CLINICAL STUDY PROTOCOL

A Multi-Center Open Label Dose Escalation and Dose Expansion Study to Evaluate Safety, Tolerability, Dosimetry, and Preliminary Efficacy of the HER2 Directed Radioligand CAM-H2 in Patients With Advanced/Metastatic HER2-Positive Breast, Gastric, and Gastro-Esophageal Junction Cancer

Investigational Product: CAM-H2 (^{131}Iodine-4-guanidinomethyl-3-iodobenzoate [GMIB]-2Rs15d)

Protocol Number: CAMH2_1001

EudraCT Number: 2020-001112-14

Investigational New Drug Number: 144706

Sponsor:
Precirix NV
Burgemeester Etienne Demunterlaan 1
B-1090 Brussels
Belgium
Telephone: +32 2 479 93 60

Version Number: 2.2

Original Study Protocol: 10 April 2020

Amendment 1: 05 February 2021

Amendment 1.2 (Canada): 14 January 2022

SIGNATURE PAGE

STUDY TITLE: A Multi-Center Open Label Dose Escalation and Dose Expansion Study to Evaluate Safety, Tolerability, Dosimetry, and Preliminary Efficacy of the HER2 Directed Radioligand CAM-H2 in Patients With Advanced/Metastatic HER2-Positive Breast, Gastric, and Gastro-Esophageal Junction Cancer

We, the undersigned, have read this protocol and agree that it contains all necessary information required to conduct the study.

Signature	Date
Steven Ramael, M.D. *Electronically signed by: Steven Ramael, M.D. Reason: Approved Date: Jan 17, 2022 15:00 GMT+1*	17-Jan-2022
Steven Ramael, MD Medical Director Precirix NV	
 *Electronically signed by: Tony Lahoutte Reason: Approved Date: Jan 19, 2022 13:42 GMT+1*	19-Jan-2022
Tony Lahoutte, MD, PhD Chief Scientific Officer Precirix NV	

INVESTIGATOR AGREEMENT

By signing below I agree that:

I have read this protocol. I approve this document and I agree that it contains all necessary details for carrying out the study as described. I will conduct this study in accordance with the design and specific provision of this protocol and will make a reasonable effort to complete the study within the time designated. I will provide copies of this protocol and access to all information furnished by Precirix NV to study personnel under my supervision. I will discuss this material with them to ensure they are fully informed about the study product and study procedures. I will let them know that this information is confidential and proprietary to Precirix NV and that it may not be further disclosed to third parties. I understand that the study may be terminated or enrollment suspended at any time by Precirix NV, with or without cause, or by me if it becomes necessary to protect the best interests of the study patients.

I agree to conduct this study in full accordance with applicable regulations, ethical and legal requirements, Institutional Review Board/Ethic Committee Regulations, and International Council for Harmonisation Guidelines for Good Clinical Practices.

_____ _____

Investigator's Signature Date

_____

Investigator's Printed Name

SYNOPSIS

TITLE: A Multi-Center Open Label Dose Escalation and Dose Expansion Study to Evaluate Safety, Tolerability, Dosimetry, and Preliminary Efficacy of the HER2 Directed Radioligand CAM-H2 in Patients With Advanced/Metastatic HER2-Positive Breast, Gastric, and Gastro-Esophageal Junction Cancer

PROTOCOL NUMBER: CAMH2_1001

INVESTIGATIONAL PRODUCT: CAM-H2 (^{131}Iodine-4-guanidinomethyl-3-iodobenzoate [GMIB]-2Rs15d)

PHASE: 1/2

INDICATIONS: Advanced/metastatic human epidermal growth factor receptor 2 (HER2)-positive breast, gastric, and gastro-esophageal junction (GEJ) cancer with disease progression following anti-HER2 standard of care treatment

OBJECTIVES:

The primary objective for the dose escalation phase is as follows:

- To evaluate the safety, tolerability, dosimetry, and pharmacodynamics (PD) of ascending doses of CAM-H2 in patients with advanced/metastatic HER2-positive breast, gastric, and GEJ cancer, including determination of dose-limiting toxicity (DLT), maximum tolerated dose (MTD), and recommended dose for Phase 2 (RDP2).

The primary objectives for the dose expansion phase are as follows:

- To evaluate the proportion of patients achieving an objective response (complete response [CR] or partial response [PR]) with the use of CAM-H2 as measured by the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (all patients with extracranial lesions) or as measured by the Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM) (patients with brain metastases without extracranial lesions);
- To measure the clinical benefit rate (CBR) of CAM-H2 using the equation CBR = CR + PR + stable disease (SD), as measured by RECIST version 1.1 (all patients with extracranial lesions) or as measured by RANO-BM (patients with brain metastases without extracranial lesions); and
- To evaluate the safety and tolerability of CAM-H2 in patients with advanced/metastatic HER2-positive breast, gastric, and GEJ cancer.

The secondary objectives are as follows:

- To assess the clinical benefit (CB) of CAM-H2 by evaluating the proportion of patients with a CR, PR, and SD in the dose escalation phase;
- To assess duration of response (DoR);

- To evaluate progression-free survival (PFS) from the time of enrollment in the study to progression of disease or death;
- To measure median overall survival (OS);
- To evaluate intra- and inter-patient dosimetry and PD of CAM-H2 (dose escalation phase only); and
- To assess for the development of anti-drug antibodies (ADAs).

POPULATION:

Inclusion Criteria

Patients who meet all of the following criteria will be eligible to participate in the study:

1. Informed consent form signed voluntarily before any study-related procedure is performed, indicating that the patient understands the purpose of, and procedures required for, the study and is willing to participate in the study;
2. Males and females ≥18 years of age at screening;
3. Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 to 1;
4. HER2-positive locally advanced or metastatic breast cancer refractory to standard cancer treatment or HER2-positive locally advanced or metastatic gastric or GEJ cancer, refractory to standard cancer treatment;
5. Patients should have a minimum of 1 measurable lesion as defined by RECIST version 1.1 or a minimum of 1 measurable lesion as defined by RANO-BM within 4 weeks of the first dose of the study drug (Day 1). The lesion has to be a new lesion or progression of an existing lesion under the current therapy;
6. Any previous anti-HER2 treatment for advanced or metastatic disease is allowed. Patients with breast cancer should have had at least 2 previous systemic anticancer treatments for recurrent, locally advanced or metastatic cancer. Patients with gastric cancer or GEJ cancer should have had at least 1 previous anti-HER2 treatment;
7. Life expectancy >6 months;
8. Adequate organ function, determined by the following laboratory tests at screening:
    - Adequate kidney function with an estimated glomerular filtration rate (eGFR) of >59 mL/minute calculated using the Chronic Kidney Disease Epidemiology Collaboration equation;
    - Adequate hepatic function defined as an alanine aminotransferase (ALT) and aspartate aminotransferase (AST) <2.5 × the upper limit of normal (ULN), or <5 × ULN in patients with liver metastases, and total bilirubin <2 × ULN;
    - Neutrophil count >1500 cells/mm^3 without growth factor support (14 days after last pegylated granulocyte colony-stimulating factor or 7 days after regular granulocyte colony-stimulating factor);
    - Platelet count >100,000 cells/mm^3 without platelet transfusion in the last 2 weeks;

- Hemoglobin >9.0 g/dL without blood transfusion in the last 2 weeks; and
- Adequate coagulation defined as an international normalized ratio (INR) ≤1.5 and activated partial thromboplastin time <1.5 × the upper limit of the institutional normal range;

9. Baseline left ventricular ejection fraction ≥50% as measured by echocardiography or multigated acquisition scan;
10. Absence of any psychological, family, sociological, or geographical circumstance that could potentially represent an obstacle to compliance with the study protocol and the follow-up schedule, as determined by the Investigator. These circumstances will be discussed with the patient before enrollment in the study; and
11. Female patients of childbearing potential (ie, ovulating, premenopausal, and not surgically sterile) must have a negative pregnancy test at screening and prior to study drug administration. Patients and their partners of childbearing potential must be willing to use 2 methods of contraception, 1 of which must be a barrier method, for the duration of the study and until 6 months after study drug administration. Medically acceptable barrier methods include condom with spermicide or diaphragm with spermicide. Medically acceptable non-barrier contraceptive methods include intrauterine devices or hormonal contraceptives (oral, implant, injection, ring, or patch).

Exclusion Criteria

Patients who meet any of the following criteria will be excluded from participation in the study:

1. Presence of frank leptomeningeal disease as a unique central nervous system feature or in association with brain parenchymal measurable lesion(s);
2. Symptomatic brain metastases;

   Note: Patients with asymptomatic treated and untreated brain metastases are eligible.
3. Previous local therapy for brain metastases, such as neurosurgery, stereotactic radiotherapy, or whole brain radiotherapy, administered within 6 weeks prior to administration of CAM-H2;

   Note: Previous therapy for brain metastases administered at least 6 weeks prior to CAM-H2 administration will be allowed.
4. For patients with brain metastases, any increase in corticosteroid dose during the 4 weeks prior to the first administration of CAM-H2;

   Note: Corticosteroid treatment in a stable dose or decreasing dose for at least 4 weeks prior to the first administration of CAM-H2 is allowed.
5. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection requiring parenteral antibiotics or psychiatric illness/social situations that would limit compliance with study requirements;
6. Uncontrolled thyroid disease, defined as free triiodothyronine (T3) and free thyroxine (T4) >3 × ULN at screening;
7. Uncontrolled diabetes defined as a fasting serum glucose >2 × ULN or glycated hemoglobin levels >8.5% at screening;

8. Gastrointestinal (GI) tract disease resulting in an inability to take oral medication, malabsorption syndrome, a requirement for intravenous (IV) alimentation, prior surgical procedures affecting absorption, or uncontrolled inflammatory GI disease (eg, Crohn's, ulcerative colitis);
9. Current active hepatic or biliary disease (exception of patients with Gilbert's syndrome, asymptomatic gallstones, liver metastases, or stable chronic liver disease per Investigator assessment);
10. Ongoing peripheral neuropathy of Grade >2 according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0;
11. Severe and/or uncontrolled medical conditions or other conditions that could affect participation in the study such as:
    - Symptomatic congestive heart failure of New York Heart Association Class III or IV;
    - Unstable angina pectoris, symptomatic congestive heart failure, myocardial infarction within 6 months of start of study drug, serious uncontrolled cardiac arrhythmia, or any other clinically significant cardiac disease; or
    - Liver disease, including cirrhosis and severe hepatic impairment;
12. Active (acute or chronic) or uncontrolled severe infections;
13. Known history of HIV, hepatitis B, or active hepatitis C virus at screening;
14. Prior investigational anticancer therapy within 4 weeks prior to the first administration of CAM-H2;
15. Patients who have had a major surgery or significant traumatic injury within 4 weeks prior to the first administration of CAM-H2, who have not recovered from side effects of any major surgery (defined as requiring general anesthesia), or have a major surgery planned during the course of the study;
16. Other malignancies within the past 3 years except for adequately treated carcinoma of the cervix or basal or squamous cell carcinomas of the skin or stage I uterine cancer;
17. Radiation therapy for metastatic disease foci outside the brain, administered within 3 weeks prior to the first administration of CAM-H2;
18. Known hypersensitivity to any of the study drugs (including inactive ingredients) including iodine allergy;
19. History of significant comorbidities that, in the Investigator's judgement, may interfere with study conduct, response assessment, or informed consent;
20. Unable or unwilling to complete the study procedures;
21. Patients that cannot be hospitalized in a radionuclide therapy room;
22. Patients with urinary incontinence;
23. Patients that are unable to comply with thyroid protective pre-medication;
24. Patients in whom bladder catheterization cannot be performed, or in patients who are unwilling to be catheterized if necessary;

25. Patients with contraindications for undergoing magnetic resonance imaging (MRI) or computed tomography (CT), including for receiving contrast agents; or
26. Patient is the Investigator or sub-Investigator, research assistant, pharmacist, study coordinator, or other staff or relative thereof, who is directly involved in the conduct of the study.

STUDY DESIGN AND DURATION:

This is a Phase 1/2 multi-center, open-label, dose escalation and dose expansion study to evaluate safety, tolerability, dosimetry, PD, and efficacy of the targeted radionuclide therapeutic CAM-H2 in patients with progressive, advanced/metastatic HER2-positive breast, gastric, and GEJ cancer with disease progression following anti-HER2 standard of care treatment.

The study will be comprised of the following:

- Dose escalation phase (up to 4 treatment cycles)
  - Screening: Week -4 to Week -1
  - Treatment period: Visit 3 (Week 0) up to Visit 38 (Week 11 of Cycle 4)
    - Cycle 1
      - Dose 1 and Safety Follow-Up Period: Week 0 to Week 3
      - Dose 2 and Safety Follow-Up Period: Week 4 to Week 11 (End of Treatment [EOT] Visit or Cycle 2 eligibility assessment)
    - Cycle 2 (to begin 2 weeks after the Cycle 2 eligibility assessment for patients with CB during Cycle 1, as long as the cumulative kidney dose remains <23 Gy [based on the dosimetry results during Cycle 1])
      - Dose 1 and Safety Follow-Up Period: Week 0 to Week 3
      - Dose 2 and Safety Follow-Up Period: Visit 16 (Week 4) to Visit 20 (Week 11) (EOT Visit or Cycle 3 eligibility assessment)
    - Cycle 3 (to begin 2 weeks after the Cycle 3 eligibility assessment for patients with CB during Cycles 1 and 2, as long as the cumulative kidney dose remains <23 Gy [based on the dosimetry results during Cycle 1])
      - Dose 1 and Safety Follow-Up Period: Week 0 to Week 3
      - Dose 2 and Safety Follow-Up Period: Week 4 to Week 11 (EOT Visit or Cycle 4 eligibility assessment)
    - Cycle 4 (to begin 2 weeks after the Cycle 4 eligibility assessment for patients with CB during Cycles 1, 2, and 3, as long as the cumulative kidney dose remains <23 Gy [based on the dosimetry results during Cycle 1])
      - Dose 1 and Safety Follow-Up Period: Week 0 to Week 3
      - Dose 2 and Safety Follow-Up Period: Week 4 to Week 11 (EOT Visit)
  - Long-term follow-up period

- Dose expansion phase (up to 2 treatment cycles)
  - Screening: Week -4 to Week -1
  - Treatment period: Visit 3 (Week 0) up to Visit 20 (Week 11 of Cycle 2)
    - Cycle 1
      - Dose 1 and Safety Follow-Up Period: Week 0 to Week 3
      - Dose 2 and Safety Follow-Up Period: Week 4 to Week 11 (EOT Visit or Cycle 2 eligibility assessment)
    - Cycle 2 (to begin 2 weeks after the Cycle 2 eligibility assessment for patients with CB during Cycle 1, as long as the cumulative kidney dose remains <23 Gy [based on the dosimetry results during Cycle 1 of dose escalation])
      - Dose 1 and Safety Follow-Up Period: Week 0 to Week 3
      - Dose 2 and Safety Follow-Up Period: Week 4 to Week 11 (EOT Visit)
  - Long-term follow-up period

One treatment cycle is defined as the timeframe of approximately 12 weeks (84 days) that includes 2 administrations of the study drug given 4 weeks apart (including the 4-week Safety Follow-Up Period after Dose 1 and the Safety Follow-Up Period after Dose 2, up to Visit 11).

However, if a patient misses a dose of study drug due to study drug production problems or due to other circumstances (in certain cases), the interval between doses may be extended up to 6 weeks (Cycles 1 and 2 of both dose escalation and dose expansion phases) or up to 12 weeks (Cycles 3 and 4 of the dose escalation phase) (see **Missed Doses**).

Dose Escalation Phase

Screening

Patients will be screened for study eligibility over 2 different study visits (Visit 1 and Visit 2) in the 29 days prior to dosing (ie, Day -28 to Day 0 of Cycle 1). Visit 2 should occur preferably within the 14 days prior to study drug administration (Visit 3). All patients will undergo pre-treatment imaging for eligibility and baseline at Visit 1 with a diagnostic CT scan for RECIST version 1.1. Patients with known brain metastases will undergo a brain MRI scan, in addition to the diagnostic CT, for RANO-BM.

After screening, approximately 15 patients who meet inclusion and exclusion criteria will be enrolled into 1 of 4 cohorts, including a minimum of 3 patients each.

The screening period may be extended up to an additional 2 weeks upon Sponsor approval in certain exceptional cases (eg, to allow for a repeat blood draw or to assess previously unavailable imaging results) following a discussion between the Principal Investigator, Medical Monitor, and Sponsor.

CAM-H2 administration

In the dose escalation phase, all patients will receive at least 1 cycle of CAM-H2. Patients with CB may receive up to 4 cycles of CAM-H2, as long as the cumulative kidney dose remains <23 Gy (based on the dosimetry results during Cycle 1). Cycles will be given as 2 IV administrations,

4 weeks apart. However, if a patient misses a dose of study drug due to study drug production problems or due to other circumstances (in certain cases), the interval between doses may be extended up to 6 weeks (Cycles 1 and 2) or up to 12 weeks (Cycles 3 and 4) (see **Missed Doses**).

Patients will be admitted to a radioactive unit for hospitalization during each IV administration for a total of 48 hours. This hospitalization can be shortened if ^{131}Iodine (^{131}I) decay and the patient's clearance allow discharge according to the applicable local regulations on radioactive compound exposure. Ancillary treatments to be given with CAM-H2 include thyroid-blocking drugs, premedication therapy (anti-emetic, anti-histamine, and anti-pyretic therapy), saline infusion, and amino acid infusion.

Cycle 1 will consist of the following:

- Dose 1 of CAM-H2: Visit 3 (Week 0);
- Safety Follow-Up Period: Visit 4 (Week 1), Visit 5 (Week 2), and Visit 6 (Week 3);
- Dose 2 of CAM-H2: Visit 7 (Week 4); and
- Safety Follow-Up Period: Visit 8 (Week 5), Visit 9 (Week 6), Visit 10 (Week 8), and Visit 11 (Week 11) (EOT Visit or Cycle 2 eligibility assessment).

If the patient has CB, and the cumulative kidney dose remains <23 Gy (based on the dosimetry results during Cycle 1), a second cycle may be initiated within 2 weeks after Visit 11 (Week 11) of Cycle 1, once the necessary Visit 11 (Week 11) safety follow-up assessments have been completed and reviewed. If the patient does not have CB, no further treatment will be administered and the patient will enter the long-term follow-up period.

If the patient has CB, Cycle 2 will then be initiated as follows:

- Dose 1 of CAM-H2: Visit 12 (Week 0);
- Safety Follow-Up Period: Visit 13 (Week 1), Visit 14 (Week 2), and Visit 15 (Week 3);
- Dose 2 of CAM-H2: Visit 16 (Week 4); and
- Safety Follow-Up Period: Visit 17 (Week 5), Visit 18 (Week 6), Visit 19 (Week 8), and Visit 20 (Week 11) (EOT Visit or Cycle 3 eligibility assessment).

If the patient has CB, and the cumulative kidney dose remains <23 Gy (based on the dosimetry results during Cycle 1), a third cycle may be initiated within 2 weeks after Visit 20 (Week 11) of Cycle 2, once the necessary Visit 20 (Week 11) safety follow-up assessments have been completed and reviewed. If the patient does not have CB, no further treatment will be administered and the patient will enter the long-term follow-up period.

If the patient has CB, Cycle 3 will then be initiated as follows:

- Dose 1 of CAM-H2: Visit 21 (Week 0);
- Safety Follow-Up Period: Visit 22 (Week 1), Visit 23 (Week 2), and Visit 24 (Week 3);
- Dose 2 of CAM-H2: Visit 25 (Week 4); and
- Safety Follow-Up Period: Visit 26 (Week 5), Visit 27 (Week 6), Visit 28 (Week 8), and Visit 29 (Week 11) (EOT Visit or Cycle 4 eligibility assessment).

If the patient has CB, and the cumulative kidney dose remains <23 Gy (based on the dosimetry results during Cycle 1), a fourth cycle may be initiated within 2 weeks after Visit 29 (Week 11) of Cycle 3, once the necessary Visit 29 (Week 11) safety follow-up assessments have been completed and reviewed. If the patient does not have CB, no further treatment will be administered and the patient will enter the long-term follow-up period.

If the patient has CB, Cycle 4 will then be initiated as follows:

- Dose 1 of CAM-H2: Visit 30 (Week 0);
- Safety Follow-Up Period: Visit 31 (Week 1), Visit 32 (Week 2), and Visit 33 (Week 3);
- Dose 2 of CAM-H2: Visit 34 (Week 4); and
- Safety Follow-Up Period: Visit 35 (Week 5), Visit 36 (Week 6), Visit 37 (Week 8), and Visit 38 (Week 11) (EOT Visit).

The dose escalation phase of the study will be an open-label 3 + 3 design, where at least 3 patients are treated at each dose level. Dose escalation will be done via increases of the nominal activity of CAM-H2 in cohorts of 3 to 6 patients. The dose escalation schedule is demonstrated in Table S1.

Table S1. Dose Escalation Schedule for Each CAM-H2 Cycle

Dose Level	Activity of CAM-H2 (GBq) [1]	Activity of CAM-H2 (mCi) [1]
Level 1 (starting activity)	2 × 1.85	2 × 50
Level 2	2 × 3.7	2 × 100
Level 3	2 × 5.55	2 × 150
Level 4 [2]	2 × 7.4	2 × 200
1. Doses will be given 4 weeks apart. All patients will receive at least 1 cycle of CAM-H2. 2. Level 4 dosing will be optional, depending on overall safety, tolerability, and dosimetry.		

