, Declan Murphy
Study Drug	PEG-AVP0458 (administered as ^{124}I-PEG-AVP0458)
Patient Population	TAG-72 positive recurrent or refractory ovarian cancer; advanced prostate cancer; or pre-prostatectomy or pre-radiotherapy primary prostate cancer
No. Patients	12-18
Dose groups	Protein dose 1 mg/m^2 and 10 mg/m^2
Radioisotope (tracer)	^{124}I 3-5 mCi
Mode of Administration	Intravenous
Regimen	One infusion administered over 1 hour
Study Objective(s)	*Primary objective*: to evaluate the safety of PEG-AVP0458 in patients with TAG-72 ovarian and prostate cancer tumours *Secondary objectives*: to assess biodistribution and tumour uptake, pharmacokinetics (PK), and immunogenicity of ^{124}I-PEG-AVP0458
Primary Endpoints	Monitoring of incidence and intensity of adverse events (AEs) (graded using NCI CTCAE v4.0) at each study visit
Secondary Endpoints	a) Biodistribution by PET scans at days 0, 1, 2 or 3, 4 or 5, and 6 or 7 b) PK: serum levels of ^{124}I-PEG-AVP0458 measured by γ counter (blood samples collected on days 0, 1, 2 or 3, 4 or 5, 6 or 7 and 14 (±2); serum levels of PEG-AVP0458 measured by ELISA at all these time points and days 21 and 28 (±2 days) c) Immunogenicity: human anti-diabody antibodies (HADA) levels in serum (blood samples collected at days 0 and then 7, 14, 21, and 28 (±2 days)
Main Inclusion Criteria	• TAG-72 positive tumours (ovarian or prostate cancer; immunohistochemistry of archived tumours) • Detectable disease deemed likely to be assessable by PET by nuclear medicine physician • ECOG Performance status 0-1 • Expected survival > 3 months • 18 years or older

Main Exclusion Criteria	• Undergoing treatment (chemotherapy, immunotherapy or radiation) within 4 weeks of entering this study or planned to receive treatment within 4 weeks after receiving the study drug • Disease-specific criteria
Study Analyses	• Interim analysis after evaluation of the last patient in the second dose level ends • Final analysis: at the end of the study
Study Duration	12 -18 months
***Anticipated* Study Start Date**	Q1 2012
***Anticipated* Enrolment Completion**	Q1 2013
***Anticipated* Study Completion**	Q1 2013

Figure 1. PROTOCOL SCHEMA



- If no patients entered in the 1st dose group experience a dose-limiting toxicity (DLT) (as defined in Section 3.1), then the next dose group may commence 30 days after the last patient on the previous dose group has received the ^{124}I-PEG-AVP0458 infusion.
- If any one patient in either cohort of 3 patients experiences a DLT, then 3 additional patients will be entered in that dose group.
- If additional patients are treated in the first dose group, all patients entered must have been observed for 30 days before a new patient may receive an infusion in the second dose group.
- In the event 2 or more patients experience DLT at the first dose level, an additional 3 patients will be entered at a 0.5mg/m^2 dose level
- Interim analysis will evaluate safety and imaging data available after the dose escalation part of the study and will determine which of the two doses be administered to the last 6 patients in the study. The dose selected will be based on imaging characteristics and pharmacokinetic data of ^{124}I-PEG-AVP0458 at each dose level.

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ABBREVIATIONS

%ID/L	% injected dose per litre
AE	Adverse Event
AIHW	Australian Institute for Health and Welfare
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
BSA	Body Surface Area
CA-125	Cancer Antigen 125
CBC	Complete Blood Count
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose-limiting toxicity
DOTA	1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form(s)
ELISA	Enzyme Linked Immunosorbent Assay
FIGO	International Federation of Gynaecology and Obstetrics
HADA	Human Anti-Diabody Antibody
HREC	Human Research Ethics Committee
HSA	Human Serum Albumin
^{124}I	Iodine radioactive isotope 124
IHC	Immunohistochemistry
ITLC	Instant Thin-Layer Chromatography
IV	Intravenous
LDH	Lactate Dehydrogenase
mAb	Monoclonal antibody
MCH	Mean corpuscular haemoglobin
MCHC	Mean corpuscular haemoglobin concentration
mCi	MilliCurie
MCV	Mean corpuscular volume
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute (USA)
PET	Positron Emission Tomography
PK	Pharmacokinetics
PSA	Prostate-Specific Antigen
rad	Ionizing radiation unit
SAE	Serious Adverse Event
SAER	SAE Report
scFv	Single-chain Fv Molecule
SC	Subcutaneously

SOP	Standard Operating Procedure
SPECT	Single Photon Emission Computed Tomography
SSKI	Saturated Solution of Potassium Iodide
ULN	Upper Limit of Normal
US	Ultrasound
USA	United States of America
TAG-72	Tumour associated glycoprotein-72
TBR	Target binding region
TPN	Total Parenteral Nutrition
TRUS	Trans-rectal ultrasound
V_H	Variable Heavy (chain)
V_L	Variable Light (chain)
WHO	World Health Organization

SCHEDULE OF EVENTS

Activity and Assessments	Screening	Baseline & ^{124}I-PEG-AVP0458 Diabody Infusion	Post Infusion Assessments						End of Study
Day in cycle	-21 to -1	0	1	2 or 3	4 or 5	6 or 7	14 (±2)	21 (±2)	28 (±2)
Visit Number	Screening[1]	Baseline	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	End of Study Visit 7
PROCEDURE									
Informed Consent*	X								
Immunohistochemistry for TAG-72 in archived tissue samples[2]	X								
CT scan[12]	X								
Inclusion/Exclusion Criteria (eligibility)	X								
Demographics	X								
Medical history	X								
Serum Pregnancy Test[3]	X								
Thyroid Function Levels (TSH)	X								X
Vital Signs[4]	X	X	X	X	X	X	X	X	X
Physical Examination	X								X
ECOG Performance	X	X	X	X	X	X	X	X	X
12 Lead Electrocardiogram	X						X		X
CBC and differential[5]	X						X		X
Serum biochemistry[6]	X						X		X
PSA or CA-125	X								
^{124}I-PEG-AVP0458 Diabody Infusion		X							
AE Assessment[7]		X	X	X	X	X	X	X	X
Concomitant medications[8]	X	X	X	X	X	X	X	X	X
SSKI administration[9]		X	X	X	X	X			
Blood for HADA		X				X	X	X	X
Blood for PK (protein)		X[10]	X	X	X	X	X	X	X
Blood for ^{124}I counting		X[10]	X	X	X	X	X		
PET Imaging		X[11]	X	X	X	X			
Total volume of blood drawn (cumulative total [mL])	15 (15)	55 (70)	10 (80)	10 (90)	10 (100)	15 (115)	30 (145)	10 (155)	25 (180)

SCHEDULE OF EVENTS (continued)

1) These tests can be done up to 21 days prior to initiating the study.
2) Immunohistochemistry for TAG-72 expression in archived tissue samples may be performed at any time prior to initiating the study, using methods outlined in Section 4.4.
3) For women of childbearing potential.
4) Vital Signs: blood pressure, pulse, respiration and temperature. On day of infusion (Day 0), vital signs are taken at baseline prior to infusion, every 15 minutes during the infusion, and at completion of infusion, and at 1, 2 and 4 hours post infusion completion.
5) CBC and differential: Haemoglobin, erythrocytes, platelet count, leukocytes, absolute neutrophil count, eosinophils, lymphocytes, basophils, monocytes, MCV, MCH, MCHC
6) Biochemistry: Electrolytes, urea, creatinine, alkaline phosphatase, bilirubin, albumin, AST, ALT, LDH, calcium, phosphate obtained at baseline. Biochemistries repeated as per Schedule of Events. Measure prostate specific antigen (PSA) in patients with prostate cancer and CA-125 in patients with ovarian cancer at Screening only.
7) AE Assessment: All AEs, serious and non-serious, will be fully documented on the electronic case report form (eCRF) during the study phase.
8) Concomitant therapies: prescription and non-prescription therapies must be documented on the eCRF at each visit. Trade or generic name, indication, quantity administered, route, and dates of administration will be listed. Treatment history will include the 4 weeks prior to the first infusion of ^{124}I-PEG-AVP0458.
9) Super-saturated potassium iodine (SSKI): 10 drops orally twice a day for 10 days, commencing prior to infusion of ^{124}I-PEG-AVP0458.
10) On day 0, before infusion, at completion of infusion, and at 1, 2, and 4 hours after completing infusion.
11) PET Scan: approximately 1 hour after infusion on day 0.
12) CT scan: may be done up to 28 days prior to initiating the study.

* Participants must give consent in writing prior to screening and only after a complete written and verbal explanation of the study has been given to the participant.

1 BACKGROUND AND RATIONALE

1.1 Ovarian Cancer

Ovarian cancer is the most common cause of death due to gynaecological cancers in developed countries. In Australia, a total of 1,226 ovarian cancer cases were diagnosed and 795 deaths from ovarian cancer were recorded in 2006 [1]. In the United States of America (USA), an estimated 21,550 new cases were diagnosed and 14,600 women died in 2009 [2]. The major reason for this high morbidity is that at least 75% of patients are diagnosed when disease is already in advanced metastatic stages.

