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# Study Protocol

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**Phase I study to evaluate the safety,  
biodistribution, radiation dosimetry and tumor  
imaging potential of [<sup>131</sup>I]-SGMIB Anti-HER2  
VHH1 in healthy volunteers and breast cancer  
patients:**

## **CAM-VHH1 study**

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**Authors:** T. Lahoutte and J. De Vos

Date:

Signature:

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EudraCT number: 2015-004840-21  
Protocol code number: CAM-VHH1

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## Abbreviations

%IA	Percentage of injected activity
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
CDTDI	Computed tomography dose index
CRF	Case report form
CTCAE	Common terminology criteria for adverse events
DSMB	Data safety monitoring board
FISH	Fluorescence in situ hybridization
GCP	Good clinical practice
HEGP	High energy general purpose
HER2	Human epidermal growth factor receptor type 2
ICH	International conference on harmonization
IMP	Investigational medical product
IV	Intravenous
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
p.i.	Post injection
PBS	Phosphate buffered saline
PET	Positron Emission Tomography
RP-HPLC	Reverse-phase high pressure liquid chromatography
SAE	Serious adverse events
SEC	Size-exclusion chromatography
SGMIB	N-succinimidyl 4-guanidinomethyl-3-iodobenzoate (SGMIB)
SPECT	Single Photon Emission Computed Tomography
t	Time
TRNT	Targeted radionuclide therapy
VHH	Variable domain of a heavy-chain-only antibody

**Study Title:**  
**Phase I study to evaluate the safety, biodistribution, radiation dosimetry and tumor imaging potential of [<sup>131</sup>I]-SGMIB Anti-HER2 VHH1 in healthy volunteers and breast cancer patients:**

CAM-VHH1 study

**Document version:** 4.0  
**Date of version:** August 4<sup>th</sup>, 2017  
**Development phase:** I  
**Project No:** CAM-VHH1  
**EURDRACT No:** 2015-004840-21  
**Sponsor:** CAMEL-IDS NV

**CONFIDENTIALITY STATEMENT**

<p>CAMEL-IDS NV Burgemeester Etienne Demunterlaan, 1 1090 Brussels <a href="http://www.camel-ids.com">www.camel-ids.com</a></p>		<p>Page 5 of 36</p>
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The information provided in this document is strictly confidential and is available for review to investigators, potential investigators and appropriate Ethics Committees and Competent Authorities only. No disclosure should take place without the written authorization from CAMEL-IDS NV.

***Investigator's approval***

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I have read with particular attention this protocol and I agree that it provides all the necessary information for the study conducting and I do accept to participate according to the protocol and applicable regulations.

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Investigator:

Date

Hospital:

**1. STUDY ADMINISTRATIVE STRUCTURE**

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## 2. INTRODUCTION

Variable domain of a heavy-chain-only antibody (VHH) fragments are the antigen-binding units derived from heavy chain only camelid antibodies. Compared to conventional antibodies or antibody fragments, VHH fragments are smaller (15 kDa) and they have the ability to bind antigens on hidden or unusual epitopes. VHHs are considered low immunogenic, have nanomolar affinities and can be produced in high yields (1).

Malignant tumors are characterized by the presence of specific proteins on their cell membrane. These cancer antigens are expressed in relatively high amounts and often their expression level is related to a signal transduction cascade that contributes or promotes the cancer phenotype. Hence, these membrane antigens represent an important target for anti-cancer treatment. Theoretically, VHHs can be generated against virtually any cancer-specific membrane-associated protein. In a series of studies, the In vivo Cellular and Molecular Imaging lab (ICMI) at the Vrije Universiteit Brussel (VUB) demonstrated that VHHs bear unusually beneficial properties for targeted radionuclide therapy (TRNT) (2-4). Indeed, in mice, radiolabeled VHHs efficiently penetrate tumors and tissues; bind biomarkers expressed on cells very fast and very specifically while unbound VHH is rapidly cleared from non-target organs and tissues. When coupled to a diagnostic radionuclide, this allows generating high contrast images as fast as 1h after tracer administration (5). As such the ICMI lab has developed them as efficient radiotracers for diagnostic imaging in various animal models of cancer, inflammation and cardiovascular diseases using Single Photon Emission Computed Tomography (SPECT) or Positron Emission Tomography (PET) (6-8).

The human epidermal growth factor receptor type 2 (HER2) is a typical example of a membrane receptor that is highly expressed on the cell membrane of breast and ovarian carcinoma. Signaling of this receptor causes cell proliferation, enhances cell mobility and reduces apoptosis. Consequently, HER2 over-expression is associated with tumor aggressiveness and an increased probability for recurrent disease. Targeted therapies for HER2 over-expressing tumors are currently available, such as monoclonal antibodies (Trastuzumab and Pertuzumab) that specifically bind the extracellular domain of HER2, and specific tyrosine kinase inhibitors (lapatinib) that interact with the intracellular domain of HER2. Information on the HER2 status of tumors is therefore of great importance since it has an enormous impact on the selection of the patients' therapy. At present, HER2 expression is assessed using tissue biopsies. The Anti-HER2 VHH1 was selected as a lead compound because of superior characteristics and the fact that it does not compete with binding of Trastuzumab and Pertuzumab (7).

The Anti-HER2 VHH1 was successfully evaluated in a first clinical study: the UZBRU-VHH1 study. In this study the Anti-HER2 VHH1 was labeled with [<sup>68</sup>Ga] to non-invasively detect HER2 expression using PET. The evaluation of safety and tolerability as primary outcome,

based on observed adverse events (AEs), was completed for all 20 patients. No related AEs were observed. The main conclusions of the HER2 diagnostic clinical study are that (i) [<sup>68</sup>Ga]-HER2 PET/CT is a safe procedure with a radiation dose comparable to other PET/CT procedures and (ii) the radiolabeled VHH imaging reveals whole-body expression of HER2 in primary tumors and metastases.

Preclinical studies with the Anti-HER2 VHH1 labeled with [<sup>131</sup>I] were performed. In these studies the compound revealed similar binding characteristics and *in vivo* blood clearance compared to the [<sup>68</sup>Ga]-labeled compound. However, the biodistribution profile was more favorable with much lower kidney values compared to the [<sup>68</sup>Ga]-labeled compound in mice. The dose delivered to the tumor remained high and was higher than the dose delivered to the kidneys. The favorable biodistribution in mice of [<sup>131</sup>I]-SGMIB Anti-HER2 VHH1, combined with the theranostic characteristics of [<sup>131</sup>I] has now triggered the interest to use this compound as a therapeutic agent in TRNT of cancer (9-10).

The rationale for the development of [<sup>131</sup>I]-SGMIB Anti-HER2 VHH1 is to allow both screening patients for the presence of the HER2 antigen using SPECT and a subsequent therapeutic approach using the identical compound (11). The screening approach will offer superior diagnostic performance because the entire tumor lesion as well as possible metastatic lesions can be evaluated with a single total body scanning procedure (SPECT). The procedure is fast, painless and sampling errors with biopsies are avoided. This screening test will allow the clinician to select patients that are susceptible to TRNT. In patients that do not have HER2 positive cancers unnecessary, expensive and potentially toxic treatment can be avoided. The SPECT scans could also be used to follow the expression of this biomarker during the disease process and act as prognostic marker.