Staggered dosing will be applied for all cohorts during dose escalation. The first dose of the first patient of each cohort will be administered at least 2 weeks before the first dose of the next 2 patients (sentinel dosing). Once the MTD or RDP2 has been established, 3 additional patients will be enrolled to receive the MTD or RDP2. The patients treated at the MTD or RDP2 in the dose escalation phase will be included in the readout for efficacy. The dose escalation will be done via increases of the nominal activity of CAM-H2 in cohorts of 3 to 6 patients until approximately 15 (or a maximum of 18) patients have been dosed. The actual dose levels administered to the patient can have a tolerance window of ±10% of the prescribed nominal activity.

Dose escalation will be decided based on a review of all the available safety data obtained after completion of Cycle 1 (ie, after 2 IV administrations) of each dose level. If a patient is not able to complete a full cycle due to adverse events (AEs) related to study drug administration, he/she will not be replaced, and the dose escalation rules will be followed.

In the instance that a patient is not able to complete a full cycle due to AEs not related to study drug administration or due to a negative PD distribution scan, he/she will be replaced to ensure safety data spanning a full treatment cycle can be considered for dose escalation.

Imaging

All imaging will be sent to the central imaging core laboratory for independent review as soon as possible within 48 hours of acquisition. Further instructions will be provided by the imaging core laboratory in separate guidelines.

Patients will undergo 4 types of imaging during the dose escalation phase: planar whole body (WB) scans, single photon emission computed tomography (SPECT)/CT scans, diagnostic CT scans, and brain MRI scans, as shown in Table S2. Imaging to evaluate the organ/target lesion uptake will be performed after each CAM-H2 administration during the dose escalation phase of the study for all patients at all dose levels. Dosimetry in tumor lesions, calculated based on consecutive SPECT/CT and planar WB scans, will be performed during Cycle 1. To evaluate disease progression, diagnostic CT scans will be performed in all patients, and brain MRI will only be performed in patients with known brain metastases. Patients with extracranial lesions will be evaluated for progression using RECIST version 1.1. Patients with brain metastases without extracranial lesions will be evaluated for progression using RANO-BM. Patients with extracranial lesions and brain metastases will be evaluated for progression using both RECIST version 1.1 (extracranial lesions) and RANO-BM (brain metastases). Additional details are provided in the Imaging Review Charter.

Table S2. Imaging During the Dose Escalation Phase

Type of Imaging	Cycle 1	Cycles 2, 3, and 4
Planar WB scans for PD distribution [1], evaluation of organ/target lesion uptake, and/or dosimetry	After each dose (Dose 1 and Dose 2): • 5 hours (±1 hour) after CAM-H2 [2]; • 24 hours (±4 hours) after CAM-H2; • 48 hours (±4 hours) after CAM-H2; and • 168 hours (±24 hours) after CAM-H2.	After each dose (Dose 1 and Dose 2): • 24 hours (±4 hours) after CAM-H2 [2].
SPECT/CT scans to evaluate organ/target lesion uptake and/or dosimetry	After each dose (Dose 1 and Dose 2): • 5 hours (±1 hour) after CAM-H2; • 24 hours (±4 hours) after CAM-H2; • 48 hours (±4 hours) after CAM-H2; and • 168 hours (±24 hours) after CAM-H2.	NA
Diagnostic CT scans to evaluate disease status	At screening and after Dose 2 only [3]: • 4 weeks after CAM-H2 at Visit 10 (Week 8); and • Every 8 weeks after Visit 10 (Week 8), as long as the patient had clinical benefit after Cycle 1 [4] and there is no disease progression.	After Dose 2 only [3]: • 4 weeks after CAM-H2 at Week 8; and • Every 8 weeks after Week 8, as long as the patient had clinical benefit after the current cycle [4] and there is no disease progression.

Table continued on the next page.

Table S2. Imaging During the Dose Escalation Phase (Continued)

Type of Imaging	Cycle 1	Cycles 2, 3, and 4
Brain MRI scans to evaluate disease status [5]	At screening and after Dose 2 only [3]: • 4 weeks after CAM-H2 at Visit 10 (Week 8); and • Every 8 weeks after Visit 10 (Week 8), as long as the patient had clinical benefit after Cycle 1 [4] and there is no disease progression.	After Dose 2 only [3]: • 4 weeks after CAM-H2 at Week 8; and • Every 8 weeks after Week 8, as long as the patient had clinical benefit after the current cycle [4] and there is no disease progression.

1. Patients with a negative PD distribution scan will not be treated further, although they will be included in the SAF. An extra patient will then be included in the same cohort as substitute.
2. During Dose 1 of the cycle, the first planar WB scan will also serve as the PD distribution scan.
3. Imaging to evaluate disease status after treatment will start 4 weeks after the last CAM-H2 infusion (Dose 2) of the cycle at Week 8. If a patient cannot receive Dose 2 of a given cycle, his/her imaging to evaluate disease status will start at the theoretical timing for Dose 2 (ie, 4 weeks after Dose 1 of the cycle).
4. Patients without clinical benefit after the current cycle will have another diagnostic CT scan and brain MRI (if indicated) at Week 11, which will be EOT.
5. Brain MRI will only be performed in patients with known brain metastases.

CT = computed tomography; EOT = End of Treatment; MRI = magnetic resonance imaging; NA = not applicable; PD = pharmacodynamic(s); SAF = Safety Analysis Set; SPECT = single photon emission computed tomography; WB = whole body.

Dose Expansion Phase

Screening

Following the completion of the dose escalation phase and determination of the MTD or RDP2, the study will be expanded so that a total of at least 52 patients will be exposed to the dose chosen to be taken forward. Of the included patients with advanced/metastatic breast cancer, at least 10 to 12 patients should have measurable brain metastases. The number of patients with gastric or GEJ cancer and brain metastases is not pre-set.

Patients will be screened for study eligibility over 2 different study visits (Visit 1 and Visit 2) in the 29 days prior to dosing (ie, Day -28 to Day 0 of Cycle 1). Visit 2 should occur preferably within the 14 days prior to study drug administration (Visit 3). All patients will undergo pre-treatment imaging for eligibility and baseline at Visit 1 with a diagnostic CT scan for RECIST version 1.1. Patients with known brain metastases will undergo a brain MRI scan, in addition to the diagnostic CT, for RANO-BM.

As in the dose escalation phase, the screening period may be extended up to an additional 2 weeks upon Sponsor approval in certain exceptional cases (eg, to allow for a repeat blood draw or to assess previously unavailable imaging results) following a discussion between the Principal Investigator, Medical Monitor, and Sponsor.

CAM-H2 administration

In the dose expansion phase of the study, the patients will be given the RDP2 determined in the dose escalation phase. Similar to the dose escalation phase, all patients will receive at least 1 cycle of CAM-H2. Patients with CB may receive up to 2 cycles of CAM-H2, as long as the cumulative kidney dose remains <23 Gy (based on the dosimetry results during Cycle 1 of dose escalation), each cycle given as 2 IV administrations, 4 weeks apart. However, if a patient misses a dose of study drug due to study drug production problems or due to other circumstances (in certain cases), the interval between doses may be extended up to 6 weeks (see **Missed Doses**).

Patients will be admitted to a radioactive unit for hospitalization during each IV administration for a total of 48 hours. This hospitalization can be shortened if ^{131}I decay and the patient's clearance allow discharge according to the applicable local regulations on radioactive compound exposure. Ancillary treatments to be given with CAM-H2 include thyroid-blocking drugs, premedication therapy (anti-emetic, anti-histamine, and anti-pyretic therapy), saline infusion, and amino acid infusion.

Cycle 1 will consist of the following:

- Dose 1 of CAM-H2: Visit 3 (Week 0);
- Safety Follow-Up Period: Visit 4 (Week 1), Visit 5 (Week 2), and Visit 6 (Week 3);
- Dose 2 of CAM-H2: Visit 7 (Week 4); and
- Safety Follow-Up Period: Visit 8 (Week 5), Visit 9 (Week 6), Visit 10 (Week 8), and Visit 11 (Week 11) (EOT Visit or Cycle 2 eligibility assessment).

If the patient has CB, an additional cycle may be initiated within 2 weeks after the EOT Visit of Cycle 1, once the necessary Visit 11 (Week 11) safety follow-up assessments have been completed and reviewed. If the patient does not have CB, no further treatment will be administered and the patient will enter the long-term follow-up period.

If the patient has CB, Cycle 2 will then be initiated as follows:

- Dose 1 of CAM-H2: Visit 12 (Week 0);
- Safety Follow-Up Period: Visit 13 (Week 1), Visit 14 (Week 2), and Visit 15 (Week 3);
- Dose 2 of CAM-H2: Visit 16 (Week 4); and
- Safety Follow-Up Period: Visit 17 (Week 5), Visit 18 (Week 6), Visit 19 (Week 8), and Visit 20 (Week 11) (EOT Visit).

Imaging

As in the dose escalation phase, all imaging will be sent to the central imaging core laboratory for independent review as soon as possible within 48 hours of acquisition. Further instructions will be provided by the imaging core laboratory in separate guidelines.

Patients in the dose expansion phase will undergo planar WB scans, SPECT/CT scans, diagnostic CT scans, and brain MRIs, as shown in Table S3. As in the dose escalation phase, imaging to evaluate the organ/target lesion uptake will be performed after each CAM-H2 administration; however, it will be performed less frequently. Imaging to evaluate disease progression will be performed as done in the dose escalation phase.

Table S3. Imaging During the Dose Expansion Phase

Type of Imaging	Cycle 1	Cycle 2
Planar WB scans for PD distribution and evaluation of organ/target lesion uptake	After each dose (Dose 1 and Dose 2): • 24 hours (±4 hours) after CAM-H2 [1].	After each dose (Dose 1 and Dose 2): • 24 hours (±4 hours) after CAM-H2 [1].
SPECT/CT scans to evaluate organ/target lesion uptake	After each dose (Dose 1 and Dose 2): • 24 hours (±4 hours) after CAM-H2.	NA
Diagnostic CT scans to evaluate disease status	At screening and after Dose 2 only [2]: • 4 weeks after CAM-H2 at Visit 10 (Week 8); and • Every 8 weeks after Visit 10 (Week 8), as long as the patient had clinical benefit after Cycle 1 [3] and there is no disease progression.	After Dose 2 only [2]: • 4 weeks after CAM-H2 at Visit 19 (Week 8); • At Visit 20 (Week 11/EOT); and • Every 8 weeks after Visit 20 (Week 11), as long as there is no disease progression.
Brain MRI scans to evaluate disease status [4]	At screening and after Dose 2 only [2]: • 4 weeks after CAM-H2 at Visit 10 (Week 8); and • Every 8 weeks after Visit 10 (Week 8), as long as the patient had clinical benefit after Cycle 1 [3] and there is no disease progression.	After Dose 2 only [2]: • 4 weeks after CAM-H2 at Visit 19 (Week 8); • At Visit 20 (Week 11/EOT); and • Every 8 weeks after Visit 20 (Week 1), as long as there is no disease progression.

1. During Dose 1 of the cycle, the first planar WB scan will also serve as the PD distribution scan.
2. Imaging to evaluate disease status after treatment will start 4 weeks after the last CAM-H2 infusion (Dose 2) of the cycle at Week 8. If a patient cannot receive Dose 2 of a given cycle, his/her imaging to evaluate disease status will start at the theoretical timing for Dose 2 (ie, 4 weeks after Dose 1 of the cycle).
3. Patients without clinical benefit after Cycle 1 will have another diagnostic CT scan and brain MRI (if indicated) at Visit 11 (Week 11), which will be EOT.
4. Brain MRI will only be performed in patients with known brain metastases.

CT = computed tomography; EOT = End of Treatment; MRI = magnetic resonance imaging; NA = not applicable; PD = pharmacodynamic(s); SPECT = single photon emission computed tomography; WB = whole body.

Long-Term Follow-Up Period

A long-term follow-up period will start after the EOT/Early Termination (ET) Visit. Follow-up will continue for a maximum of 12 months. All patients without disease progression will be monitored every 8 weeks to evaluate PFS for a maximum of 12 months or until disease progression, death, or consent is withdrawn, whichever occurs first.

The bi-monthly visits will consist of imaging to evaluate disease status, performance status evaluation using ECOG PS, and assessment for any post-investigational treatment. Other changes in medical history or concomitant medications and AEs will be assessed. Imaging to evaluate disease status will begin 8 weeks after the last diagnostic CT scan or brain MRI performed during the study treatment period. Diagnostic CT scan will be performed in all patients. Brain MRI will only be performed in patients with known brain metastases. Patients with extracranial lesions will be evaluated for progression using RECIST version 1.1. Patients with brain metastases without extracranial lesions will be evaluated for progression using RANO-BM. Patients with extracranial lesions and brain metastases will be evaluated for progression using both RECIST version 1.1 (extracranial lesions) and RANO-BM (brain metastases). Additional details are provided in the

Imaging Review Charter. As long as there is no disease progression, imaging to evaluate disease status will be performed every 8 weeks.

For patients with disease progression or starting alternative anticancer therapy, imaging to evaluate disease status will be performed according to the local site standard of care. Review of images at this point will be done locally and not by the central imaging core laboratory. Additionally, those patients will no longer be followed every 8 weeks, but every 12 weeks, to assess survival, disease status, and post-progression therapy. Follow-up contacts (by clinic visits or telephone call) will be performed every 12 weeks until death, lost to follow-up, study end (12 months post-last patient EOT/ET Visit), or study termination by the Sponsor, whichever occurs first.

DOSE ESCALATION RULES AND DOSE STAGGERING APPROACH:

Dose staggering will be applied for all cohorts during dose escalation. The first dose of the first patient will be administered at least 2 weeks before the first dose of the remainder of the cohort. After the review of AEs, dosimetry reports, vital signs, and electrocardiograms (ECGs) collected over 2 weeks, the remaining 2 patients of the cohort may receive the same dose level. Following completion of the initial safety assessments for the sentinel patient, the decision to proceed with the remaining patients in that cohort will be discussed and mutually agreed upon between the Investigator (or his/her designee) and the Sponsor. The decision of whether to escalate to the next dose will be formally confirmed by the Sponsor.

The proposed minimum 2 weeks between the sentinel patient and the remainder of the cohort is deemed sufficient as each dose of the cycle is a single IV administration, and it is expected that the most severe and acute reactions will occur during or soon after the infusion. Based on animal studies, potential side effects are expected to be related to high activity levels in the kidneys, that will decline rapidly after ending the IV infusion.

At each dose level, after completion of 1 cycle (2 doses) of CAM-H2 administration in at least 3 patients, each Investigator will provide a comprehensive Investigator Safety Report for his/her patients including (but not limited to) the following content:

- Relevant information on patients' demographics, characteristics, medical history, physical examination, and concomitant medications;
- List of all AEs, including severity, time of onset related to study drug administration, and duration, clearly highlighting serious adverse events (SAEs) and relatedness and causality of all AEs;
- Any clinically significant out of range clinical laboratory test results (as assessed by the Investigator);
- Neurological examination results including clinical significance for abnormal findings;
- ECG and vital sign results including clinically significant abnormal values; and
- Statement of the Principal Investigator's recommendation regarding dose decision.

Escalation to the next higher dose will only take place after review of the Investigator Safety Reports from the previous dose levels by the respective Investigators, in consultation with the Sponsor's representative (called hereafter the Safety Review Committee [SRC]). Dose escalation

will be based on dosimetry and emerging safety and tolerability data as defined by AEs, laboratory results, ECGs, and vital signs. Other parameters of interest will be considered ad hoc.

Definition of Dose-Limiting Toxicities

DLTs are defined as toxicities occurring **only** within Cycle 1 (ie, the approximately 12-week [84-day] period that includes 2 administrations of the study drug given 4 weeks apart [including the 4-week Safety Follow-Up Period after Dose 1]). DLTs include ≥1 of the following:

- Study drug-related SAE in at least 1 patient in 1 cohort;
- Severe study drug-related AE in at least 2 patients in 1 cohort;
- Any death not clearly due to the underlying disease or extraneous causes;
- Development of severe renal failure (eGFR <30 mL/min) or a drop of >40 mL/minute in eGFR;
- Any seizure activity that is considered to be study drug-related;
- Grade 3+ thrombocytopenia with bleeding;
- Recurrent (defined in this study as occurring after >1 dose of CAM-H2 during Cycle 1) Grade 3 or 4 thrombocytopenia;
- Grade 4+ neutropenia or thrombocytopenia >7 days;
- Recurrent (defined in this study as occurring after >1 dose of CAM-H2 during Cycle 1) Grade 3 or 4 anemia and/or neutropenia;
- Recurrent (defined in this study as occurring after >1 dose of CAM-H2 during Cycle 1) Grade 3 or 4 non-hematological toxicities as listed in the CTCAE version 5.0;
- An ALT or AST >3 × ULN accompanied by a total bilirubin of >2 × ULN (Hy's Law);
- Grade 3 or 4 fatigue for >1 week;
- Grade 3 or 4 electrolyte abnormalities that last >72 hours or any Grade 3 or 4 electrolyte abnormalities associated with clinical signs and symptoms of any duration;
- For patients with hepatic metastases, AST or ALT >8 × ULN or AST or ALT >5 × ULN for ≥14 days;
- An absorbed dose to the kidneys >23 Gy;
- An absorbed dose to the bone marrow >2 Gy; or
- Other clinically significant changes in vital signs, clinical laboratory tests, ECGs, or other safety parameters deemed as a significant safety concern by the Investigator.

All AEs of the specified grades will count as DLTs, except those that are clearly and incontrovertibly due to disease progression or extraneous causes.

Dose Escalation Rules

DLTs will determine the progression/escalation with the following rules:

- If 0 out of 3 patients experience a DLT, all patients will proceed to the next higher dose level;
- If 1 out of 3 patients experiences a DLT, the same dose will be given to 3 new patients:
  - If 0 of the 3 new patients experience a DLT, all patients will proceed to the next higher dose level; and/or
  - If 1 or more of the 3 new patients experiences a DLT (≥2 of the 6 patients) this dose will become the MTD + 1.
- If ≥2 out of 3 patients experience a DLT, the MTD has been exceeded and a lower dose should be tested between this dose and the previous dose level;
- Once the MTD + 1 has been established, 3 additional patients will be exposed to the dose below the MTD + 1; and
- If the MTD + 1 is not reached, 3 additional patients will be exposed to the highest dose.

Within the planned dose range, a dose lower than the next planned dose may also be tested, depending on emerging safety, tolerability, and/or other relevant data, such as dosimetry or PD. If the highest planned dose level is found to be safe and tolerable, also considering the PD data, additional higher doses may be added by amendment.

A period of at least 4 weeks will be maintained between 2 consecutive cohorts.

STOPPING RULES, DOSE MODIFICATIONS, AND MISSED DOSES:

Stopping Rules

During the dose escalation phase, the SRC will meet to decide on the continuation of dosing after the completion of 1 full treatment cycle in at least 3 patients at each dose level. During the dose expansion phase, the SRC will formally meet after the completion of 1 full treatment cycle in every 9 patients to review all emerging safety and tolerability data. All data must be available to the SRC ≤3 weeks after the last dose in the cohort. Additional details are described in the SRC Charter.

Safety and tolerability data; however, will be reviewed on an ongoing basis by the Medical Monitor, and stopping rules will be applicable starting with dosing of the first sentinel patient. SRC decisions will be based on the following:

- If a study drug-related SAE occurs in 1 patient or if a study drug-related severe AE occurs in 2 patients in the same cohort, the dosing in the study should be temporarily stopped in order to review additional safety data. If after review of the additional data, the study drug-relatedness assessment changes, the study can resume without substantial amendment;
- If 2 patients in a cohort experience a DLT that is related to CAM-H2 administration, dosing will be stopped until resolution of the DLT. Doses can be adapted as per the modification schemes in **Dose Modifications**;

- If at least 1 DLT is reported, the SRC recommendation will depend on the DLT profile (ie, identical DLTs in different patients), the frequency and severity of DLTs in the same patient, and the recommendation made by the Investigator; and
- If no DLT is reported, the planned dose escalation may proceed with the next cohort or phase, unless the Investigator has any other safety concerns.

All decisions will be documented in writing and communicated to the study team in a timely manner before dosing in the next cohort can start.