According to the differentiation stage of the tumours, approximately 90% of primary malignant ovarian tumours are epithelial (carcinomas). The four major types of epithelial tumours are: serous, endometrioid, clear cell, and mucinous. In addition to type of differentiation, ovarian carcinomas can be sub-classified based on degree of differentiation (tumour grade). The International Federation of Gynaecology and Obstetrics (FIGO) grading system uses 3 grades, based on architectural criteria, such as the proportion of glandular or papillary structures relative to areas of solid tumour growth. Grades 1, 2, and 3 correspond to <5%, 5–50%, and >50% solid growth, respectively.

Patients with metastatic ovarian cancer undergo surgery as initial therapy, but most of them cannot be cured by surgery alone due to residual peritoneal disease. Because ovarian cancer is a chemosensitive disease and numerous chemotherapeutic agents have been shown to produce objective responses following surgery, patients are placed on combination chemotherapy after surgery. Although about 75% of all patients with advanced ovarian cancer reach clinical complete remission, median progression-free survival ranges from 16 to 21 months, depending on the volume of disease at the time chemotherapy was initiated [3].

1.2 Prostate Cancer

Prostate cancer is the most common cancer in men in Australia and the USA. Each year, close to 3000 men in Australia die of prostate cancer and around 18,700 new cases are diagnosed. According to the Australian Institute for Health and Welfare (AIHW), there were 56,158 new cases of cancer diagnosed in males in 2005, by far the most common being prostate cancer (16,349 cases), which made up over 29% of all diagnoses [4]. As life expectancy increases, so will the incidence of this disease, thus creating possibly significant public health issues.

Prostate cancer is clinically a heterogenous disease characterized by biologic behaviour that ranges between indolent and aggressive states. The exact molecular basis for the observed disease heterogeneity is not well understood. Ultrasound (US) is used in prostate imaging for diagnostic purposes and to provide image guidance for biopsies. Prostate biopsies are performed by transrectal US (TRUS), which allows systematic sampling of the gland. Most initial biopsies involve the removal of 6–12 cores with equal distributions from base to apex and right and left sides, as well as preferential lateral sampling [5]. This widespread sampling directly targets the peripheral zone,

which is the origin for > 70% of prostate cancers. Although TRUS is used to visualise the gland and perform systematic biopsies, the detection rate of prostate cancer with TRUS is 20%–40% in men with clinical suspicion of the disease, there are a significant number of false negatives, TRUS has a low ability to distinguish between benign and malignant nodules, and patients face repeated biopsies and rising PSA levels [6]. Doctors may recommend an anaesthetic for the biopsy and a course of antibiotics before or afterwards. Even when cancers are detected, the size of the tumour is often underestimated by TRUS. The discomfort and cost of the procedure further limit its role in screening.

There are several treatments available for localised prostate cancer and they include active surveillance (watchful waiting); surgery with a radical prostatectomy; radiation, including conformal external beam radiotherapy, brachytherapy with seeds and high dose rate brachytherapy; high intensity focused ultrasound; and hormone therapy, which is used to shrink the prostate and the tumour prior to radiotherapy. If the prostate cancer has already spread to other organs or to bone at the time of diagnosis, hormone therapy becomes the primary method of treatment. Most advanced prostate cancers respond well to hormone therapy and can do so for several years.

1.3 AVP0458

1.3.1 TAG-72 Antigen

Tumour associated glycoprotein-72 (TAG-72) is a pancarcinoma antigen that was initially identified in cancer tissues by its immunoreactivity to the mouse monoclonal antibody B72.3. TAG-72 antigen is a high molecular weight glycoprotein that is expressed on adenocarcinomas of the breast, stomach, colon, prostate, and ovary [7-9]. The murine monoclonal antibody (mAb) CC49 specifically recognizes TAG-72 and has a higher affinity for this antigen and lower immunogenicity than B72.3. The higher affinity of CC49 has been shown to result in better tumour localization [10, 11] [12].

1.3.1.1 Expression of TAG-72 in prostate cancer

Expression of TAG-72 in prostatic adenocarcinomas has been evaluated using the CC49 antibody [13-15]. The study performed by Brenner and colleagues [13] reported that approximately 80% of prostatic adenocarcinomas express TAG-72, with most immunoreactivity observed in the cytoplasm of malignant cells and no immunoreactivity within benign epithelium or stroma. CC49 staining was detected in all well differentiated tumours tested (n=6; Gleason score of 2-4), 8 of 10 moderately differentiated (Gleason score of 5 to 6), and 7 of 9 poorly differentiated tumours (Gleason score of 7 to 9). In contrast to primary lesions, expression of TAG-72 in metastatic prostate cancers is downregulated, but still present in 50% of the bone lesions tested [13]. Only 50% of the specimens from men treated with androgen deprivation were immunoreactive (10 of 20, vs 21 of 25 non-hormonally treated tumours), likely due to the changes in glandular mucin triggered by hormonal therapy. However, in a more recent study, Hong et al (2011) found that TAG-72 is strongly positive in the majority of prostate cancers irrespective of grade, stage or pre-operative PSA [41].

1.3.1.2 Expression of TAG-72 in ovarian cancer

Several studies evaluated the expression of TAG-72 in ovarian cancer tissue samples and microarrays of different stages and histological subtypes [16, 17]. The study conducted by Ponnusamy and colleagues found four patterns of TAG-72 localization: cytoplasmic, membrane bound, luminal and diffused (both membrane and cytoplasmic) [17]. A total of 88% of the ovarian cancer tissue samples (n=43) showed immunoreactivity with the CC49 antibody, and expression of TAG-72 in advanced stage cancer tissues was significantly higher (p=0.035) compared to the early stage tumours. The study also reported that membrane localization of TAG-72 in tumours was significantly (p=0.0082) associated to the poor clinical outcome, while cytoplasmic staining was correlated significantly to a better prognosis (p=0.0051).

Similarly, the study conducted by Chauhan and colleagues demonstrated that 72% of all ovarian cancer types showed immunolabelling for TAG-72 [16]. Expression levels of TAG-72, MUC1 and CA125 antigens were significantly higher in advanced stage carcinomas compared with early stage ($p<0.005$). Of the 48 epithelial ovarian cancer samples, 87.5% of all cases were TAG-72 positive.

1.3.1.3 Clinical evaluation of anti-TAG-72 antibodies

Antibodies recognizing TAG-72 have been assessed in numerous Phase I/II clinical trials with modest results [11, 18-21]. Most clinical trials made use of radiolabelled *whole antibody* for radioimmunotherapy or radioimmunoguided surgery and have employed a pre-targeting strategy. Haematological toxicity most often limited the quantity of radionuclide that could be administered, whereas the amount of radiation delivered to tumour sites was still below that required to cause tumour regressions.

These clinical results clearly define the need for a recombinant anti- TAG-72 antibody fragment with improved pharmacokinetics (PK), faster blood clearance and significantly higher dose deposition.

1.3.2 Antibody based cancer therapy and radioimmunodetection

Numerous antibody-based cancer therapies have been developed in the past decades, taking advantage of the specificity and relatively easy production of antibodies. Antibodies are also the basis of other cytotoxic pharmaceutical products, such as radiolabelled antibodies for radioimmunotherapy [22], immunotoxins, chemotherapy/antibody conjugates [23], cytokine/antibody conjugates [24], and others.

Although antibody therapeutics provide significant benefit to some patients with cancer, they are seldom curative. Antibody conjugation to cytotoxic drugs enhances the antitumor activity of antibodies and reduces the systemic toxicity of the conjugated drugs [25]. By linking monoclonal antibodies to highly cytotoxic drugs, higher tumour selectivity is conferred to the drugs that are otherwise too toxic to be used on their own and may confer greater therapeutic utility compared to using monoclonal antibodies alone.

Radioimmunodetection of tumour sites may provide additional information on the stage of disease, and can also provide in-vivo evidence of expression of antigen by tumour, and subsequent likely response to targeted monoclonal antibody therapeutic approaches.

1.3.3 Recombinant Diabodies

Avibody™ products are antibody-like proteins designed and created by *Avipep Pty Ltd* (Parkville, Victoria). They are multimeric antibody fragments (diabodies, triabodies) that represent an improved alternative to antibodies [26-30], as they are characterized by increased tissue penetration, high avidity (slow off-rates) and fast blood clearance. These characteristics have been demonstrated in several animal models, in which Avibody proteins have shown excellent tumour localization [31-35].

Avibody products can be created, like intact antibodies, with at least two target binding regions, which enables them to attain very high affinity for the target antigen (e.g. cancer cells). Significant improvements in Avibody products compared with the parent Ig are:

- Tumour: blood ratios of 50:1 after 12 hours for diabodies
- Lack of Fc components and thus, undesirable effector functions (toxicity) for some clinical indications
- Reduced immunogenicity
- Small size (60~120kDa), ideal for tumour/clot targeting *in vivo.*

Avibody products are suitable for further customization of their *in vivo* properties by conjugating clinically relevant payloads (radioisotopes for imaging or with cytotoxic drugs for therapy) in a site-specific manner and with defined stoichiometry. Among the clinically relevant payloads that could be accommodated by Avibody products are imaging and fluorescent probes, and radiotracers for Positron Emission Tomography (PET) or Single Photon Emission Computed Tomography (SPECT) imaging, radiotracers for therapy and toxins or drugs for other therapeutic modalities. For therapeutics, Avipep's conjugation strategies can be associated to multiple novel linker chemistries designed to optimally deliver payloads, depending on whether or not the targeted tumour antigen internalizes.