### 3. STUDY OBJECTIVES

#### Part I

Primary objectives of the clinical study:

1. To evaluate the safety, biodistribution and radiation dosimetry of [<sup>131</sup>I]-SGMIB Anti-HER2 VHH1 in 6 healthy volunteers

#### Part II

Primary objectives of the clinical study:

1. To evaluate the safety and biodistribution of [<sup>131</sup>I]-SGMIB Anti-HER2 VHH1 in 4 patients with HER2+ breast cancer.

Secondary objective of the clinical study:

2. To evaluate the tumor uptake of [<sup>131</sup>I]-SGMIB Anti-HER2 VHH1 in 4 patients with HER2+ breast cancer.

### 4. STUDY DESIGN

Single center, open, non-randomized first-in-man clinical trial

### 5. INVESTIGATIONAL PLAN

#### 5.1 Overall Study Design

Single center, open, non-randomized first-in-man clinical trial

#### 5.2 Study groups

This study will be conducted in 2 parts.

Part I is in healthy volunteers to demonstrate the safety and to assess the biodistribution and human dosimetry of [<sup>131</sup>I]-SGMIB Anti-HER2 VHH1.

If Part I is successful according to the Data Safety Monitoring Board (DSMB) decision, Part II will be initiated. The composition, role and procedures of the DSMB will be described in the DSMB charter.

Part II is in patients with HER2+ breast cancer to demonstrate the safety and to assess the biodistribution and tumor uptake of [<sup>131</sup>I]-SGMIB Anti-HER2 VHH1.

All subjects will receive only one single intravenous injection of the investigational medical product (IMP).

### 5.3 Time schedule

First subject: December 2015

Last subject: January 2018

#### 5.3.1 Part I (Healthy volunteers)

An overview of the investigational actions for each subject in Part I of the study can be found in Table 1.

The individual subject schedule will be:

Visit 1: screening and inclusion

- Informed consent
- Inclusion / exclusion criteria
- Medical history
- Information about subject preparation: 6±2h fasting at administration of [<sup>131</sup>I]-SGMIB Anti-HER2 VHH1.
- Information about oral administration of 130 mg potassium iodide for thyroid blockade: potassium iodide dosed as 1 ingestion daily starting 24±6h before [<sup>131</sup>I]-SGMIB Anti-HER2 VHH1 administration and continued until 48±12h after administration of [<sup>131</sup>I]-SGMIB Anti-HER2 VHH1.

Visit 2: 1 day before administration

- Information about subject preparation: 6±2h fasting at administration of [<sup>131</sup>I]-SGMIB Anti-HER2 VHH1.
- First ingestion of 130 mg potassium iodide
- Blood sampling for HCG test unless postmenopausal for 2 years.
- Blood sampling for biochemical analysis: hematology, liver enzymes and renal function (urea, creatinine). Blood will be collected in dry Li-Heparin and EDTA tubes (S-Monovette®, Sarstedt). Samples will be analyzed for biochemical and hematological parameters.

Visit 3: baseline

- *Pre-administration*

- Physical exam including vital signs and medical history
- Second ingestion of 130 mg potassium iodide
- Blood sampling for activity measurement. Blood will be collected in a dry Li-Heparin tube (S-Monovette®, Sarstedt). 0.5 ml of blood will be pipetted in a counting tube, the remaining blood will be centrifuged and 0.5 ml of plasma will be put in a counting tube.
- Blood sampling for biochemical analysis: hematology, liver enzymes and renal function (urea, creatinin). Blood will be collected in dry Li-Heparin and EDTA tubes (S-Monovette®, Sarstedt). Samples will be analyzed for biochemical and hematological parameters.

-An intravenous line will be inserted in an antecubital vein for administration of the product and a similar venous access will be installed in a different vein of the opposite arm for blood sampling. A saline infusion of 250 ml will be administered before administration of [<sup>131</sup>I]-SGMIB Anti-HER2 VHH1.

- *Administration*

- IV-injection of [<sup>131</sup>I]-SGMIB Anti-HER2 VHH1 using an infusion pump within 5±3min.
- The empty syringe and intravenous line need to be removed and measured for residual radioactivity
- Remark: the study subject will not be allowed to urinate before the completion of total body planar scan 1 (t= 40±10min p.i.). In case the study subject could not withhold, urine should be collected and scanned with the subject during total body planar scan 1.

- *Post-administration*

- Dynamic scan kidneys & liver (gamma camera): t= 0-30±10min p.i.
- Vital signs 5±10min p.i.
- Blood sampling for activity measurements: 5±3min-p.i  
Blood will be collected in a dry Li-Heparin tube (S-Monovette®, Sarstedt). 0.5 ml of blood will be pipetted in a counting tube, the remaining blood will be centrifuged and 0.5 ml of plasma will be put in a counting tube.
- Blood sampling for activity measurements and metabolite analysis: 10±3min-p.i  
Blood will be collected in a dry Li-Heparin tube (S-Monovette®, Sarstedt). 0.5 ml of blood will be pipetted in a counting tube, the remaining blood will be centrifuged and 0.5 ml of plasma will be put in a counting tube. The remaining plasma will also be used for HPLC analysis. 1 ml of plasma will be filtered (0.45 µm) and 0.5 ml will be injected on the HPLC.
- Blood sampling for activity measurements: 20±5min-p.i  
Blood will be collected in a dry Li-Heparin tube (S-Monovette®, Sarstedt). 0.5 ml of blood will be pipetted in a counting tube, the remaining blood will be centrifuged and 0.5 ml of plasma will be put in a counting tube.
- Blood sampling for activity measurements: 30±5min-p.i  
Blood will be collected in a dry Li-Heparin tube (S-Monovette®, Sarstedt). 0.5 ml of blood will be pipetted in a counting tube, the remaining blood will be centrifuged and 0.5 ml of plasma will be put in a counting tube.
- Total body planar scan 1: t= 40±10min p.i.
- Blood sampling for activity measurements and metabolite analysis: 60±15min p.i.  
Blood will be collected in a dry Li-Heparin tube (S-Monovette®, Sarstedt). 0.5 ml of blood will be pipetted in a counting tube, the remaining blood will be centrifuged and 0.5 ml of plasma will be put in a counting tube. The remaining plasma will also be used for HPLC analysis. 1 ml of plasma will be filtered (0.45 µm) and 0.5 ml will be injected on the HPLC.
- Urine sample will be collected for metabolite analysis: 60±15min p.i.  
1 ml of urine will be filtered (0.45 µm) and 0.5 ml will be injected on the HPLC.