Dose Modifications

The following dose modifications will be implemented in case of toxicities:

- Grade 2, 3, or 4 thrombocytopenia:
  - Withhold dosing until resolution to Grade 0 or 1;
  - Resume CAM-H2 at 50% with complete or partial resolution;
    - If a reduced dose does not result in Grade 2, 3, or 4 thrombocytopenia, administer CAM-H2 at the full planned dose for next cycle.
  - Permanently discontinue CAM-H2 for Grade 2 or higher thrombocytopenia requiring a treatment delay of 12 weeks or longer; and
  - Permanently discontinue CAM-H2 for recurrent (defined in this study as occurring after >1 dose of CAM-H2 during Cycle 1) Grade 2, 3, or 4 thrombocytopenia.
- Grade 3 or 4 anemia and neutropenia:
  - Withhold dosing until resolution to Grade 0, 1, or 2;
  - Resume CAM-H2 at 50% in patients with complete or partial resolution;
    - If a reduced dose does not result in Grade 3 or 4 anemia or neutropenia, administer CAM-H2 at full planned dose for next cycle.
  - Permanently discontinue CAM-H2 for Grade 3 or higher anemia or neutropenia requiring a treatment delay of 12 weeks or longer; and
  - Permanently discontinue CAM-H2 for recurrent (defined in this study as occurring after >1 dose of CAM-H2 during Cycle 1) Grade 3 or 4 anemia or neutropenia.
- Renal toxicity (defined as an eGFR <40 mL/minute or a 40% decrease in baseline eGFR):
  - Withhold dosing until resolution to at least 80% of baseline eGFR;
  - Resume CAM-H2 at 50% in patients with complete or partial resolution;
    - If a reduced dose does not result in another decrease of eGFR, administer CAM-H2 at the full, planned dose for next cycle.
  - Permanently discontinue CAM-H2 for eGFR decreases requiring a treatment delay of 12 weeks or longer; and
  - Permanently discontinue CAM-H2 for recurrent (defined in this study as occurring after >1 dose of CAM-H2 during Cycle 1) toxicity.

- Hepatic toxicity (Hy's Law cases):
  - Withhold dosing until resolution to ALT and AST values <2 × baseline and total bilirubin values of <1.5 × ULN;
  - Resume CAM-H2 at 50% in patients with complete or partial resolution;
    - If a reduced dose does not result in another transaminase or total bilirubin increase, administer CAM-H2 at full planned dose for next cycle.
  - Permanently discontinue CAM-H2 for transaminase or total bilirubin decreases requiring a treatment delay of 12 weeks or longer; and
  - Permanently discontinue CAM-H2 for recurrent (defined in this study as occurring after >1 dose of CAM-H2 during Cycle 1) toxicity.
- Hepatic toxicity (patients with hepatic metastases and AST or ALT >8 × ULN or AST or ALT >5 × ULN for ≥14 days):
  - Withhold dosing until resolution to ALT and AST values of <1.2 × baseline and total bilirubin values of <1.5 × ULN;
  - Resume CAM-H2 at 50% in patients with complete or partial resolution;
    - If a reduced dose does not result in another transaminase or total bilirubin increase, administer CAM-H2 at full planned dose for next cycle.
  - Permanently discontinue CAM-H2 for transaminase or total bilirubin decreases requiring a treatment delay of 12 weeks or longer; and
  - Permanently discontinue for recurrent (defined in this study as occurring after >1 dose of CAM-H2 during Cycle 1) toxicity.
- Grade 3 or 4 non-hematological toxicities as listed in the CTCAE version 5.0:
  - Withhold dosing until resolution to Grade 0, 1, or 2;
  - Resume CAM-H2 at 50% in patients with complete or partial resolution;
    - If a reduced dose does not result in Grade 3 or 4 toxicity, administer CAM-H2 at full planned dose for next cycle.
  - Permanently discontinue CAM-H2 for Grade 3 or higher toxicity requiring a treatment delay of 12 weeks or longer; and
  - Permanently discontinue for recurrent (defined in this study as occurring after >1 dose of CAM-H2 during Cycle 1) Grade 3 or 4 toxicities.

Missed Doses

Cycles 1 and 2

During Cycles 1 and 2 (for both the dose escalation and dose expansion phases), if a patient misses Dose 1 of study drug due to study drug production problems (eg, insufficient activity yield, ^{131}I supply problem), the interval between screening and first dosing (Cycle 1) and/or the interval between the cycle eligibility assessment and first dosing (Cycle 2) may be extended up to an additional 2 weeks to allow for the production of a new batch of study drug. If the patient was

eligible per protocol, no screening procedures will be repeated unless deemed necessary following a discussion between the Principal Investigator, Medical Monitor, and Sponsor.

Similarly, if a patient misses Dose 2 of the study drug during Cycles 1 or 2 due to study drug production problems, the interval between Dose 1 and Dose 2 may be extended up to an additional 2 weeks (ie, Dose 2 may occur up to 6 weeks after Dose 1). Safety Follow-Up visits after Dose 2 will be scheduled based on the actual Dose 2 visit date.

Cycles 3 and 4

During Cycles 3 and 4 (for the dose escalation phase), if a patient misses Dose 1 of study drug due to study drug production problems (eg, insufficient activity yield, ^{131}I supply problem), the interval between the cycle eligibility assessment and first dosing may be extended up to an additional 8 weeks to allow for the production of a new batch of study drug.

Similarly, if a patient misses Dose 2 of the study drug during Cycles 3 or 4 due to study drug production problems, the interval between Dose 1 and Dose 2 may be extended up to an additional 8 weeks (ie, Dose 2 may occur up to 12 weeks after Dose 1). Safety Follow-Up visits after Dose 2 will be scheduled based on the actual Dose 2 visit date.

All Cycles

In cases of a missed dose of study drug due to other circumstances unrelated to study drug or procedures (eg, secondary to scheduling conflict, missed appointment), the Investigator should contact the Sponsor or designee to discuss available options in order to make a decision in the patient's best interest. The decision will be documented for the study and site files.

DOSAGE FORMS AND ROUTE OF ADMINISTRATION:

CAM-H2 will be provided as a clear, sterile solution for IV administration. CAM-H2 may be stored at room temperature but is also stable below ≤-70°C. CAM-H2 has a shelf life of 144 hours after production.

The clear, sterile solution contains the radioactive ^{131}I-GMIB-2Rs15d. This will be injected via a slow IV infusion. The study drug will be administered using a shielded infusion device over approximately 3 to 30 minutes, depending on the volume to be injected.

DOSIMETRY STUDY PROCEDURES:

For the dosimetry study, defined critical organs (ie, the kidneys and liver) and target lesions (ie, lesions representative of the extent of disease and deemed avid at the discretion of the central reviewer, based on qualitative visual assessment) will be delineated on planar WB scans and/or SPECT/CT scans. Further details are provided in the Imaging Review Charter.

The percentage of injected activity (%IA) will be calculated in each set of images as the ratio between the measured activity in the lesion and the total injected activity as a function of time to derive the absorbed dose. Organ time-activity curves will be generated by plotting %IA versus time to derive the absorbed dose.

Tumor dosimetry in tumor lesions will be calculated based on the consecutive SPECT/CT and/or planar WB scans during Cycle 1 of the dose escalation phase.

EFFICACY VARIABLES:

The primary efficacy endpoints are as follows:

- Proportion of patients achieving an objective response (CR or PR) with the use of CAM-H2 as measured by RECIST version 1.1 (all patients with extracranial lesions) or as measured by RANO-BM (patients with brain metastases without extracranial lesions); and
- CBR of CAM-H2 using the equation CBR = CR + PR + SD, as measured by RECIST version 1.1 (all patients with extracranial lesions) or as measured by RANO-BM (patients with brain metastases without extracranial lesions).

The secondary efficacy endpoints are as follows:

- PFS for patients receiving CAM-H2;
- DoR in patients receiving CAM-H2;
- PFS in patients with brain metastases receiving CAM-H2;
- OS for patients receiving CAM-H2; and
- Proportion of patients on CAM-H2 who develop ADAs.

DOSIMETRY VARIABLES:

The dosimetry endpoint consists of dosimetry for CAM-H2 via SPECT/CT and planar WB scans. Endpoints will include the biodistribution and PD profile of CAM-H2 dosimetry results for target lesions based on region of interest.

SAFETY VARIABLES:

Safety and tolerability will be assessed during the study and will include the following:

- Incidence and severity of treatment-emergent adverse events;
- MTD of CAM-H2;
- DLT rate of CAM-H2;
- RDP2 for CAM-H2;
- Physical examinations, including full neurologic examinations, as well as assessments of general appearance, skin, eyes, ears, nose, throat, neck, lymph nodes, chest, heart (including auscultation for heart sounds and murmurs), abdomen, extremities, and musculoskeletal systems;
- Vital signs, including systolic and diastolic blood pressure, heart rate, respiratory rate, and temperature;
- Clinical laboratory tests including thyroid panel (thyroid-stimulating hormone, free T4, and free T3), hematology assessments (white blood cell count and differential, hemoglobin, hematocrit, and platelet count), coagulation parameters (activated partial thromboplastin time, INR, and prothrombin time), and chemistry assessments (fasting glucose or glycated hemoglobin, creatinine, blood urea nitrogen, sodium, potassium, calcium, chloride,

phosphorus, bicarbonate, AST, ALT, gamma-glutamyl transferase, alkaline phosphatase, total bilirubin [or fraction of direct bilirubin if >1.5 × ULN], albumin, total protein, lactate dehydrogenase, creatine kinase [or fraction of creatine kinase-myocardial band if >1.5 × ULN], and cystatin-C);

- Urinalysis for kidney biomarkers (including kidney injury molecule-1, neutrophil gelatinase-associated lipocalin, microalbumin, creatinine, and albumin/creatinine ratio) and for microscopic evaluation of sediment (including cylinders, erythrocytes, and leukocytes);
- Pregnancy test (including serum and urine testing);
- Dosimetry results with regard to estimated absorbed dose to the most exposed organs (ie, the kidneys and liver); and
- Concomitant medications.

STATISTICAL ANALYSES:

The Safety Analysis Set (SAF) will include all patients who receive at least 1 dose of study drug. The SAF will be used for the summary of patient characteristics and safety analyses.

The Full Analysis Set (FAS) will include all patients who receive at least 1 dose of study drug. The FAS is identical to the SAF. The FAS will be used primarily for the analysis of tumor response and other efficacy-related data.

Efficacy analyses will be performed on the FAS. Overall response rate (ORR) will be assessed for each patient as well as the CBR, DoR, and PFS. A water-plot analysis of breast cancer and gastric/GEJ cancer populations will be done. Response magnitude, including CR and near-CR (defined as a >90% confirmed tumor volume reduction) will also be considered.

All dosimetry evaluations will be done using the OLINDA/EXM or equivalent software. Total dose estimates and the dose estimate for the organs with the highest dose (most likely the kidneys or liver) will be reported using classical descriptive statistics for continuous variables (N, mean, median, standard deviation, minimum, and maximum).

Safety analyses will be performed on the SAF. Descriptive statistics will be used for all safety parameters.

SAMPLE SIZE DETERMINATION:

The proposed study is a dose escalation (Phase 1) study with an expansion cohort reaching into dose expansion (Phase 2). No formal sample size calculation was performed for dose escalation (Phase 1) of the study. A maximum of 18 patients are planned for dose escalation.

No formal sample size calculation was performed for dose expansion (Phase 2). However, a planned sample size of 52 patients is deemed sufficient to obtain an initial estimate of response rates to formally power a subsequent Phase 2/3 study.

For each indication (ie, breast, gastric, or GEJ cancer), an interim evaluation of efficacy will be conducted when approximately 50% of patients complete Cycle 1 at the recommended dose for expansion based on objective responses determined from RECIST 1.1 or RANO-BM. One analysis will be performed for patients with breast cancer, and another analysis will be performed

for patients with gastric or GEJ cancer. If the ORR is <10% for a specific indication (ie, breast or gastric/GEJ), the study will be terminated for that particular indication.

The Statistical Analysis Plan will provide more details on the exact statistical approach.

SITES:

Dose escalation: Approximately 4 to 8 sites in North America

Dose expansion: Approximately 10 to 15 sites in North America

SPONSOR:

Precirix NV
Burgemeester Etienne Demunterlaan 1
B-1090 Brussels
Belgium
Telephone: +32 2 479 93 60

TABLE OF CONTENTS

Signature Page 2
Investigator Agreement 3
Synopsis 4
Table of Contents 25
List of Tables 31
List of Figures 32
List of Abbreviations and Definition of Terms 33
1 Introduction and Background Information 35
1.1 Rationale 37
1.2 Risk/Benefit 37
1.3 Starting Dose Rationale 38
1.3.1 Protein Content 38
1.3.2 Dosimetry Rationale 38
1.4 The Coronavirus Disease 2019 39
2 Study Objectives 40
2.1 Primary Objectives 40
2.2 Secondary Objectives 40
3 Study Description 41
3.1 Summary of Study Design 41
3.1.1 Dose Escalation Phase 42
3.1.1.1 Screening 42
3.1.1.2 CAM-H2 administration 43
3.1.1.3 Imaging 44
3.1.2 Dose Expansion Phase 46
3.1.2.1 Screening 46
3.1.2.2 CAM-H2 administration 46
3.1.2.3 Imaging 47
3.1.3 Long-Term Follow-Up Period 48
3.1.4 Dose Escalation Rules and Dose Staggering Approach 49
3.1.4.1 Definition of dose-limiting toxicities 50

3.1.4.2 Dose escalation rules 51
3.1.5 Stopping Rules, Dose Modifications, and Missed Doses 51
3.1.5.1 Stopping rules 51
3.1.5.2 Dose modifications 52
3.1.5.3 Missed doses 54
4 Selection and Withdrawal of Patients 55
4.1 Inclusion Criteria 55
4.2 Exclusion Criteria 56
4.3 Withdrawal Criteria 58
5 Study Treatments 59
5.1 Dose Groups 59
5.2 Drug Supplies 59
5.2.1 Formulation and Packaging 59
5.2.2 Study Drug Administration 60
5.2.2.1 Radioprotection rules 60
5.2.3 Treatment Compliance 61
5.2.4 Storage and Accountability 61
5.2.5 Ancillary Treatments to be Given With CAM-H2 62
5.2.5.1 Thyroid-blocking drugs 62
5.2.5.2 Anti-emetic, anti-histamine, and anti-pyretic premedication therapy 62
5.2.5.3 Saline infusion 62
5.2.5.4 Amino acid infusion 62
5.3 Prior and Concomitant Medications and/or Procedures 63
5.3.1 Excluded Medications and/or Procedures 63
5.3.2 Restricted Medications and/or Procedures 63
5.3.3 Documentation of Prior and Concomitant Medication Use 63
6 Study Procedures 64
6.1 Informed Consent 64
6.2 Dose Escalation Phase 64
6.2.1 Screening for the Dose Escalation Phase 64
6.2.1.1 Visit 1 (Week -4 to Week -1) 64
6.2.1.2 Visit 2 (Week -2 to Week -1) 65

6.2.2 Cycle 1 of the Dose Escalation Phase 65
6.2.2.1 Visit 3 (Week 0) 65
6.2.2.2 Visit 4 (Week 1) 66
6.2.2.3 Visit 5 (Week 2) 67
6.2.2.4 Visit 6 (Week 3) 67
6.2.2.5 Visit 7 (Week 4) 67
6.2.2.6 Visit 8 (Week 5) 69
6.2.2.7 Visit 9 (Week 6) 69
6.2.2.8 Visit 10 (Week 8) 69
6.2.2.9 Visit 11 (Week 11): End of Treatment Visit or Cycle 2 eligibility assessment 70
6.2.3 Cycles 2, 3, and 4 of the Dose Escalation Phase 71
6.2.3.1 Visit 11 (Cycle 2 eligibility assessment), Visit 20 (Cycle 3 eligibility assessment), and Visit 29 (Cycle 4 eligibility assessment) 71
6.2.3.2 Visits 12, 21, and 30 (Week 0) 71
6.2.3.3 Visits 13, 22, and 31 (Week 1) 72
6.2.3.4 Visits 14, 23, and 32 (Week 2) 72
6.2.3.5 Visits 15, 24, and 33 (Week 3) 72
6.2.3.6 Visits 16, 25, and 34 (Week 4) 73
6.2.3.7 Visits 17, 26, and 35 (Week 5) 74
6.2.3.8 Visits 18, 27, and 36 (Week 6) 74
6.2.3.9 Visits 19, 28, and 37 (Week 8) 74
6.2.3.10 Visits 20, 29, and 38 (Week 11): cycle eligibility or End of Treatment Visit 75
6.3 Dose Expansion Phase 76
6.3.1 Screening for the Dose Expansion Phase 76
6.3.1.1 Visit 1 (Week -4 to Week -1) 76
6.3.1.2 Visit 2 (Week -1) 76
6.3.2 Cycle 1 of the Dose Expansion Phase 77
6.3.2.1 Visit 3 (Week 0) 77
6.3.2.2 Visit 4 (Week 1) 78
6.3.2.3 Visit 5 (Week 2) 78
6.3.2.4 Visit 6 (Week 3) 78

6.3.2.5 Visit 7 (Week 4) 79
6.3.2.6 Visit 8 (Week 5) 80
6.3.2.7 Visit 9 (Week 6) 80
6.3.2.8 Visit 10 (Week 8) 80
6.3.2.9 Visit 11 (Week 11): End of Treatment Visit or Cycle 2 eligibility assessment 81
6.3.3 Cycle 2 of the Dose Expansion Phase 82
6.3.3.1 Visit 11 (Cycle 2 eligibility assessment) 82
6.3.3.2 Visit 12 (Week 0) 82
6.3.3.3 Visit 13 (Week 1) 83
6.3.3.4 Visit 14 (Week 2) 83
6.3.3.5 Visit 15 (Week 3) 83
6.3.3.6 Visit 16 (Week 4) 84
6.3.3.7 Visit 17 (Week 5) 85
6.3.3.8 Visit 18 (Week 6) 85
6.3.3.9 Visit 19 (Week 8) 85
6.3.3.10 Visit 20 (Week 11): End of Treatment Visit 86
6.4 Early Termination Visit and Withdrawal Procedures 86
6.5 Long-Term Follow-Up Period and End of Study 86
7 Efficacy and Dosimetry Variables 88
7.1 Primary Efficacy Variables 88
7.2 Secondary Efficacy Variables 88
7.3 Dosimetry Variables 88
7.4 Efficacy Assessments 88
7.4.1 Objective Response 88
7.4.2 Clinical Benefit Rate 88
7.4.3 Additional Clinical Measurements of Efficacy 88
7.4.4 Anti-Drug Antibodies 89
7.4.5 Exploratory Biomarkers 89
7.4.6 Dosimetry Study Procedures 89
8 Safety Assessments 90
8.1 Adverse Events 90
8.1.1 Adverse (Drug) Reaction 91

8.1.2 Unexpected Adverse Drug Reaction 91
8.1.3 Assessment of Adverse Events by the Investigator 91
8.1.4 Adverse Events of Special Interest 93
8.2 Serious Adverse Events 93
8.3 Serious Adverse Event Reporting − Procedures for Investigators 94
8.4 Pregnancy Reporting 95
8.5 Expedited Reporting 95
8.6 Special Situation Reports 96
8.7 Clinical Laboratory Tests 96
8.8 Vital Signs 97
8.9 Electrocardiograms 98
8.10 Physical Examinations 98
9 Statistics 99
9.1 Analysis Populations 99
9.2 Statistical Methods 99
9.2.1 Analysis of Efficacy 99
9.2.2 Analysis of Dosimetry 99
9.2.3 Analysis of Safety 99
9.2.4 Sample Size Determination 100
10 Data Management and Record Keeping 101
10.1 Data Management 101
10.1.1 Data Handling 101
10.1.2 Computer Systems 101
10.1.3 Data Entry 101
10.1.4 Medical Information Coding 101
10.1.5 Data Validation 101
10.2 Record Keeping 101
10.3 Study End 102
11 Investigator Requirements and Quality Control 103
11.1 Ethical Conduct of the Study 103
11.2 Institutional Review Board/Independent Ethics Committee 103
11.3 Informed Consent 103

11.4 Subject Card 104
11.5 Study Monitoring Requirements 104
11.6 Disclosure of Data 104
11.7 Retention of Records 105
11.8 Publication Policy 105
11.9 Financial Disclosure 105
11.10 Insurance and Indemnity 105
11.11 Legal Aspects 106
12 Study Administrative Information 107
12.1 Protocol Amendments 107
13 References 108
Appendix A: Schedule of Procedures 109
Appendix B: Clinical Laboratory Analytes 129
Appendix C: Eastern Cooperative Oncology Performance Status 131
Appendix D: Tumor Measurements and the Response Evaluation Criteria in Solid Tumors Version 1.1 132
Appendix E: Brain Tumor Measurements and Response Assessment in Neuro-Oncology Brain Metastases 134
Appendix F: Example of Safety Instructions for Patients Receiving Radioiodine Treatment ... 136

LIST OF TABLES

Table 1. Imaging During the Dose Escalation Phase 45
Table 2. Imaging During the Dose Expansion Phase 48
Table 3. Dose Escalation Schedule for Each CAM-H2 Cycle 59
Table 4. Thyroid-Blocking Drugs 62
Table 5. Composition of the Standard Amino Acid Solution 63
Table 6. Specification of Commercially Available Amino Acid Solutions 63
Table 7. Schedule of Procedures: Dose Escalation Phase, Cycle 1 109
Table 8. Schedule of Procedures: Dose Escalation Phase, Cycles 2, 3, and 4 115
Table 9. Schedule of Procedures: Dose Expansion Phase, Cycle 1 120
Table 10. Schedule of Procedures: Dose Expansion Phase, Cycle 2 125
Table 11. Eastern Cooperative Oncology Group Performance Status 131
Table 12. Response Evaluation Criteria in Solid Tumors Version 1.1 Guidelines 133
Table 13. Response Assessment in Neuro-Oncology Brain Metastases 135
Table 14. Summary of the Response Criteria for Central Nervous System Metastases Proposed by the Response Assessment in Neuro-Oncology Brain Metastases 135