Avipep has focused on the use of Avibody products in the diabody format, 55 kDa noncovalent scFv dimers formed by producing scFv molecules with short (4-5 amino acid) linkers between their variable heavy (V_H) and variable light (V_L) chains [36, 37]. This prevents the V_H and V_L chains in a molecule from creating a typical scFv orientation. Instead, V_L from one molecule associate with V_H from another, resulting in the formation of a rigid dimer that divalently interacts with antigen.

1.3.4 AVP0458 Drug Description

AVP0458 targets the pancarcinoma antigen TAG-72 described above in **Section 1.3.1**. The recombinant 51 kDa AVP0458 that is being evaluated in this clinical study was designed to contain the already clinically validated antibody sequence of the TAG-72 specific CC49 antibody (variable region). Two of the CC49 functional binding sites are fused in sequence to form a stable, biologically active diabody. The amino acid sequence of the variable domains of CC49 has been modified [38] in order to achieve a high-expressing and highly stable recombinant molecule.

In order to increase its hydrodynamic size, AVP0458 was PEGylated (24 PEG residues were added on specific Cysteine residues). PEGylation of a drug or pharmaceutical agent prolongs their

circulatory time by reducing renal clearance. The molecular weight of the PEGylated AVP0458 (PEG-AVP0458) is ~56kDa.

1.3.5 Biodistribution of ^{124}I-PEG-AVP0458 in LS174T Xenograft Model

The biodistribution properties and PET imaging characteristics of ^{124}I-PEG-AVP0458 have been evaluated in nude mice with the TAG-72-expressing LS174T colorectal cancer xenografts. Excellent tumour uptake (mean peak uptake 55%ID/gm at 24-48 hrs post injection) was observed, with prolonged tumour retention, and excellent imaging properties. Normal tissues showed minimal ^{124}I-PEG-AVP0458 uptake, consistent with blood pool activity only. Pharmacokinetic analysis revealed a long serum half-life, with T½α=6.77 hrs, and T½β=29.72 hrs. This data supports the use of PEG-AVP0458 as a specific targeting strategy for TAG-72 expressing tumours.

1.4 Rationale for the Study

The TAG-72 antigen has been shown to be a well defined, clinically relevant target for monoclonal antibody based therapy. Avibody™ technology has been shown to be an exciting approach to modifying antibodies to enhance tumour uptake and penetrance, and pegylation of diabodies has been shown to eliminate renal uptake and enhance pharmacokinetics. PEG-AVP0458 has been engineered to specifically target TAG-72 expressing tumours, including prostate and ovarian cancer, in both laboratory and in-vivo animal model systems. To confirm the tumour targeting potential of PEG-AVP0458, a Phase I first-in-human clinical trial is proposed to explore the safety, biodistribution and pharmacokinetics, and immunogenicity, of a single dose of ^{124}I-labelled PEG-AVP0458 in patients with prostate or ovarian cancer

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this clinical study is to evaluate the safety of a single dose of ^{124}I-PEG-AVP0458 in patients with prostate and ovarian cancer.

2.2 Secondary Objectives

The secondary objectives of this study are to evaluate the biodistribution, including tumour targeting, PK and immunogenicity of ^{124}I-PEG-AVP0458 in patients with prostate and ovarian cancer.

3 STUDY DESIGN

3.1 Summary of Design

This is a Phase I, open-label study of the safety and biodistribution of two escalating doses of PEG-AVP0458, labelled with 3-5 mCi of ^{124}I for PET imaging. A schematic diagram of the trial is presented in Protocol Synopsis, page 7. ^{124}I-PEG-AVP0458 is to be administered to patients by slow intravenous infusion over an hour, with safety monitoring during and for 4 hours post infusion. PET imaging will be performed post infusion of ^{124}I-PEG-AVP0458 on Day 0, and on a further 4 occasions over a one week period. The PEG-AVP0458 dose will be either 1 mg/m^2 (in the first dose level) or 10 mg/m^2 (second dose level), and the amount of ^{124}I radioactivity is kept constant at 3-5 mCi. The last dose group will receive either of these two doses, depending on safety and the quality of imaging results obtained in the dose-escalation part of the study; this will be determined in the interim analysis. The dose groups can be summarised as follows:

Dose Group	Number of Patients	PEG-AVP0458 dose (mg/m^2)	^{124}I-PEG-AVP0458 dose (mCi)
1	3	1	3-5
2	3	10	3-5
3	6	1 or 10	3-5

The choice of the two doses of PEG-AVP0458, 1 mg/m^2 and 10 mg/m^2, was based on the amount of AVP04-07 diabody used in the biodistribution studies in mouse xenografts [39] and on the amount of TAG-72 intact antibody (CC49) tested in previous clinical trials [11]. Prior trials of CC49 showed that optimal tumour uptake and biodistribution occurred at approximately 10mg dose levels. Results of a 14-day single dose toxicology study of PEG-AVP0458 have shown the no-adverse effect level (NOAEL) to be 20mg/kg, which corresponds to dose that is approximately 100 times the starting dose of 1mg/m^2 in this protocol (when normalised to body surface area). In view of the anticipated lack of toxicity of PEG-AVP0458, and prior experience with murine CC49 in patients, escalation from 1mg/m^2 to to the second dose level of 10mg/^{2} is considered appropriate to define the optimal biodistribution and tumour uptake dose level.

The primary endpoint of the study is the safety of a single dose of PEG-AVP0458. The secondary endpoints measured are biodistribution, PK and immunogenicity of ^{124}I-PEG-AVP0458.

Eligible patients with TAG-72-positive ovarian or prostate cancer will be entered into the study sequentially at each site until the total targeted number for each dose level is reached.

As this is a first in-human study, a single subject will receive the first dose of ^{124}I-PEG-AVP0458. Further dose administration will be sequential within each cohort to mitigate risks of anaphylactic or any other acute unexpected reactions. Administration of doses within a cohort will be staggered by 24 hours, i.e. there will be a period of 24 hours between the first, second and subsequent subjects in a cohort to observe and interpret reactions and adverse events. This time frame is sufficient to exclude any possible acute allergic or anaphylactic reactions to PEG-AVP0458.

After completion of accrual into the first cohort (1 mg/m^2 dose), the Trial Management Committee will review the safety data from these participants before a decision is made to escalate the dose to 10 mg/m^2.

If no patients entered in the 1st dose group experience a dose-limiting toxicity (DLT), and the Trial Management Committee agree, then the 2nd dose group may commence on the higher dose of 10 mg/m^2 30 days after the last patient on the first dose group has received the ^{124}I-PEG-AVP0458 infusion. If any one patient in either cohort of 3 patients experiences a DLT, then 3 additional patients will be entered in that dose group. If additional patients are treated in the 1st dose group, all patients entered must have been observed for 30 days before a new patient may receive an infusion in the 2nd dose group. If greater than or equal to two DLTs are observed at a dose, then the MTD is considered to have been exceeded.

If at most, one DLT is observed, the next 3 patients are assigned to the next highest dose. If two or more DLTs are observed, then the MTD is considered to have been exceeded.

A DLT is defined as any of the following events occurring within 30 days of study drug administration:

- Any Grade 2 or greater allergic reaction.
- Any Grade 3 toxicity. Exceptions are: fever; asymptomatic hyperglycemia; hypophosphatemia; nausea, vomiting, or diarrhoea despite the use of optimal supportive medical therapy; leukopenia or thrombocytopenia that revert to baseline within three weeks of occurrence; lymphopenia without other dose-limiting events (eg opportunistic infection).
- Any Grade 4 toxicity.

The 30 days will allow identification and mitigation of the risks of any delayed immunogenic reaction before progressing to a subsequent cohort.

In the event 2 or more patients experience DLT at the first dose level, an additional 3 patients will be entered at a 0.5mg/m^2 dose level.

After the last evaluation of the last patient enrolled in the second dose group (10 mg/m^2), an interim analysis of the safety and dosimetry data will be undertaken. This analysis will be considered by the Trial Management Committee to ascertain which of the two doses, 1 or 10 mg/m^2, produces the better safety profile and dosimetry results for PEG-AVP0458. The dose selected will be based on imaging characteristics and pharmacokinetic data of ^{124}I-PEG-AVP0458 at each dose level. This chosen dose will be used to infuse the last 6 patients in the second part of the clinical study. This last group will enrol 3 patients with prostate cancer and 3 with ovarian cancer and will continue to evaluate safety as the primary endpoint.

Because of the low PEG-AVP0458 doses tested in this study, the fact that only two dose levels are being evaluated, and the past clinical experience with the intact parent antibody (CC49), this study is not expected to identify a maximum tolerated dose. It should be noted that the tracer dose of ^{124}I-labelled to PEG-AVP0458 has not been reported to be associated with adverse events in prior clinical trials of ^{124}I-labelled compounds.

3.2 Sample Size

An anticipated total of 12-18 patients will be entered into the study. In the dose-escalating part of the study, 6 patients with either prostate or ovarian cancer will be enrolled: 3 in the 1 mg/m^2 dose group and 3 in the 10 mg/m^2 dose group. If DLTs occur, the number will increase to a maximum of 12.

In the second part of the study, a further 6 patients will be enrolled, 3 with ovarian cancer and 3 with prostate cancer. They will receive the PEG-AVP0458 dose defined in the interim analysis.

3.3 Study Duration

It is anticipated that patient accrual will require approximately 9 months and the clinical trial will end 12 months after enrolment of the first patient.