- Blood sampling for activity measurements: 105±30min p.i.  
Blood will be collected in a dry Li-Heparin tube (S-Monovette®, Sarstedt). 0.5 ml of blood will be pipetted in a counting tube, the remaining blood will be centrifuged and 0.5 ml of plasma will be put in a counting tube.
- Total body planar scan 2: t= 120±30min p.i.
- Blood sampling for activity measurements and metabolite analysis: 225±30min p.i.  
Blood will be collected in a dry Li-Heparin tube (S-Monovette®, Sarstedt). 0.5 ml of blood will be pipetted in a counting tube, the remaining blood will be centrifuged and 0.5 ml of plasma will be put in a counting tube. The remaining plasma will also be used for HPLC analysis. 1 ml of plasma will be filtered (0.45 µm) and 0.5 ml will be injected on the HPLC.
- Urine sample will be collected for metabolite analysis: 225±30min p.i.  
1 ml of urine will be filtered (0.45 µm) and 0.5 ml will be injected on the HPLC.
- Total body planar scan 3: t= 240±30min p.i.
- at t=4.5±1h p.i.: physical exam including vital signs
- Discharge of the subject

Visit 4: 24h after injection of the [<sup>131</sup>I]-SGMIB Anti-HER2 VHH1

- Third ingestion of the 130 mg potassium iodide
- Blood sampling for activity measurements and metabolite analysis: 23.75±4h p.i.  
Blood will be collected in a dry Li-Heparin tube (S-Monovette®, Sarstedt). 0.5 ml of blood will be pipetted in a counting tube, the remaining blood will be centrifuged and 0.5 ml of plasma will be put in a counting tube.
- Blood sampling for biochemical analysis: hematology, liver enzymes and renal function (ureum, creatinine): 23.75±4h p.i. Blood will be collected in dry Li-Heparin and EDTA tubes (S-Monovette®, Sarstedt). Samples will be analyzed for biochemical and hematological parameters.
- Urine sample will be collected for metabolite analysis: 23.75±4h p.i.  
1 ml of urine will be filtered (0.45 µm) and 0.5 ml will be injected on the HPLC.
- Total body planar scan 4: t= 24±4h p.i.
- Provide subject with the fourth potassium iodide dose to be taken at 48±12h after administration of [<sup>131</sup>I]-SGMIB Anti-HER2 VHH1.
- Discharge of the subject

Visit 5: 72h after injection of the [<sup>131</sup>I]-SGMIB Anti-HER2 VHH1

- Confirmation of the fourth ingestion of 130 mg potassium iodide (taken at 48±12h)
- Blood sampling for activity measurements and metabolite analysis: 71.75±4h p.i.  
Blood will be collected in a dry Li-Heparin tube (S-Monovette®, Sarstedt). 0.5 ml of blood will be pipetted in a counting tube, the remaining blood will be centrifuged and 0.5 ml of plasma will be put in a counting tube. The remaining plasma will be also used for HPLC analysis. 1 ml of plasma will be filtered (0.45 µm) and 0.5 ml will be injected on the HPLC.
- Urine sample will be collected for metabolite analysis: 71.75±4h p.i.

1 ml of urine will be filtered (0.45  $\mu$ m) and 0.5 ml will be injected on the HPLC.

- Total body planar scan:  $t= 72\pm 4$ h p.i.
- Discharge of the subject

### 5.3.2 Part II (Patients with HER2+ breast cancer)

An overview of the investigational actions for each patient in part II of the study can be found in Table 2.

The individual patient schedule will be:

#### Visit 1: screening and inclusion

- Informed consent
- Inclusion / exclusion criteria
- Medical history
- Information about patient preparation:  $6\pm 2$ h fasting at administration of [ $^{131}$ I]-SGMIB Anti-HER2 VHH1.
- Information about oral administration of 130 mg potassium iodide for thyroid blockade: potassium iodide dosed as 1 ingestion daily starting  $24\pm 6$ h before [ $^{131}$ I]-SGMIB Anti-HER2 VHH1 administration and continued until  $48\pm 12$ h after administration of [ $^{131}$ I]-SGMIB Anti-HER2 VHH1.

#### Visit 2: 1 day before administration

- Information about subject preparation:  $6\pm 2$ h fasting at administration of [ $^{131}$ I]-SGMIB Anti-HER2 VHH1.
- First ingestion of 130 mg potassium iodide
- Blood sampling for HCG test unless postmenopausal for 2 years.
- Blood sampling for biochemical analysis: hematology, liver enzymes and renal function (urea, creatinine). Blood will be collected in dry Li-Heparin and EDTA tubes (S-Monovette®, Sarstedt). Samples will be analyzed for biochemical and hematological parameters.

#### Visit 3: baseline

- *Pre-administration*
- Physical exam including vital signs
- Second ingestion of 130 mg potassium iodide
- Blood sampling for biochemical analysis: hematology, liver enzymes and renal function (urea, creatinin). Blood will be collected in dry Li-Heparin and EDTA tubes (S-Monovette®, Sarstedt). Samples will be analyzed for biochemical and hematological parameters.
- An intravenous line will be inserted in a vein or port-a-cath for administration of the product and for blood sampling. A saline infusion of 250 ml will be administered before administration of [ $^{131}$ I]-SGMIB Anti-HER2 VHH1.

- *Administration*

- IV-injection of [<sup>131</sup>I]-SGMIB Anti-HER2 VHH1 using an infusion pump within 5±3min.
- The empty syringe and intravenous line need to be removed and measured for residual radioactivity
- Remark: the patient will not be allowed to urinate before the completion of total body planar scan 1 (t= 15±10min p.i.). In case the patient could not withhold, urine should be collected and scanned with the patient during total body planar scan 1.

- *Post-administration*

- Vital signs 5±10min p.i.
- Total body planar scan 1: t= 15±10min p.i.
- Blood sampling for activity measurements and metabolite analysis: 60±15min p.i.  
Blood will be collected in a dry Li-Heparin tube (S-Monovette®, Sarstedt). 0.5 ml of blood will be pipetted in a counting tube, the remaining blood will be centrifuged and 0.5 ml of plasma will be put in a counting tube. The remaining plasma will also be used for HPLC analysis. 1 ml of plasma will be filtered (0.45 µm) and 0.5 ml will be injected on the HPLC.
- Total body planar scan 2: t= 120±30min p.i.
- SPECT/CT scan of 1 region with a cancer lesion: t= 2.5±1h p.i. The region will be selected by the PI based on the total body planar scan 2. The PI can decide not to execute a SPECT/CT scan.
- at t=3±1h p.i.: physical exam including vital signs
- Discharge of the patient

Visit 4: 24h after injection of the [<sup>131</sup>I]-SGMIB Anti-HER2 VHH1

- Third ingestion of 130 mg potassium iodide
- Blood sampling for biochemical analysis: hematology, liver enzymes and renal function (ureum, creatinine): 23.75±4h p.i. Blood will be collected in dry Li-Heparin and EDTA tubes (S-Monovette®, Sarstedt). Samples will be analyzed for biochemical and hematological parameters.
- Total body planar scan 3: t= 24±4h p.i.
- SPECT/CT scan of 1 region with a cancer lesion: t= 24.5±4h p.i. The region will be selected by the PI based on the total body planar scan 3. The PI could decide not to execute a SPECT/CT scan.
- Provide patient with the fourth potassium iodide dose to be taken at 48h±12h after administration of [<sup>131</sup>I]-SGMIB Anti-HER2 VHH1.
- Discharge of the patient

## 5.4 Selection and withdrawal of subjects

### 5.4.1 Part I (Healthy volunteers)

Inclusion Criteria:

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Subjects will only be included in the study if they meet all of the following criteria:

- Subjects who have given informed consent
- Subjects that agree not to drink alcoholic beverages or use any drugs during the study
- Subject with blood parameters within normal ranges
- Age: at least 18 years old