LIST OF FIGURES

Figure 1. CAM-H2 Composition..... 36

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
%IA	Percentage of injected activity
^{131}I	^{131}Iodine
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
CB	Clinical benefit
CBR	Clinical benefit rate
CFR	Code of Federal Regulations
CK	Creatine kinase
CK-MB	Creatine kinase-myocardial band
COVID-19	Coronavirus Disease 2019
CR	Complete response
CRA	Clinical research associate
CT	Computed tomography
CTA	Clinical trial authorization
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose-limiting toxicity
DoR	Duration of response
ECG	Electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group performance status
eCRF	Electronic case report form
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
EIU	Exposure in Utero
EOT	End of Treatment
ET	Early Termination
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GEJ	Gastro-esophageal junction
GGT	Gamma-glutamyl transferase
GI	Gastrointestinal
GMIB	4-guanidinomethyl-3-iodobenzoate
hCG	Human chorionic gonadotropin
HER2	Human epidermal growth factor receptor 2

Abbreviation	Definition
HIV	Human immunodeficiency virus
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
INR	International normalized ratio
IRB	Institutional Review Board
IV	Intravenous(ly)
KIM-1	Kidney injury molecule-1
LDH	Lactate dehydrogenase
LVEF	Left ventricular ejection fraction
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NGAL	Neutrophil gelatinase-associated lipocalin
NIMP	Non-investigational medicinal product
NOAEL	No observed adverse effect level
ORR	Overall response rate
OS	Overall survival
PD	Pharmacodynamic(s)
PFS	Progression-free survival
PR	Partial response
QTc	Corrected QT interval
RANO-BM	Response Assessment in Neuro-Oncology Brain Metastases
RDP2	Recommended dose for Phase 2
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SAF	Safety Analysis Set
SD	Stable disease
sdAb	Single-domain antibody
SPECT	Single photon emission computed tomography
SRC	Safety Review Committee
SUSAR	Suspected unexpected serious adverse reaction
T3	Triiodothyronine
T4	Thyroxine
TEAE	Treatment-emergent adverse event
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
WB	Whole body
WBC	White blood cell
WBRT	Whole brain radiation therapy
WHO	World Health Organization

1 INTRODUCTION AND BACKGROUND INFORMATION

The human epidermal growth factor receptor 2 (HER2), a member of the epidermal growth factor receptor family, is implicated in the pathogenesis of numerous cancer types.[1] HER2 is overexpressed in up to 30% of invasive breast cancers and up to 30% of gastric cancers.[1] Among gastric cancers, HER2 overexpression is most commonly found at the gastro-esophageal junction (GEJ) and is correlated with poor outcomes.[1]

Worldwide, breast cancer is the leading type of cancer in women, accounting for around 25% of all cancer types.[2] About 20% of breast cancers overall,[3] and 30% of invasive breast cancers,[1] overexpress the HER2 oncogene. Amplification of the HER2 gene in cancer cells leads to an overexpression of surface HER2 receptors and subsequently to a dysregulated and overstimulated signaling pathway. HER2-positive breast cancers can be more aggressive than other breast cancers and have been associated with a higher recurrence rate and a shorter time to recurrence.[4] The advent of targeted therapy drugs, starting with trastuzumab (Herceptin®), has greatly improved the prognosis of patients with HER2-positive breast cancer; however, metastatic disease is still incurable in the majority of cases and most patients ultimately develop progressive disease and die.[5] In HER2-positive metastatic breast cancer, approximately 30% of patients develop brain metastases despite receiving trastuzumab-based therapy and intracranial disease progression is the cause of death in about half of patients with brain metastases.[6] Therefore, control of systemic/intracranial disease is an important issue in terms of survival in patients with HER2-positive breast cancer. To date, there is no standard of care treatment for patients with relapsing/refractory HER2-positive tumors following treatment with trastuzumab, pertuzumab, ado-trastuzumab emtansine, and trastuzumab deruxtecan. For intracranial disease progression, patients are currently treated with stereotactic radiation surgery in case of limited disease in the brain or with whole brain radiation therapy (WBRT) in case of more extensive disease in the brain. WBRT is effective in controlling the disease short term but comes with severe neurological side effects such as memory loss.

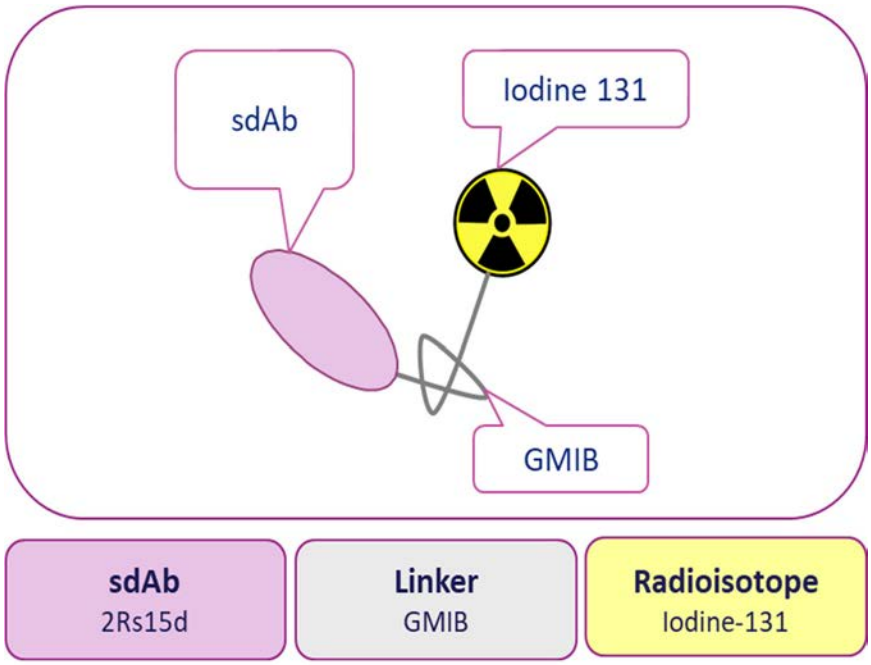
Gastric cancer, including GEJ cancer, is also a common cancer diagnosed globally. While prognosis of early-stage disease is favorable, most patients present with advanced or metastatic disease and have limited treatment options.[7] It is the fifth most commonly diagnosed cancer but the third leading cause of cancer-related death worldwide.[7] Similar to HER2-positive breast cancer, HER2-positive gastric and GEJ cancers are often more aggressive than other gastric cancers.[1] Although brain metastases are uncommon in patients with gastric or GEJ malignancies, the incidence is higher in those with HER2 positivity.[8] The presence of brain metastases worsens prognosis, and the median overall survival (OS) in these patients ranges from 1.3 to 2.4 months.[8] Currently, HER2 targeted therapies are available for gastric and GEJ cancer patients, including anti-HER2 monoclonal antibody, trastuzumab, and HER2-targeting tyrosine kinase inhibitors; however, treatment remains suboptimal.[7] Although adding trastuzumab to traditional chemotherapy can improve median OS in patients with HER2-positive gastric or GEJ cancers, it has only been shown to extend survival by 1 to 2 months.[9] In addition, the tyrosine kinase inhibitors such as lapatinib, afatinib, dacomitinib, and neratinib have not been shown to produce clinical benefit (CB) or survival benefits in clinical trials.[7] Similar to HER2-positive breast cancer, no standard of care treatment exists for patients with advanced HER2-positive gastric or GEJ tumors following treatment with trastuzumab.

Since HER2 has a key role in the development of breast, gastric, and GEJ cancers, it serves as an ideal target for anticancer strategies. The single-domain antibody (sdAb) 2Rs15d was selected as

a lead compound for the development of a targeted radionuclide therapy for progressive HER2-positive breast cancer patients because it delivers the irradiation directly on the cancer cells throughout the body, while unbound product is rapidly eliminated via the kidneys thereby limiting its toxicity. Moreover, the sdAb 2Rs15d is brain penetrant and does not compete with binding of Herceptin, Kadcyla®, Perjeta®, or biosimilar treatments, enabling the potential use of CAM-H2 in combination with these products.[10]

CAM-H2 (drug substance: ^{131}Iodine [^{131}I]-4-guanidinomethyl-3-iodobenzoate [GMIB]-2Rs15d) is a therapeutic radiopharmaceutical consisting of the following covalently-linked components: ^{131}I, the GMIB linker, and an sdAb targeting HER2 (company code: 2Rs15d, also referred to as Anti-HER2 VHH1) (see Figure 1).

Figure 1. CAM-H2 Composition



GMIB = 4-guanidinomethyl-3-iodobenzoate; sdAb = single-domain antibody.

The sdAbs are the single-domain antigen-binding fragments that are recombinantly derived from camelid heavy-chain-only antibodies. Discovered at the Vrije Universiteit Brussel in Belgium, they are more than 10 times smaller (10 to 15 kDa) than conventional monoclonal antibodies. The sdAbs are considered low immunogenic, have nanomolar affinities, and can be produced in high yields. Theoretically, they can be generated against virtually any cancer-specific membrane-associated protein. In a series of non-clinical and clinical studies, it was demonstrated that sdAbs bear beneficial properties for nuclear imaging and targeted radionuclide therapy. In mice, radiolabeled sdAbs efficiently penetrate tumors and tissues, binding biomarkers expressed on tumor cells quickly and, specifically, while unbound sdAb is rapidly cleared from non-target organs and tissues.

The protein component of CAM-H2 is 2Rs15d, a 115-amino acid sdAb that specifically binds to HER2-expressing tumor cells in vitro with nanomolar affinity. CAM-H2 is able to kill cancer cells and slow down and even prevent tumor growth progression when binding to the HER2 protein. When injected intravenously (IV) in mice, >95% of CAM-H2 is removed from the bloodstream

into the bladder within the first 2 hours. High concentration of radioactivity can be expected in the bladder and thus in urine during the first hour after infusion, showing predominant renal clearing of the product. Fast and specific uptake in HER2-expressing tumors has been observed, with only minor accumulation in healthy organs and tissues except for kidneys at early time points. This is translated in the very low dose delivered to these organs and tissues. CAM-H2 is brain-penetrant and does not compete with the monoclonal antibodies trastuzumab (Herceptin) and pertuzumab (Perjeta) for binding to HER2, allowing administration as an add-on to anti-HER2 biologics and antibody-drug conjugates.

1.1 Rationale

This multi-center, open-label, dose escalation and dose expansion study is being conducted to evaluate the safety, tolerability, dosimetry, pharmacodynamics (PD), and efficacy of the targeted radionucleotide therapeutic CAM-H2 in patients with advanced/metastatic HER2-positive breast, gastric, and GEJ cancer with disease progression following anti-HER2 standard of care treatment.

1.2 Risk/Benefit

This is the first study using this specific CAM-H2 sdAb construct in humans.

^{131}I-GMIB-2Rs15d, initially produced via a different manufacturing method under Good Manufacturing Practice, was used in a first-in-human clinical Phase 1 trial (NCT02683083; the CAM-VHH1 study) that included 2 cohorts composed of healthy volunteers and patients with HER2-positive breast cancer. In the first cohort, 6 healthy volunteers were included for the assessment of safety, biodistribution, and radiation dosimetry. In the second cohort, ^{131}I-GMIB-2Rs15d was administered IV at a low radioactive dose to 6 healthy volunteers and 3 patients with advanced HER2-positive breast cancer. During this study, no study drug-related adverse events (AEs) were observed. After IV administration, ^{131}I-GMIB-2Rs15d showed a rapid tissue distribution and a blood elimination half-life of 2.5 hours. The biological half-life in healthy subjects was 12 hours. The study drug was primarily eliminated via the kidneys. Data from this study demonstrate that CAM-H2 is concentrated in cancer lesions.

Another similar investigational sdAb construct was used in the [68Gallium]-NOTA-Anti-HER2 VHH1 diagnostic trial using the IV injection of [68Gallium]-NOTA-Anti-HER2 VHH1. This trial (EUDRACT 012-001135-31) was a first-in-human Phase 1 trial in 20 breast carcinoma patients. The study drug was found to be safe, without the occurrence of adverse effects, at protein doses up to 1 mg.

In summary, CAM-H2 is considered to be a low-risk biological compound based on the following:

- Previous human experience with the gallium-labeled protein given in total masses mounting to similar exposures anticipated in the proposed study;
- Previous human experience with a similar iodine-labeled protein in a first-in-human study;
- The fact that the target, its mode of action, and its expression in different tissues are well-known;

- Previous human experience with monoclonal antibodies targeting the same receptor demonstrating that these antibodies are safe, well tolerated, and effective; and
- The very low protein dose to be administered, ranging from 2 to 10 mg in total dose.

Refer to Sections 6 and 7 of the Investigator's Brochure for more detailed information on previous experience in humans and the overall risk/benefit assessment.

1.3 Starting Dose Rationale

1.3.1 Protein Content

The dose escalation steps are based on the radioactive content rather than on the protein mass because the radioactive content will be dose-limiting and define the potential efficacy.

The planned dose escalation steps (2 × 50 mCi, 2 × 100 mCi, 2 × 150 mCi, and 2 × 200 mCi) represent a protein mass for 2Rs15d between approximately 2 mg for the lower doses and approximately 10 mg for the higher doses.

Based on the preclinical Good Laboratory Practices toxicology studies, the no observed adverse effect level (NOAEL) in the most relevant species (non-human primate, multiple IV dose toxicity study) was 7.14 mg of 2Rs15d per kg. Based on this NOAEL approach, the human equivalent dose is 2.3 mg/kg. For a 60 kg human, this would represent a total protein dose of 138 mg. Applying a safety factor of 50, this would yield a maximum recommended starting dose of 2.76 mg. The proposed starting dose of 2 mg will provide a safety factor >50 fold. The anticipated maximum dose of 2Rs15d is in the order of magnitude of 10 mg, which still represents a dose that is approximately 13.8 times lower than the equivalent NOAEL dose in non-human primates.

1.3.2 Dosimetry Rationale

The proposed dose escalation of radioactivity is based on dosimetry extrapolations obtained in the dosimetry study in non-human primates using the study drug. The proposed dose escalation is described in Section 5.1.

Dosimetry analysis predicts that the dose-limiting organ will be the kidneys. The calculations show that the kidneys receive a mean absorbed radiation dose of 34.9 ±2 mGy/mCi (or 0.94 ±0.05 mGy/MBq) in male subjects (the most sensitive sex) when Vamin® 18 Electrolyte Free, an amino acid solution, is administered. The absorbed dose limit for the kidneys is 23 Gy.[11] Above this level, radiotoxicity could occur. As a result, it is estimated that significant kidney toxicity is unlikely to occur at levels up to 659 mCi (24.1 GBq) of CAM-H2. For the highest intended dose of 2 × 200 mCi, the estimated kidney dose is 14 Gy.

Red bone marrow is the most radiosensitive tissue in the body. CAM-H2 results in a red bone marrow exposure of 2.2 ±0.5 mGy/mCi (or 0.059 ±0.001 mGy/MBq) in male subjects, based on modeling. The absorbed dose limit for bone marrow is 2 Gy.[11] Above this level, significant hematotoxicity is expected. This level of irradiation would only occur at 909 mCi (33.6 GBq) of CAM-H2 in a single dose. Therefore, severe hematotoxicity is unlikely to occur at the doses of CAM-H2 in the current study (100 to 400 mCi). CAM-H2 at a therapeutic cumulative dose of 400 mCi (14.8 GBq) would deliver 0.88 Gy to the red bone marrow.

The dosimetry data for CAM-H2 indicate that CAM-H2 is unlikely to present clinically relevant radiotoxicity to healthy tissues up to the level of 14.8 GBq (2 × 200 mCi) administered in 1 cycle.

In order to mitigate the risk of kidney radiation injury, an amino acid infusion consisting of arginine and lysine will be administered from 30 minutes before study drug administration to 3 hours after study drug administration, a method routinely used in targeted radionuclide therapy (eg, Lutathera® [Novartis]). Preclinical studies with CAM-H2 show that infusion of arginine and lysine reduces kidney retention levels by approximately 40%.

See Section 7 of the Investigator's Brochure for a detailed description of the justifications.

1.4 The Coronavirus Disease 2019

In March 2020, the Coronavirus Disease 2019 (COVID-19), caused by infection with severe acute respiratory syndrome coronavirus 2, was characterized as a pandemic by the World Health Organization (WHO). The COVID-19 pandemic impacted clinical studies worldwide due to quarantines, site closures, travel limitations, diversion of resources, and/or general interruptions in study-related procedures.

This study protocol includes contingency plans to manage disruptions due to COVID-19 control measures. On-site monitoring should occur according to the Monitoring Plan unless cancelled by the site or by local governmental requirements. Virtual monitoring through an electronic source portal will be utilized for sites that do not allow on-site monitoring and where data monitoring is critical (eg, related to patient safety). Virtual monitoring should only be applied at a site that has a plan in place and per site policy and local regulations. In case the patient cannot reach the site to have protocol procedures performed, and the procedures are critical for patient safety or data integrity of the study, laboratory, imaging, and other diagnostic tests may be performed at a local laboratory or relevant clinical facility (ie, a facility that is authorized or certified as legally required nationally to perform such test routinely) if this can be done within local restrictions, including social distancing restrictions. The sites should inform the Sponsor about such cases. Local analyses can be used for safety decisions. The impacts of these implemented contingency plans on the outcomes of this study, including any protocol deviations that result from COVID-19 illness and/or COVID-19 control measures will be discussed in the Clinical Study Report.

Any COVID-19 safety plans generated and implemented by the sites will be documented as part of the site study file.

2 STUDY OBJECTIVES

2.1 Primary Objectives

The primary objective for the dose escalation phase is as follows:

- To evaluate the safety, tolerability, dosimetry, and PD of ascending doses of CAM-H2 in patients with advanced/metastatic HER2-positive breast, gastric, and GEJ cancer, including determination of dose-limiting toxicity (DLT), maximum tolerated dose (MTD), and recommended dose for Phase 2 (RDP2).

The primary objectives for the dose expansion phase are as follows:

- To evaluate the proportion of patients achieving an objective response (complete response [CR] or partial response [PR]) with the use of CAM-H2 as measured by the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (all patients with extracranial lesions) or as measured by the Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM) (patients with brain metastases without extracranial lesions);
- To measure the clinical benefit rate (CBR) of CAM-H2 using the equation CBR = CR + PR + stable disease (SD), as measured by RECIST version 1.1 (all patients with extracranial lesions) or as measured by RANO-BM (patients with brain metastases without extracranial lesions); and
- To evaluate the safety and tolerability of CAM-H2 in patients with advanced/metastatic HER2-positive breast, gastric, and GEJ cancer.

2.2 Secondary Objectives

The secondary objectives are as follows:

- To assess the CB of CAM-H2 by evaluating the proportion of patients with a CR, PR, and SD in the dose escalation phase;
- To assess duration of response (DoR);
- To evaluate progression-free survival (PFS) from the time of enrollment in the study to progression of disease or death;
- To measure median OS;
- To evaluate intra- and inter-patient dosimetry and PD of CAM-H2 (dose escalation phase only); and
- To assess for the development of anti-drug antibodies (ADAs).

3 STUDY DESCRIPTION

3.1 Summary of Study Design

This is a Phase 1/2 multi-center, open-label, dose escalation and dose expansion study to evaluate safety, tolerability, dosimetry, PD, and efficacy of the targeted radionuclide therapeutic CAM-H2 in patients with progressive, advanced/metastatic HER2-positive breast, gastric, and GEJ cancer with disease progression following anti-HER2 standard of care treatment.

During the dose escalation phase, patients will be enrolled at approximately 4 to 8 sites in North America. During the dose expansion phase, patients will be enrolled at approximately 10 to 15 sites in North America.

The study will be comprised of the following:

- Dose escalation phase (up to 4 treatment cycles)
  - Screening: Week -4 to Week -1
  - Treatment period: Visit 3 (Week 0) up to Visit 38 (Week 11 of Cycle 4)
    - Cycle 1
      - Dose 1 and Safety Follow-Up Period: Week 0 to Week 3
      - Dose 2 and Safety Follow-Up Period: Week 4 to Week 11 (End of Treatment [EOT] Visit or Cycle 2 eligibility assessment)
    - Cycle 2 (to begin 2 weeks after the Cycle 2 eligibility assessment for patients with CB during Cycle 1, as long as the cumulative kidney dose remains <23 Gy [based on the dosimetry results during Cycle 1])
      - Dose 1 and Safety Follow-Up Period: Week 0 to Week 3
      - Dose 2 and Safety Follow-Up Period: Visit 16 (Week 4) to Visit 20 (Week 11) (EOT Visit or Cycle 3 eligibility assessment)
    - Cycle 3 (to begin 2 weeks after the Cycle 3 eligibility assessment for patients with CB during Cycles 1 and 2, as long as the cumulative kidney dose remains <23 Gy [based on the dosimetry results during Cycle 1])
      - Dose 1 and Safety Follow-Up Period: Week 0 to Week 3
      - Dose 2 and Safety Follow-Up Period: Week 4 to Week 11 (EOT Visit or Cycle 4 eligibility assessment)
    - Cycle 4 (to begin 2 weeks after the Cycle 4 eligibility assessment for patients with CB during Cycles 1, 2, and 3, as long as the cumulative kidney dose remains <23 Gy [based on the dosimetry results during Cycle 1])
      - Dose 1 and Safety Follow-Up Period: Week 0 to Week 3
      - Dose 2 and Safety Follow-Up Period: Week 4 to Week 11 (EOT Visit)
  - Long-term follow-up period

- Dose expansion phase (up to 2 treatment cycles)
  - Screening: Week -4 to Week -1
  - Treatment period: Visit 3 (Week 0) up to Visit 20 (Week 11 of Cycle 2)
    - Cycle 1
      - Dose 1 and Safety Follow-Up Period: Week 0 to Week 3
      - Dose 2 and Safety Follow-Up Period: Week 4 to Week 11 (EOT Visit or Cycle 2 eligibility assessment)
    - Cycle 2 (to begin 2 weeks after the Cycle 2 eligibility assessment for patients with CB during Cycle 1, as long as the cumulative kidney dose remains <23 Gy [based on the dosimetry results during Cycle 1 of dose escalation])
      - Dose 1 and Safety Follow-Up Period: Week 0 to Week 3
      - Dose 2 and Safety Follow-Up Period: Week 4 to Week 11 (EOT Visit)
  - Long-term follow-up period

One treatment cycle is defined as the timeframe of approximately 12 weeks (84 days) that includes 2 administrations of the study drug given 4 weeks apart (including the 4-week Safety Follow-Up Period after Dose 1 and the Safety Follow-Up Period after Dose 2, up to Visit 11) (see Appendix A).