3.4 Participating Sites

The participating clinical trial sites for this study are:

- Austin Health
- Peter MacCallum Cancer Centre

Patients with ovarian cancer will also be referred from the Royal Women's Hospital and Mercy Hospital for Women.

4 Study population

4.1 Patient Recruitment

Patients with recurrent or refractory ovarian cancer or patients with confirmed metastatic prostate cancer, or patients with confirmed primary prostate cancer prior to local therapy (surgery or radiation), will be considered for this trial if their tumours are TAG-72 positive (evaluation performed on archived paraffin blocks) and they have disease deemed likely to be assessable by PET by nuclear medicine physician.

4.2 Inclusion Criteria

Eligibility for the study will be determined by screening tests, physical examination/medical history, and provision of written informed consent and fulfillment of eligibility criteria.

Participants will be considered eligible for enrolment in the study if they comply with all of the following criteria

4.2.1 Ovarian cancer

- Patients with relapsed or refractory ovarian cancer
- TAG-72-positive tumours (see **Section 4.4**)
- Detectable metastatic disease deemed likely to be assessable by PET by nuclear medicine physician as seen on imaging (see **Section 4.5**) performed within 21 days of enrolling in the study.
- ECOG Performance Status of 0-1 (**Appendix 1**)
- Expected survival of ≥ 3 months
- 18 years of age or greater
- Platelet count ≥100 x 10^9/L
- Absolute neutrophil count ≥ 1.5 x 10^9/L
- Aspartate Aminotransferase (AST) ≤3x upper limit of normal (ULN), or <5x ULN with liver metastases
- Total bilirubin ≤ 34 µmol/L
- Serum creatinine ≤160 µmol/L
- Provision of written informed consent.

4.2.2 Prostate cancer

- Patients with metastatic prostate cancer, or primary prostate cancer who are pre-prostatectomy or pre-radiotherapy
- TAG-72-positive tumours (see **Section 4.4**)
- Detectable disease deemed likely to be assessable by PET by nuclear medicine physician as seen on imaging (see **Section 4.5**) performed within 21 days of enrolling in the study
- ECOG Performance Status of 0 or 1 (**Appendix 1**).
- Expected survival of ≥ 3 months
- 18 years of age or greater
- Platelet count ≥100 x 10^9/L
- Absolute neutrophil count ≥ 1.5 x 10^9/L
- AST ≤3x ULN, or <5x ULN with liver metastases
- Total bilirubin ≤ 34 µmol/L
- Serum creatinine ≤160 µmol/L
- Provision of written informed consent.

4.3 Exclusion Criteria

Participants will not be entered in the study for any of the following reasons:

4.3.1 Ovarian Cancer

- Disease-specific exclusions
    - Evidence of current complete or partial bowel obstruction
    - Need for IV or TPN hydration
- Chemotherapy, immunotherapy, biologic therapy, radiation therapy, or other investigational product within 4 weeks prior to study entry or likely to be required during the 4-week on-study period
- Patients using corticosteroids or immunosuppressive agents: low dose oral corticosteroids for concomitant medical conditions are permitted. Inhaled or topical corticosteroids are permitted.
- Patients with active infections requiring antibiotics, with bleeding disorders or with other serious illness
- Women who are pregnant (positive hCG test) or lactating
- Women of child-bearing potential who are unwilling to utilize a medically acceptable method of contraception
- Patients with a concurrent active serious medical condition likely to affect participation in the study, such as a documented myocardial infarction ≤3 months prior to screening or unstable angina pectoris.
- Patients unable to sign informed consent or unwilling to comply with the procedural requirements of this clinical protocol.

4.3.2 Prostate cancer

- Chemotherapy (not including androgen deprivation therapy), immunotherapy, biologic therapy, radiation therapy, or other investigational product within 4 weeks prior to study entry or likely to be required during the 4-week on-study period
- Patients using corticosteroids or immunosuppressive agents: low dose oral corticosteroids for concomitant medical conditions are permitted. Inhaled or topical corticosteroids are permitted.
- Patients with active infections requiring antibiotics, with bleeding disorders or with other serious illness
- Patients with a concurrent active serious medical condition likely to affect participation in the study, such as a documented myocardial infarction ≤3 months prior or to screening or unstable angina pectoris
- Men who are unwilling to utilize a medically acceptable method of contraception
- Patients unable to sign informed consent or unwilling to comply with the procedural requirements of this clinical protocol.

4.4 TAG-72 Screening

Because PEG-AVP0458 is an antibody fragment specific for TAG-72, only patients with tumours positive for this antigen will be enrolled in the clinical trial. TAG-72 presence in archived tumour specimens will be evaluated using a validated immunohistochemical (IHC) method by TissuPath. Relevant controls will be run in each assay.

Tumours will be defined as TAG-72 positive if at least 20% of tumour cells are stained by IHC (either strongly or weakly).

Clinical investigators or referring physicians from clinical trial sites or CTA member hospitals respectively will obtain written informed consent from the patients under consideration for participation in this study, and arrange for archived tumour specimens to be sent from the relevant hospital department of pathology to the central laboratory (TissuPath) for TAG-72 screening. TissuPath will send results of the TAG-72 screening test to the clinical investigator or referring physician. If the results are positive, the referring physician from a CTA-member hospital will refer the patient to the appropriate clinical trial site for further screening and enrolment.

4.5 Tumour Size Screening

In order to be eligible for inclusion in this study, patients must have disease that is evaluable for ^{124}I-PEG-AVP0458 biodistribution by screening CT scan. Only patients with tumours deemed likely to be assessable by PET by study site nuclear medicine physicians will be eligible for the trial.

5 Study procedures

5.1 Screening Visits (Day -21 to -1)

Written informed consent will be obtained. Review study with subject and obtain written informed consent in accordance with TGA requirements and the policies of the responsible HREC. Patients will be informed that they will only be recruited into the Study if their TAG-72 and tumour screenings meet inclusion criteria for the Study.

5.1.1 TAG-72 Screening

The Investigator will send appropriate archived tumour tissue specimen of patient to TissuPath for screening by IHC according to section 4.4. IHC for TAG-72 expression in archived tissue samples may be performed at any time prior to initiating the study.

5.1.2 Tumour Screening (Day -28 to -1)

The Investigator will send CT scan of patient to the Principal Investigator who is a nuclear medicine physician to ascertain the tumour is deemed assessable by PET, according to section 4.5.

5.1.3 All other Screening (Day -21 to -1)

Patients who meet the inclusion criteria for TAG-72 tumour expression will undergo further screening as follows:

- Complete medical history including demographics.
- Complete physical examination
- Vital signs (blood pressure, pulse, respiratory and temperature)
- ECOG (Eastern Cooperative Oncology Group) performance
- 12-lead electrocardiogram
- Full blood profile (CBC and differential)
- Serum biochemistry (electrolytes, urea, creatinine, alkaline phosphatase, bilirubin, albumin, AST, ALT, LDH, calcium, phosphate) and thyroid function levels (TSH)
- Prostate specific antigen (PSA) levels in patients with prostate cancer and CA-125 levels in patients with ovarian cancer.
- Serum pregnancy test for women of child bearing potential
- Concomitant medications. Prescription and non-prescription therapies must be documented. Trade or generic name, indication, quantity administered, route, and dates of administration will be listed. Treatment history will include the 4 weeks prior to the infusion of ^{124}I-PEG-AVP0458.

5.2 Baseline prior to Administration of Investigational Product (Day 0)

Subjects will attend the study site (Austin Health or Peter MacCallum Cancer Centre) by approximately 8 am.

The following assessments and activities will be undertaken:

- Vital signs (blood pressure, pulse, respiratory and temperature)
- ECOG performance
- Concomitant medications. Prescription and non-prescription therapies must be documented. Trade or generic name, indication, quantity administered, route, and dates of administration will be listed.
- Blood sample taken before infusion of ^{124}I-PEG-AVP0458 for assessment of HADA and pharmacokinetics by ELISA and ^{124}I counting.
- Administer 10 drops super saturated potassium iodide (SSKI) immediately prior to infusion of ^{124}I-PEG-AVP0458 (and twice daily for a total of 10 days).

5.3 Administration of Investigational Product

The appropriate quantities of ^{124}I-PEG-AVP0458 will be drawn into a syringe with sterile sodium chloride injection and 5% human serum albumin (HSA). The resultant ^{124}I-PEG-AVP04 in the syringe will be injected into a 100 mL infusion bag of sterile sodium chloride injection and 5% HSA via a sterile 0.2 µm filter.

Patients will receive 1 mg/m^2 or 10 mg/m^2 of ^{124}I-PEG-AVP0458 infusion intravenously over approximately 1 hour. Patients will be kept reclined during the infusion and observed for the first four hours after the infusion has been completed.

PEG-AVP-0458 will be labelled with ^{124}I in laboratories of the Ludwig Institute of Cancer Research, at Austin Health, under sterile conditions and according to SOPs (see Section 9.3). Following QC testing, the dose of ^{124}I-PEG-AVP-0458 will be then distributed to the infusion room at the study site for subsequent patient infusion. The criteria for dose escalation and dose selection are provided in Section 5.14.

5.4 Post-Administration of Investigational Product (Day 0)

The following assessments are undertaken:

- Vital signs (blood pressure, pulse, respiratory and temperature) every 15 minutes during the infusion, at completion of infusion, and at 1, 2 and 4 hours after infusion completion. Note: these time points correspond to 2, 3 and 5 hours after commencement of infusion.
- Blood sample taken immediately post infusion, and then at 1, 2 and 4 hours after completion of infusion for assessments of pharmacokinetics by ELISA and ^{124}I counting.
- A PET scan is performed approximately 1 hour after infusion, according to the PET Imaging Charter.
- Adverse events, if observed, are recorded, taking special precaution for anaphylaxis, allergic and/or infusion reactions (see Section 5.9.2).