Exclusion Criteria:

Subjects will not be included in the study if one of the following criteria applies:

- Pregnant subjects
- Breast feeding subjects
- Subjects with occupational exposure to ionizing irradiation
- Subjects with clinical significant disease or on concomitant therapy (except contraception)
- Subjects with previous thyroid disorders
- Subjects that received radiolabeled compounds with a long half-life (>7h) for diagnostic or therapeutic purposes within the last 2 days.
- Subjects with absolute contra-indications for thyroid blockage with potassium iodide.
- Subjects with abnormal liver: ALT/AST > 2 times normal values; bilirubin > 1.5 time normal values.
- Subjects with abnormal kidney function: < 50 ml/min/1,73 m<sup>2</sup>
- Subjects with recent (< 1 week) gastrointestinal disorders (CTCAE v4.0 grade 3 or 4) with diarrhea as major symptom
- Subjects with any serious active infection
- Subjects who have any other life-threatening illness or organ system dysfunction, which in the opinion of the investigator would either compromise subject safety or interfere with the evaluation of the safety of the test radiopharmaceutical
- Subjects who cannot communicate reliably with the investigator
- Subjects who are unlikely to cooperate with the requirements of the study
- Subjects at increased risk of death from a pre-existing concurrent illness
- Subjects who participated already in this study
- Subjects who participated in a previous trial with Anti-HER2 VHH1

Withdrawal of subjects

The subject may withdraw from the study at any time without giving reasons and without any disadvantageous consequences for his/her subsequent medical care.

The investigator may withdraw a subject from the study at any time in case of intercurrent illness, AE, therapeutic procedure or as a general rule if further participation in the study is believed to be to the subject's detriment.

Any subject withdrawn from the study before the scheduled completion of the study procedures will be considered an early withdrawal, regardless of the reason for withdrawal. For safety

reasons, reasonable attempt should be made to contact withdrawn subjects 24h after the administration of the investigational product to gather information on AEs. For his/her own safety, subjects will be reminded to continue potassium iodide ingestion until  $48 \pm 12$ h after administration of [ $^{131}$ I]-SGMIB Anti-HER2 VHH1. Information collected as a result should be recorded on the appropriate case report form (CRF) pages. Subjects withdrawn from the study will be replaced.

### Subject recruitment

Healthy subjects will be recruited by the PI using advertising approved by the ethics committee.

#### 5.4.2 Part II (Patients with HER2+ breast cancer)

#### Inclusion Criteria:

Patients will only be included in the study if they meet all of the following criteria:

- Patients who have given informed consent
- Patients that agree not to drink alcoholic beverages or use any drugs during the study
- Age: at least 18 years old
- Patients with local, locally advanced or metastatic HER2+ breast carcinoma as diagnosed on biopsied tissue by immunohistochemistry or fluorescence in situ hybridization (FISH).

#### Exclusion Criteria

Patients will not be included in the study if one of the following criteria applies:

- Pregnant patients
- Breast feeding patients
- Patients with occupational exposure to ionizing irradiation
- Patients with active thyroid dysfunction (abnormal TSH value)
- Patients that received radiolabeled compounds with a long half-life ( $>7$ h) for diagnostic or therapeutic purposes within the last 2 days.
- Patients with absolute contra-indications for thyroid blockage with potassium iodide.
- Patients with abnormal liver: ALT/AST  $> 2$  times normal values; bilirubin  $> 1.5$  time normal values.
- Patients with abnormal kidney function:  $< 50$  ml/min/1,73 m<sup>2</sup>
- Patients with recent ( $< 1$  week) gastrointestinal disorders (CTCAE v4.0 grade 3 or 4) with diarrhea as major symptom
- Patients with any serious active infection
- Patients who have any other life-threatening illness or organ system dysfunction, which in the opinion of the investigator would either compromise patient safety or interfere with the evaluation of the safety of the test radiopharmaceutical
- Patients who cannot communicate reliably with the investigator

- Patients who are unlikely to cooperate with the requirements of the study
- Patients at increased risk of death from a pre-existing concurrent illness
- Patients who participated already in this study
- Patients who participated in a previous trial with Anti-HER2 VHH1

#### Withdrawal of patients

The patient may withdraw from the study at any time without giving reasons and without any disadvantageous consequences for his/her subsequent medical care.

The investigator may withdraw a patient from the study at any time in case of intercurrent illness, AE, therapeutic procedure or as a general rule if further participation in the study is believed to be to the patient's detriment.

Any patient withdrawn from the study before the scheduled completion of the study procedures will be considered an early withdrawal, regardless of the reason for withdrawal. For safety reasons, reasonable attempt should be made to contact withdrawn subjects 24h after the administration of the investigational product to gather information on AEs. For his/her own safety, subjects will be reminded to continue potassium iodide ingestion until  $48 \pm 12$ h after administration of [ $^{131}$ I]-SGMIB Anti-HER2 VHH1. Information collected as a result should be recorded on the appropriate CRF pages.

Patients withdrawn from the study will be replaced.

#### Patient recruitment

Patients with HER2+ breast cancer will be recruited by the PI at UZ Brussel and possibly via the ClinicoBru patient recruitment network.

### 5.5 Clinical Laboratories, Technical Department(s), Institution(s) Providing Clinical Study Services

The local department of clinical chemistry and hematology will perform the clinical laboratory testing of blood samples.

The local nuclear medicine department will provide the analyses of the blood and urine samples:

Whole blood and plasma samples will be counted against appropriate standards of known dilution in an automatic gamma well counter and, after correction for decay and background activity, expressed as a percentage of the injected activity (%IA). The blood volume of each volunteer will be estimated according to body weight and height, using Nadler's formula and the subject's hematocrit

Plasma and urine aliquots will be analyzed by size-exclusion chromatography (SEC) or reverse-

phase high pressure liquid chromatography (RP-HPLC) to identify possible metabolites.

The PI of the local nuclear medicine department will also perform the analyses of the dynamic planar scan, the total body scans and the SPECT/CT scans.

From the dynamic planar scan, time activity curves for kidney and liver activity will be drawn.

The total body scans will be used for region of interest analysis to derive input data for the OLINDA/EXM software 1.0 in order to calculate dosimetry data (12).

SPECT/CT scans will be analyzed visually and tumor uptake will be scored by the PI: intense, moderate, low or no uptake. In addition, tumor lesions will be quantified to obtain a measurement of activity per unit of volume.

## 5.6 Image acquisition parameters

The subject will be scanned feet first in supine position.