However, if a patient misses a dose of study drug due to study drug production problems or due to other circumstances (in certain cases), the interval between doses may be extended up to 6 weeks (Cycles 1 and 2 of both dose escalation and dose expansion phases) or up to 12 weeks (Cycles 3 and 4 of the dose escalation phase) (see Section 3.1.5.3).

3.1.1 Dose Escalation Phase

3.1.1.1 Screening

Patients will be screened for study eligibility over 2 different study visits (Visit 1 and Visit 2) in the 29 days prior to dosing (ie, Day -28 to Day 0 of Cycle 1). Visit 2 should occur preferably within the 14 days prior to study drug administration (Visit 3). All patients will undergo pre-treatment imaging for eligibility and baseline at Visit 1 with a diagnostic computed tomography (CT) scan for RECIST version 1.1. Patients with known brain metastases will undergo a brain magnetic resonance imaging (MRI) scan, in addition to the diagnostic CT, for RANO-BM.

After screening, approximately 15 patients who meet inclusion and exclusion criteria will be enrolled into 1 of 4 cohorts, including a minimum of 3 patients each.

The screening period may be extended up to an additional 2 weeks upon Sponsor approval in certain exceptional cases (eg, to allow for a repeat blood draw or to assess previously unavailable imaging results) following a discussion between the Principal Investigator, Medical Monitor, and Sponsor.

3.1.1.2 CAM-H2 administration

In the dose escalation phase, all patients will receive at least 1 cycle of CAM-H2. Patients with CB may receive up to 4 cycles of CAM-H2, as long as the cumulative kidney dose remains <23 Gy (based on the dosimetry results during Cycle 1). Cycles will be given as 2 IV administrations, 4 weeks apart. However, if a patient misses a dose of study drug due to study drug production problems or due to other circumstances (in certain cases), the interval between doses may be extended up to 6 weeks (Cycles 1 and 2) or up to 12 weeks (Cycles 3 and 4) (see Section 3.1.5.3).

Patients will be admitted to a radioactive unit for hospitalization during each IV administration for a total of 48 hours. This hospitalization can be shortened if ^{131}I decay and the patient's clearance allow discharge according to the applicable local regulations on radioactive compound exposure. Ancillary treatments to be given with CAM-H2 include thyroid-blocking drugs, premedication therapy (anti-emetic, anti-histamine, and anti-pyretic therapy), saline infusion, and amino acid infusion.

Cycle 1 will consist of the following:

- Dose 1 of CAM-H2: Visit 3 (Week 0);
- Safety Follow-Up Period: Visit 4 (Week 1), Visit 5 (Week 2), and Visit 6 (Week 3);
- Dose 2 of CAM-H2: Visit 7 (Week 4); and
- Safety Follow-Up Period: Visit 8 (Week 5), Visit 9 (Week 6), Visit 10 (Week 8), and Visit 11 (Week 11) (EOT Visit or Cycle 2 eligibility assessment).

If the patient has CB, and the cumulative kidney dose remains <23 Gy (based on the dosimetry results during Cycle 1), a second cycle may be initiated within 2 weeks after Visit 11 (Week 11) of Cycle 1, once the necessary Visit 11 (Week 11) safety follow-up assessments have been completed and reviewed. If the patient does not have CB, no further treatment will be administered and the patient will enter the long-term follow-up period.

If the patient has CB, Cycle 2 will then be initiated as follows:

- Dose 1 of CAM-H2: Visit 12 (Week 0);
- Safety Follow-Up Period: Visit 13 (Week 1), Visit 14 (Week 2), and Visit 15 (Week 3);
- Dose 2 of CAM-H2: Visit 16 (Week 4); and
- Safety Follow-Up Period: Visit 17 (Week 5), Visit 18 (Week 6), Visit 19 (Week 8), and Visit 20 (Week 11) (EOT Visit or Cycle 3 eligibility assessment).

If the patient has CB, and the cumulative kidney dose remains <23 Gy (based on the dosimetry results during Cycle 1), a third cycle may be initiated within 2 weeks after Visit 20 (Week 11) of Cycle 2, once the necessary Visit 20 (Week 11) safety follow-up assessments have been completed and reviewed. If the patient does not have CB, no further treatment will be administered and the patient will enter the long-term follow-up period.

If the patient has CB, Cycle 3 will then be initiated as follows:

- Dose 1 of CAM-H2: Visit 21 (Week 0);
- Safety Follow-Up Period: Visit 22 (Week 1), Visit 23 (Week 2), and Visit 24 (Week 3);

- Dose 2 of CAM-H2: Visit 25 (Week 4); and
- Safety Follow-Up Period: Visit 26 (Week 5), Visit 27 (Week 6), Visit 28 (Week 8), and Visit 29 (Week 11) (EOT Visit or Cycle 4 eligibility assessment).

If the patient has CB, and the cumulative kidney dose remains <23 Gy (based on the dosimetry results during Cycle 1), a fourth cycle may be initiated within 2 weeks after Visit 29 (Week 11) of Cycle 3, once the necessary Visit 29 (Week 11) safety follow-up assessments have been completed and reviewed. If the patient does not have CB, no further treatment will be administered and the patient will enter the long-term follow-up period.

If the patient has CB, Cycle 4 will then be initiated as follows:

- Dose 1 of CAM-H2: Visit 30 (Week 0);
- Safety Follow-Up Period: Visit 31 (Week 1), Visit 32 (Week 2), and Visit 33 (Week 3);
- Dose 2 of CAM-H2: Visit 34 (Week 4); and
- Safety Follow-Up Period: Visit 35 (Week 5), Visit 36 (Week 6), Visit 37 (Week 8), and Visit 38 (Week 11) (EOT Visit).

The dose escalation phase of the study will be an open-label 3 + 3 design, where at least 3 patients are treated at each dose level. Dose escalation will be done via increases of the nominal activity of CAM-H2 in cohorts of 3 to 6 patients. The dose escalation schedule is demonstrated in Table 3.

Staggered dosing will be applied for all cohorts during dose escalation. The first dose of the first patient of each cohort will be administered at least 2 weeks before the first dose of the next 2 patients (sentinel dosing). Once the MTD or RDP2 has been established, 3 additional patients will be enrolled to receive the MTD or RDP2. The patients treated at the MTD or RDP2 in the dose escalation phase will be included in the readout for efficacy. The dose escalation will be done via increases of the nominal activity of CAM-H2 in cohorts of 3 to 6 patients until approximately 15 (or a maximum of 18) patients have been dosed. The actual dose levels administered to the patient can have a tolerance window of ±10% of the prescribed nominal activity.

Dose escalation will be decided based on a review of all the available safety data obtained after completion of Cycle 1 (ie, after 2 IV administrations) of each dose level. If a patient is not able to complete a full cycle due to AEs related to study drug administration, he/she will not be replaced, and the dose escalation rules will be followed.

In the instance that a patient is not able to complete a full cycle due to AEs not related to study drug administration or due to a negative PD distribution scan, he/she will be replaced to ensure safety data spanning a full treatment cycle can be considered for dose escalation.

3.1.1.3 Imaging

All imaging will be sent to the central imaging core laboratory for independent review as soon as possible within 48 hours of acquisition. Further instructions will be provided by the imaging core laboratory in separate guidelines.

Patients will undergo 4 types of imaging during the dose escalation phase: planar whole body (WB) scans, single photon emission computed tomography (SPECT)/CT scans, diagnostic CT scans, and brain MRI scans, as shown in Table 1. Imaging to evaluate the organ/target lesion uptake will be performed after each CAM-H2 administration during the dose escalation phase of

the study for all patients at all dose levels. Dosimetry in tumor lesions, calculated based on consecutive SPECT/CT and planar WB scans, will be performed during Cycle 1. To evaluate disease progression, diagnostic CT scans will be performed in all patients, and brain MRI will only be performed in patients with known brain metastases. Patients with extracranial lesions will be evaluated for progression using RECIST version 1.1. Patients with brain metastases without extracranial lesions will be evaluated for progression using RANO-BM. Patients with extracranial lesions and brain metastases will be evaluated for progression using both RECIST version 1.1 (extracranial lesions) and RANO-BM (brain metastases). Additional details are provided in the Imaging Review Charter.

Table 1. Imaging During the Dose Escalation Phase

Type of Imaging	Cycle 1	Cycles 2, 3, and 4
Planar WB scans for PD distribution [1], evaluation of organ/target lesion uptake, and/or dosimetry	After each dose (Dose 1 and Dose 2): • 5 hours (±1 hour) after CAM-H2 [2]; • 24 hours (±4 hours) after CAM-H2; • 48 hours (±4 hours) after CAM-H2; and • 168 hours (±24 hours) after CAM-H2.	After each dose (Dose 1 and Dose 2): • 24 hours (±4 hours) after CAM-H2 [2].
SPECT/CT scans to evaluate organ/target lesion uptake and/or dosimetry	After each dose (Dose 1 and Dose 2): • 5 hours (±1 hour) after CAM-H2; • 24 hours (±4 hours) after CAM-H2; • 48 hours (±4 hours) after CAM-H2; and • 168 hours (±24 hours) after CAM-H2.	NA
Diagnostic CT scans to evaluate disease status	At screening and after Dose 2 only [3]: • 4 weeks after CAM-H2 at Visit 10 (Week 8); and • Every 8 weeks after Visit 10 (Week 8), as long as the patient had clinical benefit after Cycle 1 [4] and there is no disease progression.	After Dose 2 only [3]: • 4 weeks after CAM-H2 at Week 8; and • Every 8 weeks after Week 8, as long as the patient had clinical benefit after the current cycle [4] and there is no disease progression.
Brain MRI scans to evaluate disease status [5]	At screening and after Dose 2 only [3]: • 4 weeks after CAM-H2 at Visit 10 (Week 8); and • Every 8 weeks after Visit 10 (Week 8), as long as the patient had clinical benefit after Cycle 1 [4] and there is no disease progression.	After Dose 2 only [3]: • 4 weeks after CAM-H2 at Week 8; and • Every 8 weeks after Week 8, as long as the patient had clinical benefit after the current cycle [4] and there is no disease progression.

1. Patients with a negative PD distribution scan will not be treated further, although they will be included in the SAF. An extra patient will then be included in the same cohort as substitute.
2. During Dose 1 of the cycle, the first planar WB scan will also serve as the PD distribution scan.
3. Imaging to evaluate disease status after treatment will start 4 weeks after the last CAM-H2 infusion (Dose 2) of the cycle at Week 8. If a patient cannot receive Dose 2 of a given cycle, his/her imaging to evaluate disease status will start at the theoretical timing for Dose 2 (ie, 4 weeks after Dose 1 of the cycle).
4. Patients without clinical benefit after the current cycle will have another diagnostic CT scan and brain MRI (if indicated) at Week 11, which will be EOT.
5. Brain MRI will only be performed in patients with known brain metastases.

CT = computed tomography; EOT = End of Treatment; MRI = magnetic resonance imaging; NA = not applicable; PD = pharmacodynamic(s); SAF = Safety Analysis Set; SPECT = single photon emission computed tomography; WB = whole body.

3.1.2 Dose Expansion Phase

3.1.2.1 Screening

Following the completion of the dose escalation phase and determination of the MTD or RDP2, the study will be expanded so that a total of at least 52 patients will be exposed to the dose chosen to be taken forward. Of the included patients with advanced/metastatic breast cancer, at least 10 to 12 patients should have measurable brain metastases. The number of patients with gastric or GEJ cancer and brain metastases is not pre-set.

Patients will be screened for study eligibility over 2 different study visits (Visit 1 and Visit 2) in the 29 days prior to dosing (ie, Day -28 to Day 0 of Cycle 1). Visit 2 should occur preferably within the 14 days prior to study drug administration (Visit 3). All patients will undergo pre-treatment imaging for eligibility and baseline at Visit 1 with a diagnostic CT scan for RECIST version 1.1. Patients with known brain metastases will undergo a brain MRI scan, in addition to the diagnostic CT, for RANO-BM.

As in the dose escalation phase, the screening period may be extended up to an additional 2 weeks upon Sponsor approval in certain exceptional cases (eg, to allow for a repeat blood draw or to assess previously unavailable imaging results) following a discussion between the Principal Investigator, Medical Monitor, and Sponsor.

3.1.2.2 CAM-H2 administration

In the dose expansion phase of the study, the patients will be given the RDP2 determined in the dose escalation phase. Similar to the dose escalation phase, all patients will receive at least 1 cycle of CAM-H2. Patients with CB may receive up to 2 cycles of CAM-H2, as long as the cumulative kidney dose remains <23 Gy (based on the dosimetry results during Cycle 1 of dose escalation), each cycle given as 2 IV administrations, 4 weeks apart. However, if a patient misses a dose of study drug due to study drug production problems or due to other circumstances (in certain cases), the interval between doses may be extended up to 6 weeks (see Section 3.1.5.3).

Patients will be admitted to a radioactive unit for hospitalization during each IV administration for a total of 48 hours. This hospitalization can be shortened if ^{131}I decay and the patient's clearance allow discharge according to the applicable local regulations on radioactive compound exposure. Ancillary treatments to be given with CAM-H2 include thyroid-blocking drugs, premedication therapy (anti-emetic, anti-histamine, and anti-pyretic therapy), saline infusion, and amino acid infusion.

Cycle 1 will consist of the following:

- Dose 1 of CAM-H2: Visit 3 (Week 0);
- Safety Follow-Up Period: Visit 4 (Week 1), Visit 5 (Week 2), and Visit 6 (Week 3);
- Dose 2 of CAM-H2: Visit 7 (Week 4); and
- Safety Follow-Up Period: Visit 8 (Week 5), Visit 9 (Week 6), Visit 10 (Week 8), and Visit 11 (Week 11) (EOT Visit or Cycle 2 eligibility assessment).

If the patient has CB, an additional cycle may be initiated within 2 weeks after the EOT Visit of Cycle 1, once the necessary Visit 11 (Week 11) safety follow-up assessments have been completed

and reviewed. If the patient does not have CB, no further treatment will be administered and the patient will enter the long-term follow-up period.

If the patient has CB, Cycle 2 will then be initiated as follows:

- Dose 1 of CAM-H2: Visit 12 (Week 0);
- Safety Follow-Up Period: Visit 13 (Week 1), Visit 14 (Week 2), and Visit 15 (Week 3);
- Dose 2 of CAM-H2: Visit 16 (Week 4); and
- Safety Follow-Up Period: Visit 17 (Week 5), Visit 18 (Week 6), Visit 19 (Week 8), and Visit 20 (Week 11) (EOT Visit).

3.1.2.3 Imaging

As in the dose escalation phase, all imaging will be sent to the central imaging core laboratory for independent review as soon as possible within 48 hours of acquisition. Further instructions will be provided by the imaging core laboratory in separate guidelines.

Patients in the dose expansion phase will undergo planar WB scans, SPECT/CT scans, diagnostic CT scans, and brain MRIs, as shown in Table 2. As in the dose escalation phase, imaging to evaluate the organ/target lesion uptake will be performed after each CAM-H2 administration; however, it will be performed less frequently. Imaging to evaluate disease progression will be performed as done in the dose escalation phase (see Section 3.1.1.3).

Table 2. Imaging During the Dose Expansion Phase

Type of Imaging	Cycle 1	Cycle 2
Planar WB scans for PD distribution and evaluation of organ/target lesion uptake	After each dose (Dose 1 and Dose 2): • 24 hours (±4 hours) after CAM-H2 [1].	After each dose (Dose 1 and Dose 2): • 24 hours (±4 hours) after CAM-H2 [1].
SPECT/CT scans to evaluate organ/target lesion uptake	After each dose (Dose 1 and Dose 2): • 24 hours (±4 hours) after CAM-H2.	NA
Diagnostic CT scans to evaluate disease status	At screening and after Dose 2 only [2]: • 4 weeks after CAM-H2 at Visit 10 (Week 8); and • Every 8 weeks after Visit 10 (Week 8), as long as the patient had clinical benefit after Cycle 1 [3] and there is no disease progression.	After Dose 2 only [2]: • 4 weeks after CAM-H2 at Visit 19 (Week 8); • At Visit 20 (Week 11/EOT); and • Every 8 weeks after Visit 20 (Week 11), as long as there is no disease progression.
Brain MRI scans to evaluate disease status [4]	At screening and after Dose 2 only [2]: • 4 weeks after CAM-H2 at Visit 10 (Week 8); and • Every 8 weeks after Visit 10 (Week 8), as long as the patient had clinical benefit after Cycle 1 [3] and there is no disease progression.	After Dose 2 only [2]: • 4 weeks after CAM-H2 at Visit 19 (Week 8); • At Visit 20 (Week 11/EOT); and • Every 8 weeks after Visit 20 (Week 1), as long as there is no disease progression.

1. During Dose 1 of the cycle, the first planar WB scan will also serve as the PD distribution scan.
2. Imaging to evaluate disease status after treatment will start 4 weeks after the last CAM-H2 infusion (Dose 2) of the cycle at Week 8. If a patient cannot receive Dose 2 of a given cycle, his/her imaging to evaluate disease status will start at the theoretical timing for Dose 2 (ie, 4 weeks after Dose 1 of the cycle).
3. Patients without clinical benefit after Cycle 1 will have another diagnostic CT scan and brain MRI (if indicated) at Visit 11 (Week 11), which will be EOT.
4. Brain MRI will only be performed in patients with known brain metastases.

CT = computed tomography; EOT = End of Treatment; MRI = magnetic resonance imaging; NA = not applicable; PD = pharmacodynamic(s); SPECT = single photon emission computed tomography; WB = whole body.

3.1.3 Long-Term Follow-Up Period

A long-term follow-up period will start after the EOT/Early Termination (ET) Visit. Follow-up will continue for a maximum of 12 months. All patients without disease progression will be monitored every 8 weeks to evaluate PFS for a maximum of 12 months or until disease progression, death, or consent is withdrawn, whichever occurs first.

The bi-monthly visits will consist of imaging to evaluate disease status, performance status evaluation using the Eastern Cooperative Oncology Group performance status (ECOG PS), and assessment for any post-investigational treatment. Other changes in medical history or concomitant medications and AEs will be assessed. Imaging to evaluate disease status will begin 8 weeks after the last diagnostic CT scan or brain MRI performed during the study treatment period. Diagnostic CT scan will be performed in all patients. Brain MRI will only be performed in patients with known brain metastases. Patients with extracranial lesions will be evaluated for progression using RECIST version 1.1. Patients with brain metastases without extracranial lesions will be evaluated for progression using RANO-BM. Patients with extracranial lesions and brain metastases will be evaluated for progression using both RECIST version 1.1 (extracranial lesions) and RANO-BM (brain metastases). Additional details are provided in the Imaging Review Charter.

As long as there is no disease progression, imaging to evaluate disease status will be performed every 8 weeks.

For patients with disease progression or starting alternative anticancer therapy, imaging to evaluate disease status will be performed according to the local site standard of care. Review of images at this point will be done locally and not by the central imaging core laboratory. Additionally, those patients will no longer be followed every 8 weeks, but every 12 weeks, to assess survival, disease status, and post-progression therapy. Follow-up contacts (by clinic visits or telephone call) will be performed every 12 weeks until death, lost to follow-up, study end (12 months post-last patient EOT/ET Visit), or study termination by the Sponsor, whichever occurs first.

3.1.4 Dose Escalation Rules and Dose Staggering Approach

Dose staggering will be applied for all cohorts during dose escalation. The first dose of the first patient will be administered at least 2 weeks before the first dose of the remainder of the cohort. After the review of AEs, dosimetry reports, vital signs, and electrocardiograms (ECGs) collected over 2 weeks, the remaining 2 patients of the cohort may receive the same dose level. Following completion of the initial safety assessments for the sentinel patient, the decision to proceed with the remaining patients in that cohort will be discussed and mutually agreed upon between the Investigator (or his/her designee) and the Sponsor. The decision of whether to escalate to the next dose will be formally confirmed by the Sponsor.

The proposed minimum 2 weeks between the sentinel patient and the remainder of the cohort is deemed sufficient as each dose of the cycle is a single IV administration, and it is expected that the most severe and acute reactions will occur during or soon after the infusion. Based on animal studies, potential side effects are expected to be related to high activity levels in the kidneys, that will decline rapidly after ending the IV infusion.