At the end of the assessments (five hours after commencement of infusion), patients may return home if there are no ongoing adverse effects of the infusion.

5.5 Days 1, 2 or 3, 4 or 5, 6 or 7 (Study Visits 1, 2, 3 and 4 post infusion)

Patients return to the Study Site at the appointed time for the following assessments:

- Vital signs (blood pressure, pulse, respiratory and temperature)
- ECOG performance
- Concomitant medications. Prescription and non-prescription therapies must be documented. Trade or generic name, indication, quantity administered, route, and dates of administration will be listed.
- Adverse events
- Blood sample for assessments of pharmacokinetics by ELISA and ^{124}I counting
- Blood sample for assessment of HADA on day 6 or 7
- PET scan

Some flexibility is allowed in the schedule (eg. Day 2 or 3, 4 or 5, 6 or 7) to allow for availability of PET/CT scans and weekends. Such flexibility is enabled by the relatively long half-life of the ^{124}I radionuclide and the diabody being studied.

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5.6 Day 14 (±2) (Study Visit 5)

Patients return to the Study Site at the appointed time for the following assessments:

- Vital signs (blood pressure, pulse, respiratory and temperature)
- ECOG performance
- 12-lead electrocardiogram
- Full blood profile (CBC and differential)
- Serum biochemistry (electrolytes, urea, creatinine, alkaline phosphatase, bilirubin, albumin, AST, ALT, LDH, calcium, phosphate)
- Concomitant medications. Prescription and non-prescription therapies must be documented. Trade or generic name, indication, quantity administered, route, and dates of administration will be listed.
- Adverse events
- Blood sample for assessments of HADA and pharmacokinetics by ELISA and ^{124}I counting

5.7 Day 21 (±2) (Study Visit 6)

Patients return to the Study Site at the appointed time for the following assessments:

- Vital signs (blood pressure, pulse, respiratory and temperature)
- ECOG performance
- Concomitant medications. Prescription and non-prescription therapies must be documented. Trade or generic name, indication, quantity administered, route, and dates of administration will be listed.
- Adverse events
- Blood sample for assessments of HADA and pharmacokinetics by ELISA

5.8 Day 28 (±2) (End of Study Visit 7)

This is the End of Study visit. Patients return to the Study Site at the appointed time for the following assessments:

- Thyroid function levels (TSH)
- Complete physical examination
- Vital signs (blood pressure, pulse, respiratory and temperature)
- ECOG (Eastern Cooperative Oncology Group) performance
- 12-lead electrocardiogram
- Full blood profile (CBC and differential)
- Serum biochemistry (electrolytes, urea, creatinine, alkaline phosphatase, bilirubin, albumin, AST, ALT, LDH, calcium, phosphate)
- Concomitant medications. Prescription and non-prescription therapies must be documented. Trade or generic name, indication, quantity administered, route, and dates of administration will be listed.
- Adverse events
- Blood sample for assessments of HADA and pharmacokinetics by ELISA

At the end of the assessments, the patients will be discharged from the Study Site.

5.9 Safety Monitoring and Management

5.9.1 Infusion Safety Monitoring

On the day of ^{124}I-PEG-AVP0458 infusion, all patients will have baseline vital signs taken prior to the infusion. Saturated solution of Potassium Iodide (SSKI) (obtained from Hospital pharmacy), 10 drops twice daily, will be administered immediately prior to the infusion and will continue for a total of 10 days. All concomitant therapies and ongoing AEs occurring since the last visit will be reviewed and documented in the patient's medical history and eCRF.

For the infusion, vital signs and careful monitoring for symptoms such as allergic reactions will be measured and recorded during the infusion and the 4 hours post infusion completion. Vital signs and all AEs occurring during this period will be documented in the patient's medical history and eCRF.

All Grade 2 and higher AEs occurring during the infusion and up to 4 hours post-infusion are considered to be infusional toxicities regardless of relationship to drug and CTCAE v4.0 Grade.

5.9.2 Modifications for events occurring during or immediately after ^{124}I- PEG-AVP0458 infusion

There is a potential for the occurrence of allergic-type reactions during and immediately following the administration of ^{124}I-labelled PEG-AVP0458. If this occurs, the rate of infusion should be decreased or the infusion terminated completely in accordance with the following guidelines:

	Action[1]	
Clinical Manifestation	Decrease rate of ^{124}I-PEG-AVP0458 Infusion by 50%	Stop ^{124}I-PEG-AVP0458 Infusion[2]
↓ Systolic BP of 25-50 mmHg	X	
↓ Systolic BP of >50 mmHg		X
Bronchospasm		X
Severe shortness of breath		X
Rigors	X	
Chills	X	

1 = Investigator discretion is necessary for a decision to reduce the rate or stop ^{124}I-PEG-AVP0458 infusion.

2 = The infusion may be re-initiated within 1 hour at the discretion of the Investigator. Should the clinical situation require that therapy be stopped again, the ^{124}I-PEG-AVP0458 infusion will not be restarted and the patient will be removed from study.

5.9.3 Management of Toxicities

Precautions for anaphylaxis must be available. Equipment for assisted ventilation and an established free flowing line must be available at the time of each infusion.

A life-threatening anaphylactic response of a sensitized human may appear within minutes after administration of a specific antigen and is manifested by respiratory distress often followed by vascular collapse or by shock without antecedent respiratory difficulty. Cutaneous manifestations are exemplified by pruritus and urticaria with or without angioedema and may be characteristic for systemic anaphylactic reactions. Gastrointestinal manifestations may include nausea, vomiting, crampy abdominal pain, and diarrhoea.

Diagnosis of anaphylaxis or choice of treatment and drug dosing is in the responsibility and at the discretion of the individual Investigator.

Appropriate supportive therapeutic interventions may be initiated at any time. Treatment with IV corticosteroids, antihistamines, pethidine, paracetamol, or adrenaline should be considered in the event of an allergic reaction or hypersensitivity. Refer to **Appendix 2** for definition of allergic reaction or hypersensitivity according to CTCAE v4.0.

These events will be recorded in the patient's medical history and eCRF.

5.10 Criteria for Dose Escalation and Dose Selection

The Trial Management Committee is responsible for decisions regarding dose escalation (moving dose group 1 to group 2) and dose selection (moving from group 2 to 3), based on safety and dosimetry data.

For dose escalation, the decision is based on safety. If no patients in dose group 1 experience a DLT, then dose group 2 may commence 30 days after the last patient on the dose group 1 has received the PEG-AVP0458 infusion.

If any one patient in either cohort of 3 patients experiences a DLT, then 3 additional patients will be entered in that dose group. If additional patients are treated in the dose group 1, all patients entered must have been observed for 30 days before a new patient may receive an infusion in dose group 2. If greater than or equal to two DLTs are observed at a dose, then the MTD is considered to have been exceeded. If at most, one DLT is observed, the next 3 patients are assigned to the next highest dose. If two or more DLTs are observed, then the MTD is considered to have been exceeded.

In the event 2 or more patients experience DLT at the first dose level, an additional 3 patients will be entered at a 0.5mg/m^2 dose level

The Trial Management Committee will evaluate safety and dosimetry data available after the dose escalation part of the study (Interim Analysis) and determine the dose to be administered to the last 6 patients in the study.

5.11 Treatment Restrictions

The following therapies may not be used before end of Day 28 of the study:

- Chemotherapeutic or agents with known anti-cancer activity for the disease under study
- Radiation therapy
- Immunotherapy
- Immunosuppressive agents including corticosteroids, except for low dose corticosteroids used for concomitant medical conditions.
- Any other investigational agent.

Topical or inhalational steroids are permitted. Investigators may prescribe concomitant supportive medications or treatments deemed necessary to provide adequate patient care.

All prescription and non-prescription concomitant medications must be recorded in the eCRF, listing generic name, indication, dose and schedule and dates of administration.

5.12 Concomitant Diagnosis and Therapies

In this trial, a pre-existing condition (i.e., a disorder present before the AE reporting period started) should not be reported as an AE unless the condition worsens during the AE reporting period.

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE and the resulting appendectomy noted under Comments.

Concomitant supportive medications or therapy to provide adequate care may be prescribed as necessary and will be documented in the patient's medical history and eCRF. All prescription and non-prescription concomitant medications and treatments will be recorded at each visit in the eCRF. Trade or generic name, indication, quantity administered, route, and dates of administration will be listed. Treatment history will include the 4 weeks prior to the first infusion of ^{124}I-PEG-AVP0458.

SSKI (10 drops, twice daily) will be given immediately prior to the ^{124}I-PEG-AVP0458 infusion, continuing for a total of 10 days. The administration of this agent is to prevent the uptake of radioiodine in the thyroid gland.

5.13 Patient Evaluability

All patients who receive the infusion of ^{124}I-PEG-AVP0458 diabody will be evaluable for safety. Every effort will be made to obtain complete information on all AEs, with particular emphasis on serious AEs, infusional toxicities, and hypersensitivity reactions. Patients will be evaluable for biodistribution and pharmacokinetics assessment if they complete all study procedures up to Visit 4 (Day 6 or 7

visit). Patients will be evaluable for immunogenicity of PEG-AVP0458 if they have completed the Day 28 (±2 days) visit procedures.