- I-131 Dynamic planar scan kidneys&liver (gamma camera):
  - Collimator           HEGP
  - Zoom                 1 (Full field)
  - Matrix                256 x 256
  - Energy Window       20% (6% low, 6% high scatter window)
  - Frames/duration      30 frames of 60s
- I-131 Total body planar scan:
  - Collimator           HEGP
  - Zoom                 1.11 (Full field)
  - Matrix                High-resolution (1024 x 512)
  - Energy Window       20% (6% low, 6% high scatter window)
  - Scan speed           10 cm/min
- I-131 SPECT/CT scan of 1 region with a cancer lesion:
  - Collimator           HEGP
  - Matrix                128 x 128
  - Energy Window       20% (6% low, 6% high scatter window)
  - Rotation             360
  - Total projection     64
  - Time/projection      30s
- Surview CT acquisition:
  - Voltage              120 kV, 30 mA
  - Rotation             180
  - Rotation time        24s
  - Exposure             580 mAs
  - Matrix                512 x 512
  - Pixel size            1,667 mm

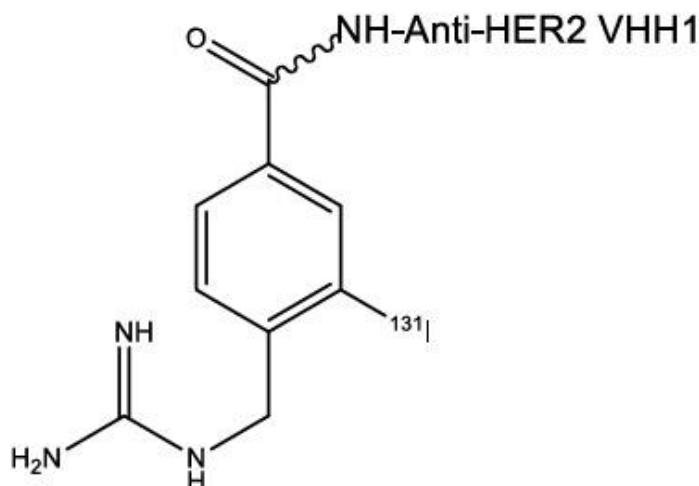
Slice thickness	1 mm
Segments	3
CTDI (mGy)	15

## 5.7 Investigational product

### Composition:

The colorless, clear, sterile solution contains the radioactive [<sup>131</sup>I]-SGMIB Anti-HER2 VHH1 in Phosphate Buffered Saline (PBS).

<sup>131</sup>I radiolabeled N-succinimidyl 4-guanidinomethyl-3-iodobenzoate (SGMIB) conjugated anti-HER2 VHH1 protein referred to as [<sup>131</sup>I]-anti-HER2 VHH1:



### Route of administration:

IV-injection of [<sup>131</sup>I]-SGMIB Anti-HER2 VHH1 using an infusion pump within 5±3min via an intravenous line inserted in a vein or port-a-cath

### Dosage regimen:

A continuous infusion of 50±40µg with radioactivity of 64±46MBq

### Treatment period:

The product will be administered as a single dose with a radioactivity of 46±28MBq for healthy volunteers.

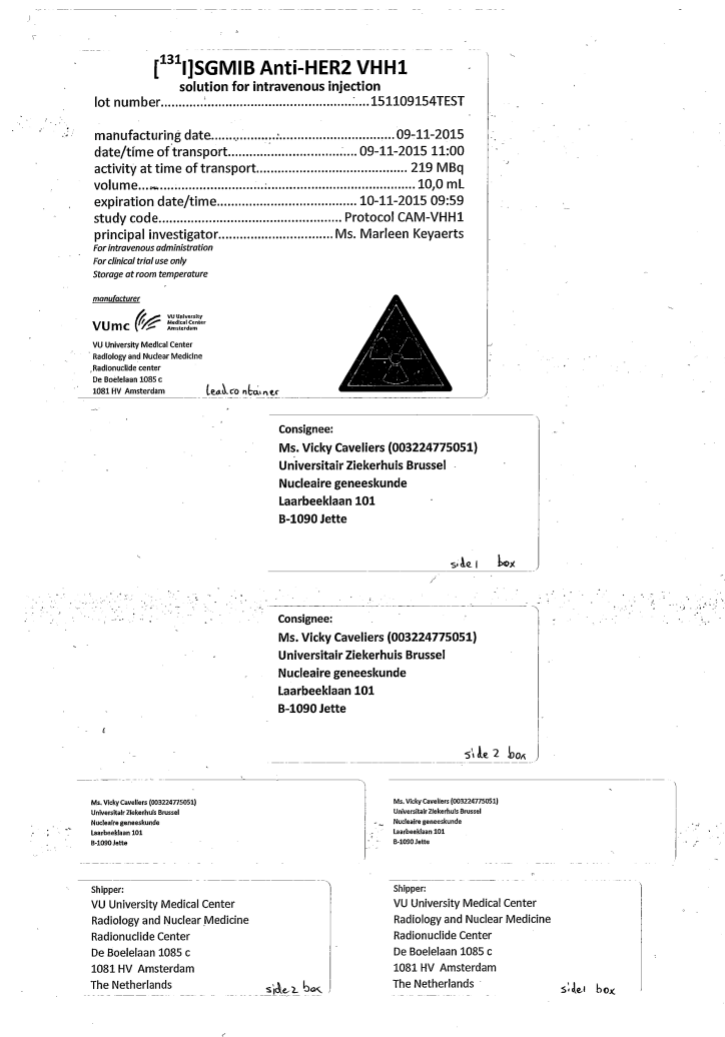
In HER2+ breast cancer patients the product will be administered as a single dose with a radioactivity of 64±46MBq.

Labeling information:

Primary label example: **[<sup>131</sup>I]-SGMIB Anti-HER2 VHH1**  
 Lot number: **151109154TEST**  
 Study code: CAM-VHH1  
 For clinical trial use only  
 For intravenous administration  
 Caution: Radioactive material  
 Principal investigator: Ms. Marleen Keyaerts  
 Details: See outer packaging



Secondary label example:



The secondary label example consists of several components:

- Main Label:**
  - Product name: [<sup>131</sup>I]SGMIB Anti-HER2 VHH1
  - Solution for intravenous injection
  - lot number: 151109154TEST
  - manufacturing date: 09-11-2015
  - date/time of transport: 09-11-2015 11:00
  - activity at time of transport: 219 MBq
  - volume: 10,0 mL
  - expiration date/time: 10-11-2015 09:59
  - study code: Protocol CAM-VHH1
  - principal investigator: Ms. Marleen Keyaerts
  - For intravenous administration
  - For clinical trial use only
  - Storage at room temperature
  - Manufacturer: VUmc (VU University Medical Center Amsterdam)
  - Address: VU University Medical Center, Radiology and Nuclear Medicine, Radionuclide center, De Boelelaan 1085 c, 1081 HV Amsterdam
  - Logo: A triangular warning symbol with a radiation symbol inside.
- Side 1 box:**
  - Consignee: Ms. Vicky Caveliers (003224775051)
  - Universitair Ziekenhuis Brussel
  - Nucleaire geneeskunde
  - Laarbeeklaan 101
  - B-1090 Jette
- Side 2 box (top):**
  - Consignee: Ms. Vicky Caveliers (003224775051)
  - Universitair Ziekenhuis Brussel
  - Nucleaire geneeskunde
  - Laarbeeklaan 101
  - B-1090 Jette
- Side 2 box (bottom left):**
  - Shipper: VU University Medical Center, Radiology and Nuclear Medicine, Radionuclide Center, De Boelelaan 1085 c, 1081 HV Amsterdam, The Netherlands
- Side 2 box (bottom right):**
  - Shipper: VU University Medical Center, Radiology and Nuclear Medicine, Radionuclide Center, De Boelelaan 1085 c, 1081 HV Amsterdam, The Netherlands

Preparation and drug administration:

The product will be received by the radiopharmacist of UZ Brussel, checked for its integrity and recorded on the Drug Receipt Form. The radiopharmacist will be responsible for receiving the batch release certificate and the QC results of the received batch from the manufacturer.