At each dose level, after completion of 1 cycle (2 doses) of CAM-H2 administration in at least 3 patients, each Investigator will provide a comprehensive Investigator Safety Report for his/her patients including (but not limited to) the following content:

- Relevant information on patients' demographics, characteristics, medical history, physical examination, and concomitant medications;
- List of all AEs, including severity, time of onset related to study drug administration, and duration, clearly highlighting serious adverse events (SAEs) and relatedness and causality of all AEs;
- Any clinically significant out of range clinical laboratory test results (as assessed by the Investigator);
- Neurological examination results including clinical significance for abnormal findings;
- ECG and vital sign results including clinically significant abnormal values; and
- Statement of the Principal Investigator's recommendation regarding dose decision.

Escalation to the next higher dose will only take place after review of the Investigator Safety Reports from the previous dose levels by the respective Investigators, in consultation with the Sponsor's representative (called hereafter the Safety Review Committee [SRC]). Dose escalation

will be based on dosimetry and emerging safety and tolerability data as defined by AEs, laboratory results, ECGs, and vital signs. Other parameters of interest will be considered ad hoc.

3.1.4.1 Definition of dose-limiting toxicities

DLTs are defined as toxicities occurring **only** within Cycle 1 (ie, the approximately 12-week [84-day] period that includes 2 administrations of the study drug given 4 weeks apart [including the 4-week Safety Follow-Up Period after Dose 1]). DLTs include ≥1 of the following:

- Study drug-related SAE in at least 1 patient in 1 cohort;
- Severe study drug-related AE in at least 2 patients in 1 cohort;
- Any death not clearly due to the underlying disease or extraneous causes;
- Development of severe renal failure (estimated glomerular filtration rate [eGFR] <30 mL/min) or a drop of >40 mL/minute in eGFR;
- Any seizure activity that is considered to be study drug-related;
- Grade 3+ thrombocytopenia with bleeding;
- Recurrent (defined in this study as occurring after >1 dose of CAM-H2 during Cycle 1) Grade 3 or 4 thrombocytopenia;
- Grade 4+ neutropenia or thrombocytopenia >7 days;
- Recurrent (defined in this study as occurring after >1 dose of CAM-H2 during Cycle 1) Grade 3 or 4 anemia and/or neutropenia;
- Recurrent (defined in this study as occurring after >1 dose of CAM-H2 during Cycle 1) Grade 3 or 4 non-hematological toxicities as listed in the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0;
- An alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 × upper limit of normal (ULN) accompanied by a total bilirubin of >2 × ULN (Hy's Law);
- Grade 3 or 4 fatigue for >1 week;
- Grade 3 or 4 electrolyte abnormalities that last >72 hours or any Grade 3 or 4 electrolyte abnormalities associated with clinical signs and symptoms of any duration;
- For patients with hepatic metastases, AST or ALT >8 × ULN or AST or ALT >5 × ULN for ≥14 days;
- An absorbed dose to the kidneys >23 Gy;
- An absorbed dose to the bone marrow >2 Gy; or
- Other clinically significant changes in vital signs, clinical laboratory tests, ECGs, or other safety parameters deemed as a significant safety concern by the Investigator.

All AEs of the specified grades will count as DLTs, except those that are clearly and incontrovertibly due to disease progression or extraneous causes.

3.1.4.2 Dose escalation rules

DLTs will determine the progression/escalation with the following rules:

- If 0 out of 3 patients experience a DLT, all patients will proceed to the next higher dose level;
- If 1 out of 3 patients experiences a DLT, the same dose will be given to 3 new patients:
  - If 0 of the 3 new patients experience a DLT, all patients will proceed to the next higher dose level; and/or
  - If 1 or more of the 3 new patients experiences a DLT (≥2 of the 6 patients) this dose will become the MTD + 1.
- If ≥2 out of 3 patients experience a DLT, the MTD has been exceeded and a lower dose should be tested between this dose and the previous dose level;
- Once the MTD + 1 has been established, 3 additional patients will be exposed to the dose below the MTD + 1; and
- If the MTD + 1 is not reached, 3 additional patients will be exposed to the highest dose.

Within the planned dose range, a dose lower than the next planned dose may also be tested, depending on emerging safety, tolerability, and/or other relevant data, such as dosimetry or PD. If the highest planned dose level is found to be safe and tolerable, also considering the PD data, additional higher doses may be added by amendment.

A period of at least 4 weeks will be maintained between 2 consecutive cohorts.

3.1.5 Stopping Rules, Dose Modifications, and Missed Doses

3.1.5.1 Stopping rules

During the dose escalation phase, the SRC will meet to decide on the continuation of dosing after the completion of 1 full treatment cycle in at least 3 patients at each dose level. During the dose expansion phase, the SRC will formally meet after the completion of 1 full treatment cycle in every 9 patients to review all emerging safety and tolerability data. All data must be available to the SRC ≤3 weeks after the last dose in the cohort. Additional details are described in the SRC Charter.

Safety and tolerability data; however, will be reviewed on an ongoing basis by the Medical Monitor, and stopping rules will be applicable starting with dosing of the first sentinel patient. SRC decisions will be based on the following:

- If a study drug-related SAE occurs in 1 patient or if a study drug-related severe AE occurs in 2 patients in the same cohort, the dosing in the study should be temporarily stopped in order to review additional safety data. If after review of the additional data, the study drug-relatedness assessment changes, the study can resume without substantial amendment;
- If 2 patients in a cohort experience a DLT that is related to CAM-H2 administration, dosing will be stopped until resolution of the DLT. Doses can be adapted as per the modification schemes in Section 3.1.5.2;

- If at least 1 DLT is reported, the SRC recommendation will depend on the DLT profile (ie, identical DLTs in different patients), the frequency and severity of DLTs in the same patient, and the recommendation made by the Investigator; and
- If no DLT is reported, the planned dose escalation may proceed with the next cohort or phase, unless the Investigator has any other safety concerns.

All decisions will be documented in writing and communicated to the study team in a timely manner before dosing in the next cohort can start.

3.1.5.2 Dose modifications

The following dose modifications will be implemented in case of toxicities:

- Grade 2, 3, or 4 thrombocytopenia:
  - Withhold dosing until resolution to Grade 0 or 1;
  - Resume CAM-H2 at 50% with complete or partial resolution;
    - If a reduced dose does not result in Grade 2, 3, or 4 thrombocytopenia, administer CAM-H2 at the full planned dose for next cycle.
  - Permanently discontinue CAM-H2 for Grade 2 or higher thrombocytopenia requiring a treatment delay of 12 weeks or longer; and
  - Permanently discontinue CAM-H2 for recurrent (defined in this study as occurring after >1 dose of CAM-H2 during Cycle 1) Grade 2, 3, or 4 thrombocytopenia.
- Grade 3 or 4 anemia and neutropenia:
  - Withhold dosing until resolution to Grade 0, 1, or 2;
  - Resume CAM-H2 at 50% in patients with complete or partial resolution;
    - If a reduced dose does not result in Grade 3 or 4 anemia or neutropenia, administer CAM-H2 at full planned dose for next cycle.
  - Permanently discontinue CAM-H2 for Grade 3 or higher anemia or neutropenia requiring a treatment delay of 12 weeks or longer; and
  - Permanently discontinue CAM-H2 for recurrent (defined in this study as occurring after >1 dose of CAM-H2 during Cycle 1) Grade 3 or 4 anemia or neutropenia.
- Renal toxicity (defined as an eGFR <40 mL/minute or a 40% decrease in baseline eGFR):
  - Withhold dosing until resolution to at least 80% of baseline eGFR;
  - Resume CAM-H2 at 50% in patients with complete or partial resolution;
    - If a reduced dose does not result in another decrease of eGFR, administer CAM-H2 at the full, planned dose for next cycle.
  - Permanently discontinue CAM-H2 for eGFR decreases requiring a treatment delay of 12 weeks or longer; and
  - Permanently discontinue CAM-H2 for recurrent (defined in this study as occurring after >1 dose of CAM-H2 during Cycle 1) toxicity.

- Hepatic toxicity (Hy's Law cases):
  - Withhold dosing until resolution to ALT and AST values <2 × baseline and total bilirubin values of <1.5 × ULN;
  - Resume CAM-H2 at 50% in patients with complete or partial resolution;
    - If a reduced dose does not result in another transaminase or total bilirubin increase, administer CAM-H2 at full planned dose for next cycle.
  - Permanently discontinue CAM-H2 for transaminase or total bilirubin decreases requiring a treatment delay of 12 weeks or longer; and
  - Permanently discontinue CAM-H2 for recurrent (defined in this study as occurring after >1 dose of CAM-H2 during Cycle 1) toxicity.
- Hepatic toxicity (patients with hepatic metastases and AST or ALT >8 × ULN or AST or ALT >5 × ULN for ≥14 days):
  - Withhold dosing until resolution to ALT and AST values of <1.2 × baseline and total bilirubin values of <1.5 × ULN;
  - Resume CAM-H2 at 50% in patients with complete or partial resolution;
    - If a reduced dose does not result in another transaminase or total bilirubin increase, administer CAM-H2 at full planned dose for next cycle.
  - Permanently discontinue CAM-H2 for transaminase or total bilirubin decreases requiring a treatment delay of 12 weeks or longer; and
  - Permanently discontinue for recurrent (defined in this study as occurring after >1 dose of CAM-H2 during Cycle 1) toxicity.
- Grade 3 or 4 non-hematological toxicities as listed in the CTCAE version 5.0:
  - Withhold dosing until resolution to Grade 0, 1, or 2;
  - Resume CAM-H2 at 50% in patients with complete or partial resolution;
    - If a reduced dose does not result in Grade 3 or 4 toxicity, administer CAM-H2 at full planned dose for next cycle.
  - Permanently discontinue CAM-H2 for Grade 3 or higher toxicity requiring a treatment delay of 12 weeks or longer; and
  - Permanently discontinue for recurrent (defined in this study as occurring after >1 dose of CAM-H2 during Cycle 1) Grade 3 or 4 toxicities.

3.1.5.3 Missed doses

Cycles 1 and 2

During Cycles 1 and 2 (for both the dose escalation and dose expansion phases), if a patient misses Dose 1 of study drug due to study drug production problems (eg, insufficient activity yield, ^{131}I supply problem), the interval between screening and first dosing (Cycle 1) and/or the interval between the cycle eligibility assessment and first dosing (Cycle 2) may be extended up to an additional 2 weeks to allow for the production of a new batch of study drug. If the patient was eligible per protocol, no screening procedures will be repeated unless deemed necessary following a discussion between the Principal Investigator, Medical Monitor, and Sponsor.

Similarly, if a patient misses Dose 2 of the study drug during Cycles 1 or 2 due to study drug production problems, the interval between Dose 1 and Dose 2 may be extended up to an additional 2 weeks (ie, Dose 2 may occur up to 6 weeks after Dose 1). Safety Follow-Up visits after Dose 2 will be scheduled based on the actual Dose 2 visit date.

Cycles 3 and 4

During Cycles 3 and 4 (for the dose escalation phase), if a patient misses Dose 1 of study drug due to study drug production problems (eg, insufficient activity yield, ^{131}I supply problem), the interval between the cycle eligibility assessment and first dosing may be extended up to an additional 8 weeks to allow for the production of a new batch of study drug.

Similarly, if a patient misses Dose 2 of the study drug during Cycles 3 or 4 due to study drug production problems, the interval between Dose 1 and Dose 2 may be extended up to an additional 8 weeks (ie, Dose 2 may occur up to 12 weeks after Dose 1). Safety Follow-Up visits after Dose 2 will be scheduled based on the actual Dose 2 visit date.

All cycles

In cases of a missed dose of study drug due to other circumstances unrelated to study drug or procedures (eg, secondary to scheduling conflict, missed appointment), the Investigator should contact the Sponsor or designee to discuss available options in order to make a decision in the patient's best interest. The decision will be documented for the study and site files.

4 SELECTION AND WITHDRAWAL OF PATIENTS

4.1 Inclusion Criteria

Patients who meet all of the following criteria will be eligible to participate in the study:

1. Informed consent form (ICF) signed voluntarily before any study-related procedure is performed, indicating that the patient understands the purpose of, and procedures required for, the study and is willing to participate in the study;
2. Males and females ≥18 years of age at screening;
3. ECOG PS of 0 to 1 (see Appendix C);
4. HER2-positive locally advanced or metastatic breast cancer refractory to standard cancer treatment or HER2-positive locally advanced or metastatic gastric or GEJ cancer, refractory to standard cancer treatment;
5. Patients should have a minimum of 1 measurable lesion as defined by RECIST version 1.1 or a minimum of 1 measurable lesion as defined by RANO-BM within 4 weeks of the first dose of the study drug (Day 1). The lesion has to be a new lesion or progression of an existing lesion under the current therapy;
6. Any previous anti-HER2 treatment for advanced or metastatic disease is allowed. Patients with breast cancer should have had at least 2 previous systemic anticancer treatments for recurrent, locally advanced or metastatic cancer. Patients with gastric cancer or GEJ cancer should have had at least 1 previous anti-HER2 treatment;
7. Life expectancy >6 months;
8. Adequate organ function, determined by the following laboratory tests at screening:
    - Adequate kidney function with an eGFR of >59 mL/minute calculated using the Chronic Kidney Disease Epidemiology Collaboration equation;[12]
    - Adequate hepatic function defined as an ALT and AST <2.5 × ULN, or <5 × ULN in patients with liver metastases, and total bilirubin <2 × ULN;
    - Neutrophil count >1500 cells/mm^3 without growth factor support (14 days after last pegylated granulocyte colony-stimulating factor or 7 days after regular granulocyte colony-stimulating factor);
    - Platelet count >100,000 cells/mm^3 without platelet transfusion in the last 2 weeks;
    - Hemoglobin >9.0 g/dL without blood transfusion in the last 2 weeks; and
    - Adequate coagulation defined as an international normalized ratio (INR) ≤1.5 and activated partial thromboplastin time <1.5 × the upper limit of the institutional normal range;
9. Baseline left ventricular ejection fraction (LVEF) ≥50% as measured by echocardiography or multigated acquisition scan;

10. Absence of any psychological, family, sociological, or geographical circumstance that could potentially represent an obstacle to compliance with the study protocol and the follow-up schedule, as determined by the Investigator. These circumstances will be discussed with the patient before enrollment in the study; and
11. Female patients of childbearing potential (ie, ovulating, premenopausal, and not surgically sterile) must have a negative pregnancy test at screening and prior to study drug administration. Patients and their partners of childbearing potential must be willing to use 2 methods of contraception, 1 of which must be a barrier method, for the duration of the study and until 6 months after study drug administration. Medically acceptable barrier methods include condom with spermicide or diaphragm with spermicide. Medically acceptable non-barrier contraceptive methods include intrauterine devices or hormonal contraceptives (oral, implant, injection, ring, or patch).

4.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from participation in the study:

1. Presence of frank leptomeningeal disease as a unique central nervous system feature or in association with brain parenchymal measurable lesion(s);
2. Symptomatic brain metastases;

   Note: Patients with asymptomatic treated and untreated brain metastases are eligible.
3. Previous local therapy for brain metastases, such as neurosurgery, stereotactic radiotherapy, or whole brain radiotherapy, administered within 6 weeks prior to administration of CAM-H2;

   Note: Previous therapy for brain metastases administered at least 6 weeks prior to CAM-H2 administration will be allowed.
4. For patients with brain metastases, any increase in corticosteroid dose during the 4 weeks prior to the first administration of CAM-H2;

   Note: Corticosteroid treatment in a stable dose or decreasing dose for at least 4 weeks prior to the first administration of CAM-H2 is allowed.
5. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection requiring parenteral antibiotics or psychiatric illness/social situations that would limit compliance with study requirements;
6. Uncontrolled thyroid disease, defined as free triiodothyronine (T3) and free thyroxine (T4) >3 × ULN at screening;
7. Uncontrolled diabetes defined as a fasting serum glucose >2 × ULN or glycated hemoglobin levels >8.5% at screening;
8. Gastrointestinal (GI) tract disease resulting in an inability to take oral medication, malabsorption syndrome, a requirement for IV alimentation, prior surgical procedures affecting absorption, or uncontrolled inflammatory GI disease (eg, Crohn's, ulcerative colitis);
9. Current active hepatic or biliary disease (exception of patients with Gilbert's syndrome, asymptomatic gallstones, liver metastases, or stable chronic liver disease per Investigator assessment);

10. Ongoing peripheral neuropathy of Grade >2 according to the CTCAE version 5.0;
11. Severe and/or uncontrolled medical conditions or other conditions that could affect participation in the study such as:
    - Symptomatic congestive heart failure of New York Heart Association Class III or IV;
    - Unstable angina pectoris, symptomatic congestive heart failure, myocardial infarction within 6 months of start of study drug, serious uncontrolled cardiac arrhythmia, or any other clinically significant cardiac disease; or
    - Liver disease, including cirrhosis and severe hepatic impairment;
12. Active (acute or chronic) or uncontrolled severe infections;
13. Known history of HIV, hepatitis B, or active hepatitis C virus at screening;
14. Prior investigational anticancer therapy within 4 weeks prior to the first administration of CAM-H2;
15. Patients who have had a major surgery or significant traumatic injury within 4 weeks prior to the first administration of CAM-H2, who have not recovered from side effects of any major surgery (defined as requiring general anesthesia), or have a major surgery planned during the course of the study;
16. Other malignancies within the past 3 years except for adequately treated carcinoma of the cervix or basal or squamous cell carcinomas of the skin or stage I uterine cancer;
17. Radiation therapy for metastatic disease foci outside the brain, administered within 3 weeks prior to the first administration of CAM-H2;
18. Known hypersensitivity to any of the study drugs (including inactive ingredients) including iodine allergy;
19. History of significant comorbidities that, in the Investigator's judgement, may interfere with study conduct, response assessment, or informed consent;
20. Unable or unwilling to complete the study procedures;
21. Patients that cannot be hospitalized in a radionuclide therapy room;
22. Patients with urinary incontinence;
23. Patients that are unable to comply with thyroid protective pre-medication;
24. Patients in whom bladder catheterization cannot be performed, or in patients who are unwilling to be catheterized if necessary;
25. Patients with contraindications for undergoing MRI or CT, including for receiving contrast agents; or
26. Patient is the Investigator or sub-Investigator, research assistant, pharmacist, study coordinator, or other staff or relative thereof, who is directly involved in the conduct of the study.

4.3 Withdrawal Criteria

Participation of a patient in this clinical study may be discontinued for any of the following reasons:

- Withdrawal of consent or a request to discontinue from the study for any reason;
- Occurrence of any medical condition or circumstance that exposes the patient to substantial risk and/or does not allow the patient to adhere to the requirements of the protocol;
- Occurrence of any SAE, clinically significant AE, severe laboratory abnormality, intercurrent illness, or other medical condition which indicates to the Investigator that continued participation is not in the best interest of the patient;
- Pregnancy;
- Requirement of prohibited concomitant medication;
- Patient failure to comply with protocol requirements or study-related procedures; or
- Termination of the study by the Sponsor or the regulatory authority.

If a patient withdraws prematurely from the study due to the above criteria or any other reason, study staff should make every effort to complete the full panel of assessments scheduled for the EOT Visit (Visit 11 in Cycle 1 or Visit 20 in Cycle 2 of either the dose escalation or dose expansion phases). The reason for patient withdrawal must be documented in the electronic case report form (eCRF).

In the case of patients lost to follow-up, a minimum of 3 attempts to contact the patient (ie, 2 phone calls and 1 certified letter) must be made and documented in the patient's eCRF.

Withdrawn patients may be replaced to ensure adequate numbers of evaluable patients at the discretion of the Sponsor with agreement from the Investigator.

5 STUDY TREATMENTS

5.1 Dose Groups

The planned dose levels of CAM-H2 to be used in the dose escalation phase are demonstrated in Table 3. All patients will receive at least 1 cycle of CAM-H2. During the dose escalation phase, patients with CB may receive up to 4 cycles of CAM-H2, as long as the cumulative kidney dose remains <23 Gy (based on the dosimetry results during Cycle 1).

The dose escalation phase of the study will be an open-label 3 + 3 design, where at least 3 patients are treated at each dose level. Dose escalation will be done via increases of the nominal activity of CAM-H2 in cohorts of 3 to 6 patients.

Staggered dosing will be applied for all cohorts during dose escalation. The first dose of the first patient of a cohort will be administered at least 2 weeks before the first dose of the next 2 patients (sentinel dosing). Dose levels per cycle will start at 2 × 1.85 GBq (2 × 50 mCi) for cohort 1. A maximum dose of 2 × 7.40 GBq (2 × 200 mCi) is planned for cohort 4 if neither the MTD nor RDP2 is reached at cohort 3.

Table 3. Dose Escalation Schedule for Each CAM-H2 Cycle

Dose Level	Activity of CAM-H2 (GBq) [1]	Activity of CAM-H2 (mCi) [1]
Level 1 (starting activity)	2 × 1.85	2 × 50
Level 2	2 × 3.7	2 × 100
Level 3	2 × 5.55	2 × 150
Level 4 [2]	2 × 7.4	2 × 200

1. Doses will be given 4 weeks apart. All patients will receive at least 1 cycle of CAM-H2.
2. Level 4 dosing will be optional, depending on overall safety, tolerability, and dosimetry.