5.14 Criteria and rules for stopping patient treatment

An Investigator may stop a patient's participation for the following reasons:

- The patient withdraws consent.
- The patient is no longer able to participate.
- A patient can be withdrawn after discussion between the Sponsor and Investigator if eligibility criteria are violated or if the patient fails to comply with the protocol (e.g., non-adherence to study assessment visits).
- The Investigator's judgment that continued participation is no longer in the patient's interest.

Documentation of the details of withdrawal will be included in the eCRF. All patients who receive the ^{124}I-PEG-AVP0458 infusion will be evaluated for safety.

5.15 Patient Replacement

Any patient who does not complete the scheduled visits (up to 4 weeks after receiving the therapeutic infusion) for reasons unrelated to study drug administration may be replaced.

6 Study assessments

6.1 Safety Evaluation

Safety of ^{124}I-PEG-AVP0458 will be determined by the ongoing monitoring of the incidence and intensity of AEs graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v4.0 (**Appendix 2**), with special emphasis on DLT events and infusional toxicities. A copy of CTCAE v4.0 also may be downloaded from the Cancer Therapy Evaluation Program home page (http:\\ctep.info.nih.gov).

A DLT is defined as any of the following events occurring within 30 days of study drug administration:

- Any Grade 2 or greater allergic reaction.
- Any Grade 3 toxicity. Exceptions are: fever; asymptomatic hyperglycemia; hypophosphatemia; nausea, vomiting, or diarrhoea despite the use of optimal supportive medical therapy ; leukopenia or thrombocytopenia that revert to baseline within three weeks of occurrence; lymphopenia without other dose-limiting events (eg opportunistic infection).
- Any Grade 4 toxicity.

To be dose-limiting, a toxicity must be possibly, probably, or definitely related to the administration of ^{124}I-PEG-AVP0458. All DLTs must be discussed with the study Coordinating Principal Investigator.

AEs will be collected after the patient has been enrolled. AEs occurring after signing informed consent but prior to receiving study drug (ie before enrolment) should only be reportable if related to study procedures. **All** AEs occurring after enrolment must be recorded until 30 days following the end of treatment exposure. Refer to Section 7.2.1. AEs include adverse drug reactions, any unfavourable sign or symptom (related and unrelated), illnesses with onset during the study, or exacerbations of pre-existing illnesses or conditions. Progression of the patient's malignancy should not be considered an AE, unless, in the Investigator's opinion, study treatment resulted in an exacerbation of the patient's condition. Exceptions are if disease progression results in death or hospitalization while on study or within 30 days of the last dose. If either occurs, progressive disease will be reported as a SAE (see *Section 8.2.2*) and will also be documented on an AE eCRF. All observed or volunteered AEs, regardless of treatment group or suspected causal relationship to study drug, will be recorded on the AE eCRF.

Clinically significant changes in physical examination findings and new abnormal objective test findings (i.e. laboratory, x-ray, ECG) should also be recorded as AEs. The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- associated with accompanying symptoms,
- requires additional diagnostic testing or medical/surgical intervention,
- leads to discontinuation from the study,
- requires additional concomitant drug treatment or other therapy, or
- considered clinically significant by the Investigator or Sponsor.

Any abnormality on blood testing should be confirmed by a repeat test.

The sign or symptom should be recorded as an AE, not as the objective test finding. (Correct: Hypokalemia. Incorrect: potassium of 3.3 mEq/L)

Minor abnormalities in laboratory tests compared to baseline, and repeat of these tests in the absence of any of the above conditions, do not meet the criteria for reporting as an AE. An abnormal test result that is later determined to be an error does not require reporting as an AE, even if it did meet one or more of the above conditions.

For all AEs, the Investigator must pursue and obtain information adequate to determine the causality (i.e. study drug or other cause) and outcome of the event and to assess whether it meets the criteria for classification as a SAE (see **Section 7.1.2**). Follow-up of the event is required until the event or its sequelae resolve or stabilize at a level acceptable to the Investigator and the study Sponsor/monitor.

There are no anticipated severe AEs associated with the administration of the investigational product, which will be given as a one dose infusion. Clinical experience with the parent antibody, CC49, used in larger doses and in radioimmunotherapy studies, demonstrated hematologic dose-limiting toxicities, but they were most likely due to the radiation dose to red marrow from radioimmunotherapy treatment [19, 40].

6.2 Biodistribution Measurements

Biodistribution assessments include qualitative analysis of distribution of ^{124}I-PEG-AVP0458 within the blood pool, normal organ distribution, and tumour uptake. PET/CT whole body imaging (see PET Imaging Charter) will be performed at the following 5 time-points upon administration of ^{124}I-PEG-AVP0458: Day 0 (approximately 1 hour after infusion), day 1, day 2 or 3, day 4 or 5, and day 6 or 7.

Quantitative analysis will be performed by regions of interest defined for whole body, normal organs and tumour at each of the imaging time points. The individual PET/CT scans will be analysed to derive the concentration of ^{124}I-PEG-AVP0458 in the tumours per gram of tissue. The OLINDA program will be used for all dosimetry evaluations.

Qualitative PET/CT image and dosimetric analysis will be performed by the Austin PET Centre using the PET/CT images obtained at each study site.

6.3 Pharmacokinetic Measurements

PK analyses have the goal of defining C_{max}, AUC, C_L, and $T_{1/2}$. Levels of PEG-AVP0458 in the serum will also be evaluated. Descriptive statistics of serum concentrations and pharmacokinetic parameters will be calculated.

Standard PK analyses will be performed on ^{124}I-PEG-AVP0458 serum radioactivity data and serum concentrations of PEG-AVP0458 as measured in ELISA. Serum concentrations will be plotted graphically vs. time for all patients. PK analyses will be performed to estimate the maximal plasma concentrations (C_{max}), area under the curve (AUC), total serum clearance (C_L), and $T_{1/2}$. At the time points indicated in the **Schedule of Events**, blood serum samples (10 mL peripheral blood) will be obtained for PK of both administered radioactivity and PEG-AVP0458 protein. On Day 0, blood samples should be obtained prior to infusion, at completion of infusion, and at 1, 2 and 4 hours following completion of infusion.

Radioactive counting of serum samples will be performed in laboratories of the Ludwig Institute of Cancer Research. Results will be analysed and expressed as % injected dose per litre (%ID/L) and µg/mL.

The concentration of PEG-AVP0458 will be measured in the peripheral blood by RDDT Laboratories using a validated ELISA assay method.

6.4 Immunogenicity

Human Anti-Diabody Antibody (HADA) levels will be measured in serum by ELISA to monitor the immunogenicity associated with the diabody. Time points for collecting the bloods for assays are listed in the **Schedule of Events**.

Immunogenicity (HADA titres) will be analysed with the goal of determining whether PEG-AVP0458 triggers any immune reaction against it and how much of an immunologic response is potentially associated with AEs.

7 ADVERSE EVENTS

Investigators are responsible for monitoring the safety of patients who have entered this study and for alerting the Principal Investigator to any event that seems unusual, even if this event may be considered an unanticipated benefit to the patient.

The Investigator is responsible for appropriate medical care of patients during the study. The Investigator remains responsible to follow, through an appropriate health care option, AEs that are serious or that caused the patient to discontinue before completing the study. The patient should be followed until the event resolves or is explained.

7.1 Definitions

7.1.1 Adverse Events (AEs)

An AE is any untoward medical occurrence in a patient or trial patient following administration of a drug or biologic (medicinal product) or using a medical device and that does not necessarily have a causal relationship with that treatment or usage.

Any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite).

Each AE is a unique representation of a specific event used for medical documentation and scientific analysis.

7.1.2 Serious Adverse Events (SAEs)

A Serious Adverse Event (SAE) is any untoward medical occurrence that:

- Results in death;
- Is life-threatening;
- Results in inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity;
- Results in congenital anomaly/birth defect;
- Is medically significant in the opinion of the Investigator.

A life-threatening AE is defined as any adverse experience that places the patient at immediate risk of death from the reaction as it occurred; i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

Hospitalization is defined as any inpatient admission (even if less than 24 hours) as a result of a precipitating, treatment-emergent AE. Hospitalizations for administrative reasons or a non-worsening pre-existing condition should not be considered AEs (e.g., admission for workup of a

persistent pre-treatment lab abnormality, yearly physical exam, protocol-specified admission, elective surgery). Pre-planned treatments or surgical procedures should be noted in the baseline documentation. However, if a hospitalization due to an unknown event occurs, other than for elective admissions for pre-existing conditions, it should be considered as a SAE. Hospitalization for reasons of disease progression is not considered a SAE.

Prolongation of hospitalization is defined as any extension of an inpatient hospitalization beyond the stay anticipated/required for the original reason for admission, as determined by the Investigator or treating physician.

Disability is a substantial disruption of a person's ability to conduct normal life functions.

An AE that is not fatal, life-threatening, or requires hospitalization may be considered medically significant and therefore serious when, in the opinion of the Investigator, it could jeopardize the patient and may require medical or surgical intervention to prevent any of the above outcomes. Examples of such medical events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias that do not result in inpatient hospitalization, or the development of drug dependency or abuse.

7.2 Reporting Procedures

7.2.1 Adverse Events (AEs)

AEs will be collected after the patient has been enrolled.