The radiopharmacist will contact the QP of the manufacturer to have the authorization of use.

The product will be stored at  $5\pm 3^{\circ}\text{C}$  until use. The product will normally be used within 24h after production by the manufacturer. The radiopharmacist of UZ Brussel could ask the QP of the manufacturer for authorization to use the product at a later time point based on stability data.

The product will be drawn into a 20ml syringe and a 0.9% NaCl solution for injection will be added to obtain a final volume of 15ml. The injection syringe will need to be labeled with the appropriate identification label. The product will only be administered in the presence of a physician.

The radiopharmacy and the investigators will keep adequate records for the receipt, preparation, administration and return of study medication. They would not allow the study medication to be used for purposes other than as directed by this protocol. All data regarding the study medication must be recorded in the relevant forms provided by the Sponsor.

The radiopharmacy will allow the used study drug (empty vials) to decay and be destroyed according to the local procedures for destruction of radioactive waste.

In case of remaining treatment (vials not used), these will have to be destroyed according to the local procedures for destruction of radioactive waste.

## 5.8 Previous and concomitant medication/therapy

The subject should not have received radiolabeled compounds with a long half-life ( $>7\text{h}$ ) for diagnostic or therapeutic purposes within the last 2 days.

Other medication to treat AEs might only be prescribed after consultation of the PI, unless in case of an emergency situation.

### 5.8.1 Potential risks and benefits to human subjects

Potential Risks

All medicinal products can have known or unforeseeable side effects. The previous study UZBRU-VHH1 has shown that a similar product was well-tolerated, without any side effects. However unknown side effects or discomforts could appear.

The administration of the product in a vein and blood sampling (around 5ml of blood) might (rarely) cause pain, bleeding, bruising or infection localised around the injection site. Similarly, some subjects might feel dizzy or even faint during the procedure. The clinical team that will perform this procedure will do all they can to keep these discomforts to a minimum.

During this investigation the subjects will be exposed to a low amount of ionizing radiation. The past study involving a similar product showed that the exposure to radiation was very low, and lower than the exposure caused by a routinely performed FDG-PET scan.

No information is available that can predict an interaction with the current product. Preclinical studies showed no interactions with anti-HER2 treatments such as PertuzumAb and TrastuzumAb (7).

### Benefits

For the healthy volunteers, no benefits are expected.

For the HER2+ breast cancer patients the investigated diagnostic product might or might not prove beneficial in diagnosing and treatment of the disease.

The information obtained thanks to this study might contribute to a better knowledge of the use of this investigational product or to the development of a new medicinal product for the diagnosis and treatment of breast cancer in patients.

## 5.9 Outcome measures of safety, tolerability and tumor targeting

### 5.9.1 Primary outcome measures of safety and tolerability

Tolerability and safety of [<sup>131</sup>I]-SGMIB Anti-HER2 VHH1 will be assessed by the collection and evaluation of data pertaining to all AEs experienced by subjects during the study. Subjects will undergo a physical examination including vital signs and be asked about changes in concomitant diseases and general physical and emotional state using open, non-leading questions. Blood will be collected for hematology and clinical chemistry.

A physical examination including vital signs (arterial blood pressure and pulse rate) will be performed pre-administration. Additionally the vital signs will be monitored at 5±10min post-administration. A second physical exam will be performed at 4.5±1h post-administration for the healthy subjects and at 3±1h for the HER2+ breast cancer patients.

Safety laboratory examination: A blood sampling will be performed before and at 24±4h after the administration of the [<sup>131</sup>I]-SGMIB Anti-HER2 VHH1, using 1 lithium/heparin sample of 5ml and 1 EDTA sample of 2.6ml at each time point.

Any clinically relevant change from a baseline laboratory value will be recorded as an AE in the CRF unless it can reasonably be assumed to result from improper handling, a measurement error or some other technical cause.

From the hematology and clinical chemistry we expect no major changes (±20% deviation of the baseline value and outside of the laboratory reference values).



We expect no significant changes in the physical exam in comparison with the physical exam before product administration.

From the blood sampling we expect to obtain the time-activity curve of the product in blood to be biphasic with a rapid distribution and elimination phase. After 24h we expect that less than 10% IA will be present in the blood.

From the urine sampling we will measure the fraction of un-metabolized product.

Human biodistribution will be assessed for the healthy volunteers using the dynamic scan and planar total body scans.

From the imaging results we expect to visualize liver and kidney as primary elimination routes and potentially uptake in tissues with physiological HER2 expression such as thyroid, pituitary, salivary, lacrimal, sweat glands and intestines.

Human dosimetry will be quantified using region of interest measurements on the total body scan of the different subjects. OLINDA/EXM software 1.0 will be used to generate dosimetry estimates for the healthy subjects (12).

#### 5.9.2 Secondary outcome measures of tumor targeting

The tumor targeting potential will be visually scored as positive (intense, moderate or low) or negative by the PI.

We expect that patients with measurable HER2+ cancer lesions (lesions above 3cm) will be detectable using SPECT/CT. The activity per unit of volume will be quantified by the PI.

### 5.10 Adverse events / serious adverse events

#### 5.10.1 Definitions

The definitions of the AEs and related terminology are those in the ICH E6 guidance. Grading will be evaluated according to CTCAE v4.0. AE coding will be performed with the MedDRA dictionary v18.1.

#### 5.10.2 Documentation and reporting

All observed or volunteered AEs regardless of suspected causal relationship to the IMP will be recorded on the AE page(s) of the case report form. The investigator must assess all AEs for seriousness, severity and relation to IMP.

The investigator will follow all AEs, regardless of seriousness or severity, until the event or its sequelae resolve or stabilize at a level acceptable to the investigator.

The investigator is responsible for ensuring appropriate clinical management of all AEs until they are resolved or stabilized at a level acceptable to the investigator. Appropriate clinical management of AEs is at the discretion of the investigator.

All clinically significant abnormal laboratory tests occurring during the study will be repeated at appropriate intervals until they return to baseline or to a level deemed acceptable by the investigator, or until the abnormality is explained by an appropriate diagnosis.

#### 5.10.3 Expedited reporting of serious adverse events (SAEs)

Any SAE must be reported to the sponsor within 24h of awareness. Such events will be documented in the best possible detail on the SAE Report Form to be transmitted to the sponsor by fax or email. The immediate report shall be followed by detailed, written reports. The immediate and follow-up reports shall identify subjects by unique code numbers assigned to the latter. AEs and/or laboratory abnormalities identified in the protocol as critical to safety evaluations shall be reported to the sponsor.

The contact information is as follows:

Sponsor's QPPV:  
Paul Willems, MD  
Semaphar sprl  
Rue Francourt 31  
1370 Lathuy  
Belgium  
Mobile: +32 476 777 987  
E-mail: pwillems.md@icloud.com

Emergency 24-hour Contact:  
Tony Lahoutte, MD, PhD  
Camel-IDS NV  
Phone: +32 2 476 31 12  
Mobile: +32 472 81 12 14  
E-mail: tony.lahoutte@camel-ids.com

For all these SAEs, the investigator is obligated to pursue and provide information as requested by the Sponsor or its designated representative in addition to that on the CRF. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on

other possible causes of the event, including concomitant medications and illnesses must be provided. The investigator's assessment of causality must also be provided. If causality is unknown and the investigator does not know whether or not study drug caused the event, then it should be attributed to the study drug.