In the dose expansion phase of the study, the patients will be given the RDP2 determined in the dose escalation phase. Similar to the dose escalation phase, all patients will receive at least 1 cycle of CAM-H2. During the dose expansion phase, patients with CB may receive up to 2 cycles of CAM-H2, as long as the cumulative kidney dose remains <23 Gy (based on the dosimetry results during Cycle 1 of dose escalation).

5.2 Drug Supplies

5.2.1 Formulation and Packaging

CAM-H2 contains the radioactive [^{131}I]-GMIB-2Rs15d. Dosing of CAM-H2 will be done via dose escalation as described in Section 5.1 for the dose escalation phase. Once the RDP2 is determined, that RDP2 dose will be given in the dose expansion phase.

CAM-H2 will be provided as a clear, sterile solution for IV administration. The solution is provided in a 30 mL round glass vial with a rubber stopper and aluminum seal. The vial is then covered with a 2-piece lead pig, closed with 2 metal screws, and wrapped in protective bubble wrap. See the Investigator's Brochure or Investigational Medicinal Product manual for more information.

CAM-H2 will be manufactured and prepared for administration at the manufacturing unit for direct supply to the site. The shipment from the manufacturing unit to the site will be within a secondary shielding container and will be temperature-controlled.

Both primary and secondary packaging will be labeled in accordance with local regulations.

5.2.2 Study Drug Administration

Two plastic IV catheters should be inserted into the patient's peripheral veins using 2 different lines. The catheters should be connected to the infusion set: 1 for the study drug and 1 for the amino acid infusion. If, for practical reasons, 2 peripheral lines are not possible, the study drug and the amino acid infusion can be administered using a central line (dual lumen catheter) or a single peripheral catheter. In case of a single peripheral catheter, the amino acid infusion needs to be temporarily halted during the study CAM-H2 infusion and resumed once the catheter has been flushed. In any case, separate lines are to be prepared to minimize the mixing of substances. If a patient has a port-a-cath (or equivalent) system, then this entry port can be used for the amino acid (and saline) infusion.

The study drug will be administered at the sites by qualified study personnel. CAM-H2 is injected via a slow IV infusion. The study drug will be administered using a shielded infusion device over approximately 3 to 30 minutes, depending on the volume to be injected. The study drug can be infused at a rate compatible with the radioprotection guidance for site staff and in a time adequate to ensure patient safety. The time can be reduced to 1 minute if deemed feasible by the Investigator, depending on the total volume to be infused.

5.2.2.1 Radioprotection rules

CAM-H2 should always be infused through an IV catheter placed exclusively for its infusion. The adequate position of the catheter should be checked before and during infusion.

Patients will be admitted to a radioactive unit for hospitalization during each IV administration for a total of 48 hours. This hospitalization can be shortened if ^{131}I decay and the patient's clearance allow discharge according to the applicable local regulations on radioactive compound exposure. Each patient treated with CAM-H2 should be kept away from others during the administration and up to reaching the radiation emission limits stipulated by applicable laws. The nuclear medicine physician should determine when the patient can leave the controlled area of the hospital (ie, when the radiation exposure to third parties does not exceed regulatory thresholds).

The patient should be encouraged to urinate as much as possible after study drug administration. Patients should be instructed to drink substantial quantities of water (ie, 1 glass every hour) on the day of infusion and the day after infusion to facilitate elimination. The patient should also be encouraged to defecate every day and to use laxatives if needed. Urine and feces should be disposed according to the national regulations.

As long as the patient's skin is not contaminated, such as from the leakage of the infusion system or because of urinary incontinence, radioactivity contamination is not expected on the skin or vomited mass. However, it is recommended that when conducting standard of care procedures or examinations with medical devices or other instruments which contact the skin (eg, ECG), basic protection measures are observed, including wearing gloves, installing the material or electrode before the start of radiopharmaceutical infusion, changing the material or electrode after measurement, and monitoring the radioactivity of equipment after use.

Before the patient is released, the nuclear physician should explain the necessary radioprotection rules of interacting with family members and third parties and the general precautions the patient must follow during daily activities after treatment to minimize radiation exposure to others. A leaflet containing this information, which is in accordance with the Practice Recommendations of the American Thyroid Association,[13] will be distributed (see Appendix F).

Close contact with other people should be restricted during the 7 days following an administration of the study drug. For children and pregnant women, patient contact should be limited to less than 15 minutes daily while keeping a distance of at least 1 meter. Patients should sleep in a separate bedroom from other individuals for at least 7 days, or at least 15 days in the case of children or pregnant partners.

Recommended measures in case of extravasation

In the case of extravasation of study drug, disposable waterproof gloves should be worn, the infusion of the study drug must be immediately ceased, and the administration device (eg, catheter) must be removed. The nuclear medicine physician and the radiopharmacist should be informed.

All the administration device materials should be kept in order to measure the activity actually administered and eventually the absorbed dose. The extravasation area should be delimited with an indelible pen and a picture should be taken if possible. It is also recommended to record the time of extravasation and the estimated volume extravasated. To continue study drug infusion, it is mandatory to use a new catheter, possibly placing it in a contralateral venous access.

No additional medicinal product can be administered to the same side where the extravasation occurred. In order to accelerate medicinal product dispersion and to prevent its stagnation in tissue, it is recommended to increase blood flow by elevating the affected arm. Depending on the case, the aspiration of extravasation fluid, a flush injection of sodium chloride 9 mg/mL (0.9%) solution, or the application of warm compresses or a heating pad to the infusion site to accelerate vasodilation should be considered.

Symptoms, especially inflammation and/or pain, should be treated. Depending on the situation, the nuclear medicine physician should inform the patient about the risks linked to extravasation injury and give advice about potential treatment and necessary follow-up requirements. The extravasation area must be monitored until the patient is discharged from the hospital. Depending upon its seriousness, this event should be declared as an adverse reaction.

5.2.3 Treatment Compliance

Study drug will be administered at the site by a qualified staff member. The exact times of study drug administration and the dose administered will be recorded in the eCRF.

Total activity administered will be equal to the activity in the vial before the infusion minus the activity remaining in the vial after the infusion. The measurements should be performed using a calibrated system. See the Pharmacy Manual for the exact procedure.

5.2.4 Storage and Accountability

CAM-H2 may be stored at room temperature but is also stable below ≤-70°C. CAM-H2 has a shelf life of 144 hours after production. The vial should never be stored in an inverted orientation.

CAM-H2 will be stored in a secure area with access limited to authorized personnel. The site will perform an ongoing inventory of study drug on behalf of Precirix NV. The responsible staff at the site will keep an accurate inventory of study drug shipments received and the amount of study drug used per patient. A full reconciliation of study drug inventory will be performed at the end of the study and the results of the inventory recorded.

See the Pharmacy Manual for more information.

5.2.5 Ancillary Treatments to be Given With CAM-H2

5.2.5.1 Thyroid-blocking drugs

Acceptable thyroid-blocking drugs and their recommended doses are presented in Table 4. Patients will not always take the thyroid-blocking drugs on the same day that they are delivered. All patients will take potassium iodide 130 mg daily (or equivalent) starting 24 hours before study drug administration, 1 hour before study drug administration, and 24 and 48 hours after study drug administration as indicated. Depending on the site's standard operating procedures and local availability, this formulation can be adapted as per applicable guidance.

Confirmation of ingestion of thyroid-blocking drugs will be performed by directly asking the patient and by counting pills left in his/her medication bottle.

Table 4. Thyroid-Blocking Drugs

Compound	Formulation	Daily Dose
Potassium iodate	Capsule	170 mg
Potassium iodide	Capsule	130 mg
Lugol's 1%	Solution	1 drop/kg to a maximum of 40 drops (20 drops twice daily)
Potassium perchlorate	Capsule	400 mg

5.2.5.2 Anti-emetic, anti-histamine, and anti-pyretic premedication therapy

Anti-emetic, anti-histamine, and anti-pyretic premedication should be administered approximately 30 minutes prior to the start of the amino acid infusion during the study, according to the site's standard operating procedures.

Sites will administer ondansetron 8 mg IV (or equivalent), diphenhydramine 50 mg IV (or equivalent anti-histamine dose orally), and acetaminophen or paracetamol 500 to 1000 mg orally.

In the case of severe nausea or vomiting during the study drug or amino acid infusion, additional anti-emetic therapy can be initiated as per local procedures.

5.2.5.3 Saline infusion

Saline 0.9% infusion will be initiated 30 minutes prior to study drug administration and continued for up to 3 hours after, at a rate of 200 to 300 mL/hour.

5.2.5.4 Amino acid infusion

Administration of the amino acid solution should be initiated 30 minutes prior to study drug administration with an infusion rate of 250 to 500 mL/hour. Amino acid solution infusion should be continued for 3 hours after study drug administration. Rates lower than 320 mL/hour are not recommended for commercial solutions.

If needed, in case of poor venous access, a 3-way stopcock may be used for the amino acid infusion, the study drug, and saline. The dose of the amino acid solution should not be decreased if the dose of CAM-H2 is reduced.

The amino acid solution will be prepared as a compounded product, in compliance with the hospital's sterile medicinal product preparation good practices and according to the composition specified in Table 5.

Table 5. Composition of the Standard Amino Acid Solution

Compound	Amount
Lysine	25 g
Arginine	25 g
Sodium chloride 9 mg/mL solution for injection	1 L

Alternatively, some commercially available amino acid solutions can be used if compliant with the specification described in Table 6.

Table 6. Specification of Commercially Available Amino Acid Solutions

Characteristic	Specification
Lysine content	Between 18 and 24 g
Arginine content	Between 18 and 24 g
Volume	1.5 to 2.2 L
Osmolarity	<1.050 mOsmol

Considering the high quantity of amino acids and the significant volume that commercially available solutions may require to meet the above specifications, the compounded solution is considered the medicinal product of choice, due to its lower total volume to be infused and lower osmolarity.

5.3 Prior and Concomitant Medications and/or Procedures

5.3.1 Excluded Medications and/or Procedures

The excluded medications and/or procedures include the following:

- Local therapy for brain metastases, such as neurosurgery, stereotactic radiotherapy, or whole brain radiotherapy, administered within 6 weeks prior to the first administration of CAM-H2;

  Note: Previous therapy for brain metastases administered at least 6 weeks prior to the first administration of CAM-H2 will be permitted.

- Any major surgery requiring general anesthesia within 4 weeks prior to the first administration of CAM-H2;
- Other investigational anticancer therapy within 4 weeks prior to the first administration of CAM-H2; or
- Radiation therapy for metastatic disease foci outside the brain, administered within 3 weeks prior to the first administration of CAM-H2.

5.3.2 Restricted Medications and/or Procedures

The use of corticosteroid treatment is allowed in patients with known brain metastases, but treatment must be stable for at least 4 weeks prior to the first administration of CAM-H2 or decreasing in dose.

5.3.3 Documentation of Prior and Concomitant Medication Use

All medications, both prescription and non-prescription, taken within 1 month before the first administration of CAM-H2 and at any time during the study, will be recorded in the appropriate eCRF. Prior and concomitant medication use documentation should include information on any thyroid-blocking drugs.

6 STUDY PROCEDURES

A schedule of procedures for all patients is provided in Appendix A. Table 7 and Table 8 describe the procedures performed during the dose escalation phase. Table 9 and Table 10 describe the procedures performed during the dose expansion phase.

6.1 Informed Consent

Informed consent by the patient will be obtained at screening prior to any study assessments or procedures being performed. For additional details regarding informed consent, see Section 11.3.

6.2 Dose Escalation Phase

6.2.1 Screening for the Dose Escalation Phase

6.2.1.1 Visit 1 (Week -4 to Week -1)

The following procedures will be performed at the first screening visit (Week -4 to Week -1) prior to the initiation of the dose escalation phase:

- Obtain informed consent;
- Assess inclusion and exclusion criteria;
- Record demographics and medical history, including confirmation of lesion size;
- Record prior and concomitant medications, including information on any thyroid-blocking drugs;
- Perform serum human chorionic gonadotropin (hCG) testing in all female patients of childbearing potential (ie, ovulating, premenopausal, and not surgically sterile);
- Assess AEs;
- Measure height and weight;
- Perform physical examination;
- Measure vital signs;
- Perform clinical laboratory tests;
- Perform triplicate 12-lead ECGs;
- Perform echocardiogram;

  Note: LVEF may alternatively be measured using a multigated acquisition scan.
- Perform urinalysis for kidney biomarkers and for microscopic evaluation of sediment;
- Assess performance status using the ECOG PS; and
- Perform pre-treatment imaging for eligibility and baseline with diagnostic CT scan and brain MRI (if indicated).

  Note: Diagnostic CT scan will be performed in all patients. Brain MRI will only be performed in patients with known brain metastases.

6.2.1.2 Visit 2 (Week -2 to Week -1)

The following procedures will be performed preferably within the 14 days prior to study drug administration:

- Deliver thyroid-blocking drugs;

  Note: Patients will not take the thyroid-blocking drugs at this visit but will be instructed to take them 24 hours prior to their next visit (ie, 24 hours prior to study drug administration).
- Perform serum hCG testing in all female patients of childbearing potential (ie, ovulating, premenopausal, and not surgically sterile);
- Collect blood to evaluate serum for ADAs and to measure exploratory biomarkers;
- Assess AEs;
- Perform clinical laboratory tests; and
- Perform urinalysis for kidney biomarkers and for microscopic evaluation of sediment.

6.2.2 Cycle 1 of the Dose Escalation Phase

6.2.2.1 Visit 3 (Week 0)

Dose 1 of Cycle 1 will be administered at Visit 3. The following procedures will be performed at Visit 3 (Week 0):

- Admit to radioactive unit for hospitalization prior to study drug administration;

  Note: Patients will be admitted during each IV administration for a total of 48 hours. This hospitalization can be shortened if ^{131}I decay and the patient's clearance allow discharge according to the applicable local regulations on radioactive compound exposure.

  Note: Before the patient is released, a leaflet containing information on radioprotection rules and general precautions after radiation treatment will be distributed (see Appendix F).
- Confirm the ingestion of thyroid-blocking drugs at least 24 hours prior to study drug administration;
- Deliver and confirm the ingestion of thyroid-blocking drugs 1 hour prior to study drug administration;
- Deliver and confirm the ingestion of thyroid-blocking drugs 24 and 48 hours after study drug administration;

  Note: If the patient is discharged prior to 48 hours, deliver the thyroid-blocking drugs for 48 hours at 24 hours. Patients will still take the thyroid-blocking drugs 48 hours after study drug administration.
- Perform urine hCG testing in all female patients of childbearing potential (ie, ovulating, premenopausal, and not surgically sterile) prior to study drug administration;
- Assess AEs;
- Perform physical examination prior to study drug administration and at 24 hours after study drug administration;

- Measure vital signs prior to study drug administration and 30 minutes, 5 hours, 24 hours, and 48 hours after study drug administration;
- Perform clinical laboratory tests 24 hours after study drug administration;

  Note: Clinical laboratory tests should be performed prior to the planar WB scan and SPECT/CT scan scheduled at 24 hours after study drug administration.
- Perform triplicate 12-lead ECGs prior to study drug administration and 48 hours after study drug administration;
- Perform urinalysis for kidney biomarkers and for microscopic evaluation of sediment 24 hours after study drug administration;
- Administer anti-emetic, anti-histamine, and anti-pyretic premedication therapy approximately 30 minutes prior to the start of the amino acid infusion, according to the site's standard operating procedures;
- Administer saline 0.9% infusion, starting 30 minutes prior to study drug administration and continuing for up to 3 hours after, at a rate of 200 to 300 mL/hour;
- Administer an amino acid solution beginning 30 minutes prior to study drug administration and ending 3 hours after study drug administration, at a rate of 250 to 500 mL/hour;
- Administer study drug via slow IV infusion, ie, administer using a shielded infusion device over approximately 3 to 30 minutes, depending on the volume to be injected; and
- Perform a planar WB scan and SPECT/CT scan at 5 (±1) hours, 24 (±4) hours, and 48 (±4) hours after study drug administration.

  Note: The planar WB scan done at 5 hours will also serve as the PD distribution scan.

6.2.2.2 Visit 4 (Week 1)

The following procedures will be performed at Visit 4 (Week 1):

- Assess AEs;
- Perform physical examination;
- Measure vital signs;
- Perform clinical laboratory tests;

  Note: Clinical laboratory tests should be performed prior to any imaging.
- Perform triplicate 12-lead ECGs;
- Perform urinalysis for kidney biomarkers and for microscopic evaluation of sediment; and
- Perform a planar WB scan and a SPECT/CT scan 168 (±24) hours after study drug administration.

6.2.2.3 Visit 5 (Week 2)

The following procedures will be performed at Visit 5 (Week 2):

- Assess AEs;
- Perform physical examination;
- Measure vital signs;
- Perform clinical laboratory tests;
- Perform triplicate 12-lead ECGs; and
- Perform urinalysis for kidney biomarkers and for microscopic evaluation of sediment.

6.2.2.4 Visit 6 (Week 3)

The following procedures will be performed at Visit 6 (Week 3):

- Record prior and concomitant medications, including information on any thyroid-blocking drugs;
- Deliver thyroid-blocking drugs;

  Note: Patients will not take the thyroid-blocking drugs at this visit but will be instructed to take them 24 hours prior to their next visit (ie, 24 hours prior to study drug administration).
- Assess AEs;
- Perform physical examination;
- Measure vital signs;
- Perform clinical laboratory tests;
- Perform triplicate 12-lead ECGs; and
- Perform urinalysis for kidney biomarkers and for microscopic evaluation of sediment.

6.2.2.5 Visit 7 (Week 4)

Dose 2 of Cycle 1 will be administered at Visit 7. The following procedures will be performed at Visit 7 (Week 4):

- Admit to radioactive unit for hospitalization prior to study drug administration;

  Note: Patients will be admitted during each IV administration for a total of 48 hours. This hospitalization can be shortened if ^{131}I decay and the patient's clearance allow discharge according to the applicable local regulations on radioactive compound exposure.

  Note: Before the patient is released, a leaflet containing information on radioprotection rules and general precautions after radiation treatment will be distributed (see Appendix F).
- Confirm the ingestion of thyroid-blocking drugs at least 24 hours prior to study drug administration;
- Deliver and confirm the ingestion of thyroid-blocking drugs 1 hour prior to study drug administration;

- Deliver and confirm the ingestion of thyroid-blocking drugs 24 and 48 hours after study drug administration;

  Note: If the patient is discharged prior to 48 hours, deliver the thyroid-blocking drugs for 48 hours at 24 hours. Patients will still take the thyroid-blocking drugs 48 hours after study drug administration.

- Perform urine hCG testing in all female patients of childbearing potential (ie, ovulating, premenopausal, and not surgically sterile) prior to study drug administration;
- Collect blood to evaluate serum for ADAs and to measure exploratory biomarkers (from patients who have consented to the procedure) prior to study drug administration;
- Assess AEs;
- Perform physical examination prior to study drug administration and at 24 hours after study drug administration;
- Measure vital signs prior to study drug administration and 30 minutes, 5 hours, 24 hours, and 48 hours after study drug administration;
- Perform clinical laboratory tests prior to study drug administration and 24 hours after study drug administration;

  Note: Clinical laboratory tests 24 hours after study drug administration should be performed prior to the planar WB scan and SPECT/CT scan scheduled at 24 hours after study drug administration.

- Perform triplicate 12-lead ECGs prior to study drug administration and 48 hours after study drug administration;
- Perform urinalysis for kidney biomarkers and for microscopic evaluation of sediment prior to study drug administration and 24 hours after study drug administration;
- Administer anti-emetic, anti-histamine, and anti-pyretic premedication therapy approximately 30 minutes prior to the start of the amino acid infusion, according to the site's standard operating procedures;
- Administer saline 0.9% infusion, starting 30 minutes prior to study drug administration and continuing for up to 3 hours after, at a rate of 200 to 300 mL/hour;
- Administer an amino acid solution beginning 30 minutes prior to study drug administration and ending 3 hours after study drug administration, at a rate of 250 to 500 mL/hour;
- Administer study drug via slow IV infusion, ie, administer using a shielded infusion device over approximately 3 to 30 minutes, depending on the volume to be injected; and
- Perform a planar WB scan and SPECT/CT scan at 5 (±1) hours, 24 (±4) hours, and 48 (±4) hours after study drug administration.

6.2.2.6 Visit 8 (Week 5)

The following procedures will be performed at Visit 8 (Week 5):

- Assess AEs;
- Perform physical examination;
- Measure vital signs;
- Perform clinical laboratory tests;

  Note: When performed on the same calendar day, clinical laboratory tests should be performed prior to any imaging.
- Perform urinalysis for kidney biomarkers and for microscopic evaluation of sediment; and
- Perform a planar WB scan and a SPECT/CT scan 168 (±24 hours) after study drug administration.

  Note: Although Visit 8 has a visit window of ±3 days, the SPECT/CT and planar WB scans have a window of ±24 hours for completion (ie, they must be completed 168 hours [±24 hours] after Visit 7 [Week 4]). The imaging may be performed on a different day than the rest of the assessments if needed.

6.2.2.7 Visit 9 (Week 6)

The following procedures will be performed at Visit 9 (Week 6):

- Assess AEs;
- Perform physical examination;
- Measure vital signs;
- Perform clinical laboratory tests;
- Perform triplicate 12-lead ECGs; and
- Perform urinalysis for kidney biomarkers and for microscopic evaluation of sediment.