If a patient experiences an AE after the informed consent document is signed (entry), but prior to enrolment (assignment to treatment), the event will NOT be reported unless the Investigator feels that the event may have been caused by a protocol procedure.

All AEs occurring after enrolment must be documented in the source records and reported on the eCRF, regardless of the assumption of a causal relationship. Documentation of "AE Summaries" for these AEs is reported to the Sponsor.

Documentation of AEs includes: date of suspected onset and resolution, severity, seriousness, related interventions and outcome. The Investigator must also evaluate the probability of a causal relationship of the AE to the study medication as defined in **Section 7.3**.

7.2.2 Serious Adverse Events (SAEs)

After becoming aware that an SAE has occurred, all sites must report it to the Sponsor or designee within 24 hours of awareness of the event, regardless of suspected relationship to study drug. Sites will be provided with contact information for SAE reporting before enrolling their first patient.

The initial report should include at minimum the following information: patient number and initials, sex, age; event term; and Investigator's preliminary assessment of causality. Follow-up information including causality, severity, outcome, action taken, and concomitant medications should be communicated to the Sponsor immediately.

Any SAE or death must be reported immediately regardless of the circumstances or suspected cause if it occurs or comes to the attention of the Investigator any time a patient is on study (as soon as the informed consent has been signed) or within 30 days of study drug

administration. Any SAE or death occurring more than 30 days after drug administration must be reported if a causal relationship to study drug is suspected.

It is the Investigator's responsibility to notify the Ethics Committees of all SAEs that occur at his or her site.

Study site personnel must fax the completed SAE form(s) within one working day to Medpace Serious Adverse Event Reporting fax: 0011.800.1000.2009. Attach a photocopy of all examinations carried out and the dates on which these examinations were performed. For laboratory results, include the normal ranges.

Type of Event	Reporting Time to Designee by Site	Reporting Time to TGA	Type of Report
Fatal or Life-threatening	Within 24 hours	Within 7 calendar days	Initial report
	Within 7 days	Within 8 additional calendar days	Complete report
All Other Serious	Within 24 hours		Initial report on SAE Report – Form
	Within 7 working days	Within 15 calendar days	Updated information on the original SAE Report - Form
Non-serious	Per eCRF submission procedure		AE Report - Form

7.2.3 Pregnancy Reporting

Any pregnancy that occurs in a study subject or his partner during the study or occurring up to 30 days after the last dose of study medication must be reported. Study site personnel must complete and fax the Exposure in Utero form within one working day to Medpace Clinical Safety fax: 0011.800.1000.2009.

Follow-up should be documented in source notes and should be continued until final outcome is known. Study site personnel must complete and fax the follow-up Exposure in Utero form to Medpace Clinical Safety when new information or the final outcome of the pregnancy is available.

7.3 Attribution of AEs to Investigational Agent

The relationship of an AE to the investigational agent will be determined by the Investigator on the basis of their clinical judgement, using one of the following terms, as described in the NCI Guidelines

Attribution	Description
Unrelated	The AE *is clearly NOT related* to the intervention
Unlikely	The AE *is doubtfully related* to the intervention
Possible	The AE *is possibly related* to the intervention
Probable	The AE *is likely related* to the intervention
Definite	The AE *is clearly related* to the intervention

7.4 Severity of AEs

All toxicities or adverse experiences will be graded according to NCI CTCAE v4.0 (**Appendix 2**).

8 BIOSTATISTICS

This is an open-label, non-randomized study of the safety and biodistribution of PEG-AVP0458. The analyses in this trial are descriptive and exploratory.

8.1 Sample Size/Accrual Rate

TAG-72 is expressed in more than 70% of ovarian cancer tumours, and more so in advanced cases [17].

Approximately 80-85% of primary prostate tumours and approximately 50% of metastatic tumours can be expected to overexpress TAG-72, indicating that the patient resource is available for this clinical study [13-15].

An anticipated total of 12-18 patients will be entered into the study. See Section 3.2.

8.2 Primary and Secondary Study Variables

8.2.1 Primary Endpoint

The primary endpoint is to evaluate the safety of a single dose of PEG-AVP0458 in patients with prostrate and ovarian cancer. Safety will be evaluated by adverse events, ECOG performance status, vital signs, 12-lead ECG and laboratory parameters. Adverse events (AEs) will be coded using the standard Medical Dictionary for Regulatory Activities (MedDRA) and grouped by system organ class. AEs will be graded by the investigator according to the NCI-CTCAE (version 4.0). Special emphasis will be considered for any dose limiting toxic adverse event and infusion related adverse events.

8.2.2 Secondary Endpoints

The secondary objectives of this study are to evaluate the biodistribution of ^{124}I-PEG-AVP0458, including tumour targeting, dosimetric analysis, PK analysis performed on ^{124}I-PEG-AVP0458 serum radioactivity data and serum concentrations of PEG-AVP0458 and immunogenicity of ^{124}I-PEG-AVP0458 in patients with prostate and ovarian cancer.

8.3 Populations

There will be two populations for consideration.

8.3.1 Safety Analysis Population

The safety analysis population includes all patients who were administered study drug and have at least one safety assessment after their infusion.

8.3.2 Evaluable Analysis Population

The evaluable analysis population includes patients who were administered study drug and completed the 4 weeks of scheduled assessments after receiving the infusion.

8.4 Interim Data Analysis

A Trial Management Committee will be responsible for decisions regarding dose escalation and dose selection. See Section 5.10 on Criteria for Dose Escalation and Dose Selection.

An interim analysis will be performed after the last patient has been enrolled in the second cohort (10mg/m^2). Safety and dosimetry data obtained from dose groups 1 and 2 will be analysed and provided to the Trial Management Committee, who will assess which of the two doses, 1 or 10mg/m^2, will be administered to the last 6 patients (dose group 3) in the study.

8.5 Final Data Analysis

8.5.1 Baseline Data

Listings and summary tables of the following demographic and baseline characteristics will be produced for each cohort.

- Demography
- Medical history
- Serum pregnancy test
- Thyroid function levels

Descriptive statistics (mean, median, standard deviation, 25th percentile, 75th percentile, and range) will be presented for continuous variables such and frequency counts will be presented for categorical variables.

8.5.2 Primary Safety Assessments

Adverse events will be summarised and listed by each cohort. Other adverse event summaries include: serious adverse events, grade 3 or 4 adverse events and treatment related adverse events.

Laboratory parameters include serum biochemistry, complete blood count and differentials. Descriptive summary tables and listings at each scheduled assessment based on System International (SI) units will be produced.

Vital signs include blood pressure, pulse, respiration and temperature. The results will be listed and summarised descriptively at the scheduled assessments for each cohort.

Other safety assessments include physical examination, ECOG performance status and 12- lead ECG. The results will be summarised and listed at the scheduled assessments for each cohort.

8.5.3 Secondary Efficacy Assessments

The biodistribution assessments of ^{124}I-PEG-AVP0458 within the blood pool, normal organ distribution and tumour uptake will be carried out on PET/CT scans performed on day 0, day 1, day 2 or 3, day 4 or 5, and day 6 or 7. Qualitative and quantitative analyses will be performed, and the concentration ^{124}I-PEG-AVP0458 in the tumour will be derived. This analysis will be performed by the Ludwig Institute of Cancer Research and results will be presented in the final study report. Descriptive statistical analysis comparing patients at each dose level will be performed.

Observed PK serum concentrations (by ELISA) for PEG-AVP0458 will be summarised for each cohort at each specified PK sampling time-points. Descriptive statistics will include arithmetic means, standard deviations, co-efficient of variation, medians and ranges (if the data allow). The serum concentrations will be graphed over time for each patient, and for each cohort. PK analyses will be performed to estimate the maximal plasma concentrations (Cmax), area under the curve (AUC), total serum clearance (CL), and T½ .

Radioactive content in the peripheral blood will be measured by gamma well scintillation counting. Results will be expressed as % injected dose per litre (%ID/L) and µg/mL. PK parameter estimates will also be applied to this data and will be analysed by the Ludwig Institute of Cancer Research. The results will be described in the final study report. Descriptive statistical analysis of data will be performed.

Human Anti-Diabody Antibody (HADA) levels will be measured in serum by ELISA to monitor the immunogenicity associated with the diabody. HADA levels (titres) will be summarised descriptively and listed at each scheduled assessment. The HADA levels will also be graphed over time for each patient, and for each cohort. This analysis will determine whether increased levels of HADA (titres) are potentially associated with adverse events.

9 INVESTIGATIONAL DRUG

9.1 Investigational Drug: PEG-AVP0458

The PEG-AVP0458 diabody was manufactured by Hospira Adelaide Pty Ltd in accordance with applicable Good Manufacturing Practice. The product consists of the TAG-72 specific diabody that is PEGylated at two Cys residues with PEG24. The diabody was transferred to Radpharm Scientific where it was formulated into an injection in compliance with the Codes of Good Manufacturing Practice.

PEG-AV0458 injection is a clear, light yellow, 5.5 mg/mL sterile solution a pH 7.4 Phosphate Buffer Solution. It is supplied in 1 mL volumes in 2mL clear Type I glass vials for IV administration. The vials are closed with 13 mm butyl stoppers and 13 mm plastic flip-off caps. No preservative is used since the vial is designed for single use.

9.2 Packaging and Labelling

PEG-AV0458 injection will be shipped from Radpharm to Austin Health where it is receipted and stored refrigerated in the Pharmacy at 2 - 8°C. Each vial of PEG-AVP04 injection contains 1 mL of product solution at a concentration of 5 mg/mL of PEG-AVP0458 in phosphate buffer.