In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to the Sponsor or its designated representative. For reported deaths of a subject, the investigator shall supply the sponsor, the Ethics Committee and regulatory authorities with any additional information requested.

The sponsor shall keep detailed records of all AEs that are reported to him by the investigator or sub-investigators.

## 5.11 Statistical methods planned

### 5.11.1 Sample size justification

No statistical hypothesis has to be tested. Therefore, no formal sample size calculations have been made. The sample size has been determined based on literature (12).

Overall, 10 humans (healthy volunteers and patients pooled together) are going to be exposed to the IMP. For a sample size of 10, the probability of observing at least one event will be 90% (power) when the actual probability of the event is 20.6%, and a power of 80% will be ensured for an actual probability of the event of 14.9%. The probability (power) of observing an event having a frequency of 10% will be 65.1% and that of observing an event having a frequency of 5% will be 40.1%.

### 5.11.2 Safety

Safety of the [<sup>131</sup>I]-SGMIB Anti-HER2 VHH1 will be evaluated based on the adverse effects, their intensity and relationship to the investigational product. The evaluation is of a qualitative manner and no statistical inferential methods are planned for this objective. Classical descriptive statistics for categorical variables (N, n and %) will be used.

### 5.11.3 Biodistribution and dosimetry

For the biodistribution evaluation, all organs with an uptake higher than the background (surrounding soft tissues) will be included in the evaluation as source organs.

The percentage of injected activity (%IA) will be calculated, in each set of images, as the ratio between the measured activity in the organ and the injected activity. Organ time activity curves

will be generated, plotting %IA vs. time. The individual and mean blood and plasma time-activity curves will be obtained using the measured activity in blood and plasma samples.

All dosimetric evaluations will be done using the OLINDA/EXM 1.0 software (12). Total dose estimates and the dose estimate for the organs with the highest dose (most likely kidney and bladder) will be reported using classical descriptive statistics for continuous variables (N, n, mean, median, standard deviation, minimum and maximum).

#### 5.11.4 Tumor uptake

Tumor uptake will be scored visually as positive or negative in all known tumor lesions. Classical descriptive statistics for categorical variables (N, n and %) will be used to characterize this variable.

#### 5.12 Criteria for termination of the study

In case a SAE related to the IMP occurs, the trial will be stopped.

When the number of subjects that achieved the trial is equal to 6 healthy volunteers, the DSMB will evaluate the safety profile of the product and take the decision to include the 4 HER2+ breast cancer patients.

### 5.13 Overview of investigational actions

Table 1. Overview of the investigational actions that need to be performed at different visit times for each subject in part I of the study. V1: Visit 1; V2: Visit 2; V3: Visit 3; V4: Visit 4; V5: Visit 5

Action	Total	V1	V2	V3												V4		V5	
		pre	0min	5min	10min	20min	30min	40min	60min	105min	120min	225min	240min	4.5h	23.75h	24h	71.75h	72h	
Informed consent	1	x																	
Inclusion/exclusion criteria	1	x																	
Medical history	1	x																	
Subject information: fasting&thyroid blocking drugs	2	x	x																
Delivery thyroid blocking drugs	4	x	x													2x			
Confirmation of ingestion thyroid blocking drugs	4	x	x													x		x	
Blood sample for HCG test	1	x																	
Physical exam	2		x												x				
Vital signs	3		x		x										x				
Blood sample lithium heparine	13	x	2x		x	x	x	x		x	x		x			2x		x	
Blood sample EDTA	3	x	x													x			
Urine sampling	4									x			x			x		x	
Intravenous line&saline infusion	1		x																
Administration [ <sup>131</sup> I]-Anti-HER2 VHH1	1			x															
Measurement of residual activity in syringe and line	1			x															
If subject cannot withhold: urine collection&scan TB1	1								x										
Dynamic renal scan (30 min)	1			x															
Total body (TB) planar scan	5								x			x		x			x		x
Counting blood/plasma (radioactivity)	10		x		x	x	x	x		x	x		x			x		x	
HPLC analysis (metabolites in blood)	5				x					x			x			x		x	
HPLC analysis (metabolites in urine)	4									x			x			x		x	
Clinical chemistry/Hematology analysis	3	x	x													x			
HCG test	1	x																	
Dosimetry analysis Total body planar scans	5									x			x		x		x		x

Table 2. Overview of the investigational actions that need to be performed at different visit times for each patient in part II of the study.  
V1: Visit 1; V2: Visit 2; V3: Visit 3; V4: Visit 4

Action	Total	V1	V2	V3								V4		
				pre	0min	5min	15min	60min	120min	2.5h	3h	23.75h	24h	24.5h
Informed consent	1	x												
Inclusion/exclusion criteria	1	x												
Medical history	1	x												
Patient information: fasting& thyroid blocking drugs	2	x	x											
Delivery thyroid blocking drugs	4		x	x								2x		
Confirmation of ingestion thyroid blocking drugs	3		x	x								x		
Blood sample for HCG test	1		x											
Physical exam	2			x							x			
Vital signs	3			x		x					x			
Blood sample lithium heparine	4		x	x				x				x		
Blood sample EDTA	3		x	x								x		
Intravenous line&saline infusion	1			x										
Administration [ <sup>131</sup> I]-Anti-HER2 VHH1	1				x									
Measurement of residual activity in syringe and line	1				x									
If patient cannot withhold: urine collection&scan TB1	1								x					
Total body (TB) planar scan	3						x		x				x	
SPECT/CT scan	2									x				x
Counting blood/plasma (radioactivity)	1							x						
HPLC analysis (metabolites in blood)	1							x						
Clinical chemistry/Hematology analysis	3		x	x								x		
HCG test	1		x											

## **6. DATA HANDLING AND RECORD KEEPING**

### **6.1 Case report form**

A paper CRF will be completed for each screened subject.

This CRF will include specific pages for inclusion and exclusion criteria conclusions, for general and technical examination during the screening visit, and for reporting each visit and biological results. Other specific pages will be dedicated to potential supplementary visit, in case of subject stop or withdrawal, and to the recording of concomitant treatments and AEs (non-serious and serious).

The investigator will review, approve and validate each completed CRF; the investigator's signature (validation) serving as attestation of the investigator's responsibility for ensuring that all clinical and laboratory data entered on the CRF are complete, accurate and authentic.

## **7. DIRECT ACCESS TO SOURCES**

The investigator will provide direct access to source data and documents to Sponsor. The Sponsor representatives will have the authorization to access of medical records of each subject participating to the clinical trial.

### **7.1 Source data and documents**

Source data are all the information in original records and certified copies of original records of clinical findings, observations, or other activities in the study, which are necessary for the reconstruction and evaluation of the study. Source data are contained in source documents (originals or certified copies).

All information recorded on the CRFs for this study must be consistent with the subject's source documentation. The source documents (i.e. hospital records) must contain the first, middle (where applicable) and the last name of the subject, the date of birth and address, the information that the informed consent was signed and dated prior to the study screening, the date of entry in the study, the date of the visits, the code number of the subject, the dosing, the number of used IMPs, the efficacy data if applicable, the safety data and the date of completion of the study.

Source records should be preserved for the maximum period of time permitted by local requirements (30 years in Belgium). For each subject enrolled, the investigator will indicate in the source record(s) that the subject participates in this study, and record the following information: subject number, identification of the subjects (name, address, etc.), dates of drug administration, vital signs, any AEs, study completion date, and main reason for discontinuation, if applicable.

## 7.2 Direct access to source data and documents

Besides the monitor, regulatory authorities, members of ethics committees and the sponsor's clinical quality assurance representative or the sponsor's monitors, may carry out source data checks and/or on-site audits or inspections. Direct access to source data will be required for these audits and inspections; they will be carried out giving due consideration to data protection and medical confidentiality. The investigator will assure the authorities and the sponsor of the necessary support at all times.

## 7.3 Confidentiality and subject anonymity

Secret must be respected regarding the identity of persons participating in a clinical study and all information of a personal or medical nature concerning these subjects. Any information which might permit identification of subject must be kept confidential. This confidentiality must be guaranteed to all subjects participating in the study.

In all reports involving the subjects included in the study, each subject will be identified only by a subject number with three characters and the birthday year.

The investigator will ensure that the confidentiality of subjects' data will be preserved. On CRFs or any other documents submitted to the sponsor, the subjects will not be identified by their names, but by an identification system, which consists of their number in the study. Documents that identify the names of participants against their study number, i.e. the confidential subject identification log will be maintained by the investigator in strict confidence and will not be sent to the sponsor in any circumstances.

The investigator will be personally responsible for the updating of a subject identification log which relates subject numbers to the names and means of contact of each subject in the study. This log will be kept in the investigator's file so that the investigator can contact the subjects.

The confidentiality of these data will be preserved in accordance with the applicable national and/or local laws and regulations on personal data protection.

Monitors, auditors and other authorized agents of Camel-IDS NV will be granted direct access to study subject's original medical records for verification of clinical study procedures and/or data, without violating the confidentiality of the subjects, to the extent permitted by the law and regulations. In any presentations of the results of this study at meetings or in publications, the subjects' identity will remain confidential.

## 8. QUALITY CONTROL

The investigator will permit direct access of the study monitors and appropriate regulatory authorities to the study data and to the corresponding source data and documents to verify the accuracy of this data.



Quality control measures will be followed throughout the study. The clinical study monitor will observe the progress of the study. Contacts with the investigator and on-site visits at regular intervals for the purpose of data review, including the comparison of source documents with data recorded in the CRFs will occur. He or she will also ensure compliance of the study site with the protocol, applicable SOPs and guidelines as described in this protocol. The review of the subjects' medical records will be performed in a manner to ensure that subject confidentiality is maintained. The principal investigator or his/her representative will need to be available during these visits.

On-site visits will be made before study initiation and in eligible time intervals during the study. Communication by telephone and mail may be used as needed to supplement (but not substitute) visits.

The monitor will have the responsibility of reviewing the ongoing study with the investigator to verify adherence to the protocol and to deal with any problems if and when they arise. Special items to be monitored are: subject enrolment, completeness, exactness and plausibility of data entered in the CRF, verification against source data, drug accountability and occurrence of AEs. The confidentiality of study documents will be maintained at all times. The investigator agrees to allow the monitor access to any or all of the study materials needed for the monitor to properly review the study progress. The investigator (or deputy) agrees to assist the monitor in resolving any problem that may be detected during the monitoring visit.

Monitor should write a monitoring report of visit performed on investigator sites and a monitoring letter to the visited investigator.

Quality control must also be performed on an ongoing basis at various stages in the data cleaning process. Quality control documentation is required for biometrics activities. Contractor should prove validation of computerized system used for clinical data recording.

## 8.1 Audits and inspections

The investigator should understand that source documents for this study should be made available to appropriately qualified personnel from the Sponsor, Quality Assurance Unit or its designees, or to Health Authority Inspectors after appropriate notification. The investigator's site, facilities and all data (including source data) and documentation could be made available for audit by an independent quality assurance unit and for EC or regulatory authorities according to the guideline of the international conference on harmonization (ICH)-good clinical practice (GCP). The investigator agrees to co-operate with the auditor during his/her visit and will be available to supply the auditor with CRFs or other files necessary to conduct that audit. Any findings will be strictly confidential.

In the event that a regulatory authority informs the investigator that it intends to conduct an inspection, sponsor shall be notified immediately.

The main purposes of an audit or inspection are to confirm that the rights and well-being of the subjects have been adequately protected, and that all data relevant for the evaluation of the investigational product have been processed and reported in compliance with GCP and

applicable regulatory requirements. The verification of the CRF data must be done by direct control of source documents.

## **9. ETHICS**

### **9.1 Ethics Committee Approval**

The sponsor will obtain, from the Ethics Committee of UZ Brussel and from each participating hospital's local Ethics Committee, a prospective approval of the clinical study protocol and corresponding informed consent form(s); modifications to the protocol and corresponding informed consent form(s), and advertisements (i.e., directed at potential research subjects) for study recruitment.

The Ethics Committee of UZ Brussel operates in compliance with European regulations and in conformance with applicable ICH-GCP guideline.

In the event that the Ethics Committee requires, as a condition of approval, substantial changes to the clinical protocol, or in the event of a sponsor's decision to modify the previously accepted clinical protocol, the investigator will submit (i.e., in advance of implementing the change) a Protocol Amendment describing any change to the clinical protocol that significantly affects the safety of the subjects. For changes that do not affect critical safety assessments, the revisions to the clinical protocol will be notified to the Ethics Committee(s).

### **9.2 Ethical and scientific conduct of the clinical study**

The clinical study will be conducted in accordance with the current Ethics committee-approved clinical study protocol; Declaration of Helsinki principles; ICH Guidelines on GCP; and relevant policies, requirements, and regulations.

## **10. FINANCING AND INSURANCES**

### **10.1 Financing**

The study is financed by Camel-IDS SA/NV, a spin-off company of the VUB and with the support of Innoviris.

### **10.2 Insurances**

The subjects taking part in this study will be covered by the insurance taken by the sponsor, if they were to suffer any prejudice as a result of taking part in the study and according to ICH-

GCP requirements, the Sponsor has taken out personal liability insurance with an Insurance company following the Belgian regulations. This insurance was taken out with Ethias NV, polis number 45.349.418.

## **11. PUBLICATION POLICY**

The results may be published or presented at scientific meetings upon prior written agreement of the sponsor. Any manuscript or abstract will be submitted to the sponsor prior to its submission to an editorial board or scientific review committee.

A draft study report will be prepared after the completion of the study according the ICH recommendations. The principal investigator will sign the final study report intended to be submitted to regulatory authorities.

## **12. REFERENCE LIST**

- (1) Vaneycken I., D'huyvetter M., Hernot S., De Vos J., Xavier C., Devoogdt N., Caveliers V., Lahoutte T. Immuno-imaging using nanobodies. *Curr Opin Biotechnol.* 2011;22(6):877-81.
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