On the day before administration to the patient (Day -1), the Ludwig Institute of Cancer Research requisitions the appropriate number of vials from Austin Health Pharmacy. Radiolabelling with ^{124}I is performed at the Ludwig Institute of Cancer Research on the morning of Day 0, prior to infusion to patients.

9.3 Preparation of ^{124}I-PEG-AVP0458 Infusion

PEG-AVP0458 will be radiolabelled with ^{124}I at the Ludwig Institute of Cancer Research on the day of administration (Appendix 3), and then will be transferred to the PET centre of the appropriate study site for patient infusion. ^{124}I-PEG-AVP0458 is mixed with unlabelled PEG-AVP0458 in a 100mL Normal Saline infusion bag containing 5% human serum albumin to obtain the correct total PEG-AVP0458 protein amount (either 1 or 10 mg/m^2) for infusion.

9.4 Storage

The investigational drug, PEG-AVP0458 will be stored at the Austin Health Pharmacy. Non-radiolabelled drug should be stored refrigerated at 2 – 8°C.

Drug supplies must be kept in a secure, limited access storage area under the storage conditions defined in this protocol. A temperature log must be maintained to make certain that the drug supplies are stored at the correct temperature.

9.5 Drug Supply and Return

The investigational product will be shipped by the Sponsor to Austin Health's authorized

Designee, who will check the amount and condition of the investigational product received. Shipments of investigational product will include a packing slip, which must be signed by the designee and returned to the shipper to verify receipt of the product.

The Investigator and/or Pharmacist must maintain records of the product's delivery to the trial site, the inventory at the site, the use by each patient, and the return to the Sponsor or alternative disposition of unused product(s). These records will include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the investigational product(s) and trial patients. Investigators will maintain records that document adequately that the patients were provided the doses specified by the protocol and reconcile all investigational product(s) received from the Sponsor.

Unused non-radiolabelled product must be returned to the Sponsor at the end of the study. The Investigator must verify that all unused drug supplies have been returned and that no remaining supplies are in the Investigator's possession. At the time of return to the Sponsor (at the end of the study or as directed), the Investigator must verify that all unused or partially used drug supplies have been returned by the clinical trial patient and that no remaining supplies are in the Investigator's possession. Any disposal or transfer of investigational agent shall be noted on the investigational drug disposition log.

^{124}I- PEG-AVP0458 is prepared at the Ludwig Institute of Cancer Research and transported to the appropriate PET Centre for infusion on the day of patient administration (Day 0). For the patient treated at the Peter MacCallum PET Centre, the Ludwig Institute for Cancer Research will place the radiolabelled PEG-AVP0458 into a lead-lined receptacle, and transfer that to the Peter MacCallum PET Centre by a courier licensed to transport radioactive material. Both the Ludwig Institute of Cancer Research and Peter MacCallum PET Centre will keep appropriate records of the product's despatch, delivery and receipt. Any unused radiolabelled investigational product will be disposed of at the Institution according to the Institution's own Standard Operating Procedures for handling and disposal of radioactive material, and the disposition recorded on the investigational drug disposition log.

9.6 Drug Accountability

An investigational product dispensing record will be kept current by Austin Health Pharmacy and will contain the following information:

- Patient's identification (number and initials)
- Date, quantity, and batch number of dispensed drug
- Date and quantity of agent returned to the Investigator/pharmacy (if applicable)
- Date and quantity of accidental loss of study agent (when necessary)

These records must be made available for inspection by the study monitor. The Investigator at each site has to ensure that all used and unused trial drug is accounted for.

10 INFORMED CONSENT AND ETHICAL REVIEW

10.1 Informed Consent

Prior to undergoing any screening assessments, written informed consent will be obtained from each patient (or the patient's legally accepted representative) according to regulatory and legal requirements. Each signature must be dated by each signatory and the informed consent and any additional patient information form retained by the Investigator as part of the study records. A signed copy of the informed consent and any additional patient information must be given to each patient or the patient's legally authorized representative.

The patient must be informed that his / her medical records may be examined by authorized monitors or Clinical Quality Assurance auditors, by Human Research Ethics Committee members and by inspectors from regulatory authorities.

Should a protocol amendment be made, the patient consent form and patient information form may need to be revised to reflect the changes to the protocol. It is the responsibility of the Investigator to ensure that an amended consent form is reviewed and received approval from the Ethics Committees, and that it is signed by all patients subsequently entered in the trial and those currently in the trial, if affected by the amendment.

10.2 Ethics Committees

The trial will be carried out in compliance with the protocol, the principles laid down in the NHMRC National Statement for Ethical Conduct in Human Research (2007), the Declaration of Helsinki (last revised version), and in accordance with the ICH Guidance for Good Clinical Practice (GCP) and applicable regulatory requirements.

The trial will not be initiated before the protocol and informed consent have been reviewed and received approval from the Human Research Ethics Committees (HREC) from all clinical sites. Should a protocol amendment be made that needs HREC approval, the changes in the protocol will not be instituted until the amendment and revised informed consent (if appropriate) has been reviewed and received approval from the HREC. A protocol amendment intended to eliminate an apparent immediate hazard to patients may be implemented immediately providing that the appropriate regulatory authorities and HREC are notified as soon as possible and an approval is requested.

11 ADMINISTRATIVE AND LEGAL OBLIGATIONS

11.1 Protocol Amendments

Amendments of this clinical protocol must be approval by HREC and will be implemented only after a copy of the approval letter has been transmitted to the Sponsor. Administrative amendments, such as changes of phone numbers, which do not affect the patients' safety should be implemented according to HREC's requirements.

11.2 Trial Documentation and Data Storage

The Investigator must retain and file all trial-related documentation in the Study Master File. This documentation should be made available for inspection by the Sponsor, its designates, and representatives of regulatory authorities.

The Principal Investigator must submit a clinical study summary report to the Sponsor and HREC upon completion of the trial.

The Principal Investigator will need to retain the Study Master File until at least two years have elapsed since the formal discontinuation of clinical development of the investigational product.

11.3 Data Collection, Management and Quality Assurance

Data for this study will be recorded via an Electronic Data Capture (EDC) system using electronic case report forms (eCRFs). It will be transcribed by the site from the paper source documents onto the eCRF. In no case is the eCRF to be considered as source data for this trial. The data is entered by site staff onto a desktop/laptop computer using a standard web browser. An audit trail will maintain a record of initial entries and changes made; reasons for change; time and date of entry; and user name of person authorizing entry or change. For each patient enrolled, an eCRF must be completed and electronically signed by the principal investigator or authorized delegate from the study staff. This also applies to records for those patients who fail to complete the study (even during a pre-randomization screening period if an eCRF was initiated). If a patient withdraws from the study, the reason must be noted on the electronic case report form. If a patient is withdrawn from the study because of a treatment-limiting adverse event, thorough efforts should be made to clearly document the outcome.

Accurate and reliable data collection will be assured by verification and cross–check of the eCRFs against the investigator's records by the study monitor (source document verification), and the maintenance of a drug–dispensing log by the investigator.
A comprehensive validation check program utilizing front-end checks in the eCRF and back-end checks issued by Data Management, will verify the data and discrepancies will be generated accordingly. These are transferred electronically to the eCRF at the site for resolution by the investigator.

The investigator should ensure the accuracy, completeness and timeliness of the data reported to the sponsor in the eCRFs and in all required reports.

Patients are not to be identified on the eCRF by name. Appropriate coded identification (e.g. Patient Number) must be used. The Investigator must make a separate confidential record of these details (patient identification code list) to permit identification of all patients enrolled in a clinical trial in case follow-up is required.

Relevant medical history prior to enrolment will be documented at the baseline visit. Thereafter during the trial narrative statements relative to the patient's progress during the trial will be maintained.

The Investigators will be responsible for retaining all records pertaining to the trial and must make them available to monitors as well as to authorised regulatory bodies who wish to inspect the study.

11.4 Monitoring

An outside monitor and other authorized regulatory personnel may contact and visit the Investigators. They will be allowed direct access to all medical records, the Investigator's trial related files and correspondence, and the informed consent documentation that is relevant to this clinical trial for the purpose of monitoring, audits, HREC review, and regulatory inspection.

The monitor will inspect the eCRFs at regular intervals throughout the trial to verify adherence to the protocol (especially informed consent and patient eligibility), the completeness, accuracy and consistency of the data, as well as adherence to ICH Guideline E6 (Good Clinical Practice). The monitor must have access to patient charts, laboratory reports, drug accountability forms and patient informed consents, as well as all other source documents and patient records needed to verify the entries on the eCRFs.

The Investigators must work with the monitor to ensure that any issues detected in the course of these monitoring visits are properly resolved.

12 STATEMENT OF CONFIDENTIALITY

The Investigator must ensure that the patient's privacy is maintained. A patient should only be identified by his/her patient number on the eCRFs or other documents submitted to the Sponsor. The Investigator should keep documents that are not submitted to the Sponsor (e.g., signed informed consent forms) in a strictly confidential file.

Individual patient medical information obtained as a result of this study will be considered confidential and disclosure to third parties is prohibited with the following exception. The Investigator must allow the Sponsor, its designates, and authorized representatives of regulatory agencies to review the patient's medical record, as it relates to the study. As part of the required content of informed consent, the patient must be informed that his/her records will be reviewed in this manner.