6.2.2.8 Visit 10 (Week 8)

The following procedures will be performed at Visit 10 (Week 8):

- Assess AEs;
- Perform physical examination;
- Measure vital signs;
- Perform clinical laboratory tests;

  Note: Clinical laboratory tests should be performed prior to any imaging.
- Perform urinalysis for kidney biomarkers and for microscopic evaluation of sediment;

- Assess performance status using the ECOG PS; and
- Perform imaging to evaluate disease status.

  Note: Diagnostic CT scan will be performed in all patients. Brain MRI will only be performed in patients with known brain metastases.

6.2.2.9 Visit 11 (Week 11): End of Treatment Visit or Cycle 2 eligibility assessment

This visit will also serve as the screening visit for Cycle 2 of the dose escalation phase. Cycle 2 eligibility will be assessed by evaluating disease state and safety. This visit will serve as the EOT Visit for patients who do not have CB.

The following procedures will be performed at Visit 11 (Week 11):

- Update demographics and medical history, including confirmation of lesion size;
- Record prior and concomitant medications, including information on any thyroid-blocking drugs;
- Deliver thyroid-blocking drugs for next visit (only patients eligible for and continuing to Cycle 2);

  Note: Patients will not take the thyroid-blocking drugs at this visit but will be instructed to take them 24 hours prior to their next visit (ie, 24 hours prior to study drug administration).
- Perform urine hCG testing in all female patients of childbearing potential (ie, ovulating, premenopausal, and not surgically sterile);
- Collect blood to evaluate serum for ADAs and to measure exploratory biomarkers (from patients who have consented to the procedure);
- Assess AEs;
- Measure weight;
- Perform physical examination;
- Measure vital signs;
- Perform clinical laboratory tests;

  Note: Clinical laboratory tests should be performed prior to any imaging.
- Perform triplicate 12-lead ECGs;
- Perform echocardiogram;

  Note: LVEF may alternatively be measured using a multigated acquisition scan.
- Perform urinalysis for kidney biomarkers and for microscopic evaluation of sediment; and
- Perform imaging to evaluate disease status (EOT Visit only).

  Note: Diagnostic CT scan will be performed in all patients. Brain MRI will only be performed in patients with known brain metastases.

  Note: If the patient is continuing to Cycle 2, imaging to evaluate disease status will not be performed.

6.2.3 Cycles 2, 3, and 4 of the Dose Escalation Phase

Procedures during Cycles 2, 3, and 4 will be identical unless otherwise specified.

6.2.3.1 Visit 11 (Cycle 2 eligibility assessment), Visit 20 (Cycle 3 eligibility assessment), and Visit 29 (Cycle 4 eligibility assessment)

See the list of procedures for Visit 11 (Week 11) in Cycle 1 of the dose escalation phase in Section 6.2.2.9.

6.2.3.2 Visits 12, 21, and 30 (Week 0)

Dose 1 will be administered at Visits 12, 21, and 30 of Cycles 2, 3, and 4, respectively. Week 0 will occur within 2 weeks after the prior eligibility assessment visit. The following procedures will be performed at Visits 12, 21, and 30 (Week 0):

- Admit to radioactive unit for hospitalization prior to study drug administration;

  Note: Patients will be admitted during each IV administration for a total of 48 hours. This hospitalization can be shortened if ^{131}I decay and the patient's clearance allow discharge according to the applicable local regulations on radioactive compound exposure.

  Note: Before the patient is released, a leaflet containing information on radioprotection rules and general precautions after radiation treatment will be distributed (see Appendix F).
- Confirm the ingestion of thyroid-blocking drugs at least 24 hours prior to study drug administration;
- Deliver and confirm the ingestion of thyroid-blocking drugs 1 hour prior to study drug administration;
- Deliver and confirm the ingestion of thyroid-blocking drugs 24 and 48 hours after study drug administration;

  Note: If the patient is discharged prior to 48 hours, deliver the thyroid-blocking drugs for 48 hours at 24 hours. Patients will still take the thyroid-blocking drugs 48 hours after study drug administration.
- Perform urine hCG testing in all female patients of childbearing potential (ie, ovulating, premenopausal, and not surgically sterile) prior to study drug administration;
- Assess AEs;
- Perform physical examination prior to study drug administration and at 24 hours after study drug administration;
- Measure vital signs prior to study drug administration and 30 minutes, 5 hours, 24 hours, and 48 hours after study drug administration;
- Administer anti-emetic, anti-histamine, and anti-pyretic premedication therapy approximately 30 minutes prior to the start of the amino acid infusion, according to the site's standard operating procedures;
- Administer saline 0.9% infusion, starting 30 minutes prior to study drug administration and continuing for up to 3 hours after, at a rate of 200 to 300 mL/hour;

- Administer an amino acid solution beginning 30 minutes prior to study drug administration and ending 3 hours after study drug administration at a rate of 250 to 500 mL/hour;
- Administer study drug via slow IV infusion, ie, administer using a shielded infusion device over approximately 3 to 30 minutes, depending on the volume to be injected; and
- Perform a planar WB scan 24 (±4) hours after study drug administration. The planar WB scan done at this visit will also serve as the PD distribution scan.

6.2.3.3 Visits 13, 22, and 31 (Week 1)

The following procedures will be performed at Visits 13, 22, and 31 (Week 1):

- Assess AEs;
- Perform physical examination;
- Measure vital signs;
- Perform clinical laboratory tests;
- Perform triplicate 12-lead ECGs; and
- Perform urinalysis for kidney biomarkers and for microscopic evaluation of sediment.

6.2.3.4 Visits 14, 23, and 32 (Week 2)

The following procedures will be performed at Visits 14, 23, and 32 (Week 2):

- Assess AEs;
- Perform physical examination;
- Measure vital signs; and
- Perform clinical laboratory tests.

6.2.3.5 Visits 15, 24, and 33 (Week 3)

The following procedures will be performed at Visits 15, 24, and 33 (Week 3):

- Record prior and concomitant medications, including information on any thyroid-blocking drugs;
- Deliver thyroid-blocking drugs for next visit;

  Note: Patients will not take the thyroid-blocking drugs at this visit but will be instructed to take them 24 hours prior to their next visit (ie, 24 hours prior to study drug administration).
- Assess AEs;
- Perform physical examination;
- Measure vital signs;
- Perform clinical laboratory tests;
- Perform triplicate 12-lead ECGs; and
- Perform urinalysis for kidney biomarkers and for microscopic evaluation of sediment.

6.2.3.6 Visits 16, 25, and 34 (Week 4)

Dose 2 of Cycles 2, 3, or 4 will be administered at Visits 16, 25, and 34 of Cycles 2, 3, and 4, respectively. The following procedures will be performed at Visits 16, 25, and 34 (Week 4):

- Admit to radioactive unit for hospitalization prior to study drug administration;

  Note: Patients will be admitted during each IV administration for a total of 48 hours. This hospitalization can be shortened if ^{131}I decay and the patient's clearance allow discharge according to the applicable local regulations on radioactive compound exposure.

  Note: Before the patient is released, a leaflet containing information on radioprotection rules and general precautions after radiation treatment will be distributed (see Appendix F).
- Confirm the ingestion of thyroid-blocking drugs at least 24 hours prior to study drug administration;
- Deliver and confirm the ingestion of thyroid-blocking drugs 1 hour prior to study drug administration;
- Deliver and confirm the ingestion of thyroid-blocking drugs 24 and 48 hours after study drug administration;

  Note: If the patient is discharged prior to 48 hours, deliver the thyroid-blocking drugs for 48 hours at 24 hours. Patients will still take the thyroid-blocking drugs 48 hours after study drug administration.
- Perform urine hCG testing in all female patients of childbearing potential (ie, ovulating, premenopausal, and not surgically sterile) prior to study drug administration;
- Collect blood to evaluate serum for ADAs and to measure exploratory biomarkers (from patients who have consented to the procedure) prior to study drug administration;
- Assess AEs;
- Perform physical examination prior to study drug administration and at 24 hours after study drug administration;
- Measure vital signs prior to study drug administration and 30 minutes, 5 hours, 24 hours, and 48 hours after study drug administration;
- Perform clinical laboratory tests prior to study drug administration;
- Administer anti-emetic, anti-histamine, and anti-pyretic premedication therapy approximately 30 minutes prior to the start of the amino acid infusion, according to the site's standard operating procedures;
- Administer saline 0.9% infusion, starting 30 minutes prior to study drug administration and continuing for up to 3 hours after, at a rate of 200 to 300 mL/hour;
- Administer an amino acid solution beginning 30 minutes prior to study drug administration and ending 3 hours after study drug administration at a rate of 250 to 500 mL/hour;

- Administer study drug via slow IV infusion, ie, administer using a shielded infusion device over approximately 3 to 30 minutes, depending on the volume to be injected; and
- Perform a planar WB scan 24 (±4) hours after study drug administration.

6.2.3.7 Visits 17, 26, and 35 (Week 5)

The following procedures will be performed at Visits 17, 26, and 35 (Week 5):

- Assess AEs;
- Perform physical examination;
- Measure vital signs;
- Perform clinical laboratory tests;
- Perform triplicate 12-lead ECGs; and
- Perform urinalysis for kidney biomarkers and for microscopic evaluation of sediment.

6.2.3.8 Visits 18, 27, and 36 (Week 6)

The following procedures will be performed at Visits 18, 27, and 36 (Week 6):

- Assess AEs;
- Perform physical examination;
- Measure vital signs; and
- Perform clinical laboratory tests.

6.2.3.9 Visits 19, 28, and 37 (Week 8)

The following procedures will be performed at Visits 19, 28, and 37 (Week 8):

- Assess AEs;
- Perform physical examination;
- Measure vital signs;
- Perform clinical laboratory tests;

  Note: Clinical laboratory tests should be performed prior to any imaging.
- Perform triplicate 12-lead ECGs;
- Perform urinalysis for kidney biomarkers and for microscopic evaluation of sediment;
- Assess performance status using the ECOG PS; and
- Perform imaging to evaluate disease status.

  Note: Diagnostic CT scan will be performed in all patients. Brain MRI will only be performed in patients with known brain metastases.

6.2.3.10 Visits 20, 29, and 38 (Week 11): cycle eligibility or End of Treatment Visit

For Cycles 2 and 3, this visit will also serve as eligibility assessment for the next cycle in patients with CB and a cumulative kidney dose <23 Gy (based on the dosimetry results during Cycle 1). This visit will serve as the EOT Visit for patients who do not have CB and/or a cumulative kidney dose <23 Gy. This will serve as the EOT Visit for all patients in Cycle 4.

The following procedures will be performed at Visits 20, 29, and 38 (Week 11):

- Update demographics and medical history, including confirmation of lesion size;
- Record prior and concomitant medications, including information on any thyroid-blocking drugs;
- Deliver thyroid-blocking drugs for next visit (only patients eligible for and continuing to another cycle);

  Note: Patients will not take the thyroid-blocking drugs at this visit but will be instructed to take them 24 hours prior to their next visit (ie, 24 hours prior to study drug administration).
- Perform urine hCG testing in all female patients of childbearing potential (ie, ovulating, premenopausal, and not surgically sterile);
- Collect blood to evaluate serum for ADAs and to measure exploratory biomarkers (from patients who have consented to the procedure);

  Note: Clinical laboratory tests should be performed prior to any imaging.
- Assess AEs;
- Measure weight;
- Perform physical examination;
- Measure vital signs;
- Perform clinical laboratory tests;

  Note: Clinical laboratory tests should be performed prior to any imaging.
- Perform triplicate 12-lead ECGs;
- Perform echocardiogram;

  Note: LVEF may alternatively be measured using a multigated acquisition scan.
- Perform urinalysis for kidney biomarkers and for microscopic evaluation of sediment; and
- Perform imaging to evaluate disease status (EOT Visit only).

  Note: Diagnostic CT scan will be performed in all patients. Brain MRI will only be performed in patients with known brain metastases.

6.3 Dose Expansion Phase

6.3.1 Screening for the Dose Expansion Phase

6.3.1.1 Visit 1 (Week -4 to Week -1)

The following procedures will be performed at the first screening visit (Week -4 to Week -1) prior to the initiation of the dose expansion phase:

- Obtain informed consent;
- Assess inclusion and exclusion criteria;
- Record demographics and medical history, including confirmation of lesion size;
- Record prior and concomitant medications, including information on any thyroid-blocking drugs;
- Perform serum hCG testing in all female patients of childbearing potential (ie, ovulating, premenopausal, and not surgically sterile);
- Assess AEs;
- Measure height and weight;
- Perform physical examination;
- Measure vital signs;
- Perform clinical laboratory tests;
- Perform triplicate 12-lead ECGs;
- Perform echocardiogram;

  Note: LVEF may alternatively be measured using a multigated acquisition scan.
- Perform urinalysis for kidney biomarkers and for microscopic evaluation of sediment;
- Assess performance status using the ECOG PS; and
- Perform imaging to evaluate disease status.

  Note: Diagnostic CT scan will be performed in all patients. Brain MRI will only be performed in patients with known brain metastases.

6.3.1.2 Visit 2 (Week -1)

The following procedures will be performed preferably within the 14 days prior to study drug administration:

- Deliver thyroid-blocking drugs;

  Note: Patients will not take the thyroid-blocking drugs at this visit but will be instructed to take them 24 hours prior to their next visit (ie, 24 hours prior to study drug administration).
- Perform serum hCG testing in all female patients of childbearing potential (ie, ovulating, premenopausal, and not surgically sterile);

- Collect blood to evaluate serum for ADAs and to measure exploratory biomarkers (from patients who have consented to the procedure);
- Assess AEs;
- Perform clinical laboratory tests; and
- Perform urinalysis for kidney biomarkers and for microscopic evaluation of sediment.

6.3.2 Cycle 1 of the Dose Expansion Phase

6.3.2.1 Visit 3 (Week 0)

Dose 1 of Cycle 1 will be administered at Visit 3. The following procedures will be performed at Visit 3 (Week 0):

- Admit to radioactive unit for hospitalization prior to study drug administration;

  Note: Patients will be admitted during each IV administration for a total of 48 hours. This hospitalization can be shortened if ^{131}I decay and the patient's clearance allow discharge according to the applicable local regulations on radioactive compound exposure.

  Note: Before the patient is released, a leaflet containing information on radioprotection rules and general precautions after radiation treatment will be distributed (see Appendix F).
- Confirm the ingestion of thyroid-blocking drugs at least 24 hours prior to study drug administration;
- Deliver and confirm the ingestion of thyroid-blocking drugs 1 hour prior to study drug administration;
- Deliver and confirm the ingestion of thyroid-blocking drugs 24 and 48 hours after study drug administration;

  Note: If the patient is discharged prior to 48 hours, deliver the thyroid-blocking drugs for 48 hours at 24 hours. Patients will still take the thyroid-blocking drugs 48 hours after study drug administration.
- Perform urine hCG testing in all female patients of childbearing potential (ie, ovulating, premenopausal, and not surgically sterile) prior to study drug administration;
- Assess AEs;
- Perform physical examination prior to study drug administration and at 24 hours after study drug administration;
- Measure vital signs prior to study drug administration and 30 minutes, 5 hours, 24 hours, and 48 hours after study drug administration;
- Administer anti-emetic, anti-histamine, and anti-pyretic premedication therapy approximately 30 minutes prior to the start of the amino acid infusion, according to the site's standard operating procedures;
- Administer saline 0.9% infusion, starting 30 minutes prior to study drug administration and continuing for up to 3 hours after, at a rate of 200 to 300 mL/hour;

- Administer an amino acid solution beginning 30 minutes prior to study drug administration and ending 3 hours after study drug administration at a rate of 250 to 500 mL/hour;
- Administer study drug via slow IV infusion, ie, administer using a shielded infusion device over approximately 3 to 30 minutes, depending on the volume to be injected; and
- Perform a planar WB scan and a SPECT/CT scan 24 (±4) hours after study drug administration. The planar WB scan done at this visit will also serve as the PD distribution scan.

6.3.2.2 Visit 4 (Week 1)

The following procedures will be performed at Visit 4 (Week 1):

- Collect blood to evaluate serum for ADAs and to measure exploratory biomarkers (from patients who have consented to the procedure);
- Assess AEs;
- Perform physical examination;
- Measure vital signs;
- Perform clinical laboratory tests;
- Perform triplicate 12-lead ECGs; and
- Perform urinalysis for kidney biomarkers and for microscopic evaluation of sediment.

6.3.2.3 Visit 5 (Week 2)

The following procedures will be performed at Visit 5 (Week 2):

- Assess AEs;
- Perform physical examination;
- Measure vital signs; and
- Perform clinical laboratory tests.

6.3.2.4 Visit 6 (Week 3)

The following procedures will be performed at Visit 6 (Week 3):

- Record prior and concomitant medications, including information on any thyroid-blocking drugs;
- Deliver thyroid-blocking drugs for next visit;

  Note: Patients will not take the thyroid-blocking drugs at this visit but will be instructed to take them 24 hours prior to their next visit (ie, 24 hours prior to study drug administration).
- Assess AEs;
- Perform physical examination;
- Measure vital signs;
- Perform clinical laboratory tests;

- Perform triplicate 12-lead ECGs; and
- Perform urinalysis for kidney biomarkers and for microscopic evaluation of sediment.

6.3.2.5 Visit 7 (Week 4)

Dose 2 of Cycle 1 will be administered at Visit 7. The following procedures will be performed at Visit 7 (Week 4):

- Admit to radioactive unit for hospitalization prior to study drug administration;

  Note: Patients will be admitted during each IV administration for a total of 48 hours. This hospitalization can be shortened if ^{131}I decay and the patient's clearance allow discharge according to the applicable local regulations on radioactive compound exposure.

  Note: Before the patient is released, a leaflet containing information on radioprotection rules and general precautions after radiation treatment will be distributed (see Appendix F).
- Confirm the ingestion of thyroid-blocking drugs at least 24 hours prior to study drug administration;
- Deliver and confirm the ingestion of thyroid-blocking drugs 1 hour prior to study drug administration;
- Deliver and confirm the ingestion of thyroid-blocking drugs 24 and 48 hours after study drug administration;

  Note: If the patient is discharged prior to 48 hours, deliver the thyroid-blocking drugs for 48 hours at 24 hours. Patients will still take the thyroid-blocking drugs 48 hours after study drug administration.
- Perform urine hCG testing in all female patients of childbearing potential (ie, ovulating, premenopausal, and not surgically sterile) prior to study drug administration;
- Collect blood to evaluate serum for ADAs and to measure exploratory biomarkers (from patients who have consented to the procedure) prior to study drug administration;
- Assess AEs;
- Perform physical examination prior to study drug administration and at 24 hours after study drug administration;
- Measure vital signs prior to study drug administration and 30 minutes, 5 hours, 24 hours, and 48 hours after study drug administration;
- Perform clinical laboratory tests prior to study drug administration;
- Administer anti-emetic, anti-histamine, and anti-pyretic premedication therapy approximately 30 minutes prior to the start of the amino acid infusion, according to the site's standard operating procedures;
- Administer saline 0.9% infusion, starting 30 minutes prior to study drug administration and continuing for up to 3 hours after, at a rate of 200 to 300 mL/hour;
- Administer an amino acid solution beginning 30 minutes prior to study drug administration and ending 3 hours after study drug administration at a rate of 250 to 500 mL/hour;

- Administer study drug via slow IV infusion, ie, administer using a shielded infusion device over approximately 3 to 30 minutes, depending on the volume to be injected; and
- Perform a planar WB scan and a SPECT/CT scan 24 (±4) hours after study drug administration.

6.3.2.6 Visit 8 (Week 5)

The following procedures will be performed at Visit 8 (Week 5):

- Assess AEs;
- Perform physical examination;
- Measure vital signs;
- Perform clinical laboratory tests;
- Perform triplicate 12-lead ECGs; and
- Perform urinalysis for kidney biomarkers and for microscopic evaluation of sediment.

6.3.2.7 Visit 9 (Week 6)

The following procedures will be performed at Visit 9 (Week 6):

- Assess AEs;
- Perform physical examination;
- Measure vital signs; and
- Perform clinical laboratory tests.

6.3.2.8 Visit 10 (Week 8)

The following procedures will be performed at Visit 10 (Week 8):

- Collect blood to evaluate serum for ADAs and to measure exploratory biomarkers (from patients who have consented to the procedure);
- Assess AEs;
- Perform physical examination;
- Measure vital signs;
- Perform clinical laboratory tests;

  Note: Clinical laboratory tests should be performed prior to any imaging.
- Perform triplicate 12-lead ECGs;
- Perform urinalysis for kidney biomarkers and for microscopic evaluation of sediment;
- Assess performance status using the ECOG PS; and
- Perform imaging to evaluate disease status.

  Note: Diagnostic CT scan will be performed in all patients. Brain MRI will only be performed in patients with known brain metastases.

6.3.2.9 Visit 11 (Week 11): End of Treatment Visit or Cycle 2 eligibility assessment

This visit will also serve as the eligibility assessment for Cycle 2 of the dose expansion phase. Cycle 2 eligibility will be assessed by evaluating disease state and safety. This visit will serve as the EOT Visit for patients who do not see CB.

The following procedures will be performed at Visit 11 (Week 11):

- Update demographics and medical history, including confirmation of lesion size;
- Record prior and concomitant medications, including information on any thyroid-blocking drugs;
- Deliver thyroid-blocking drugs for next visit (only patients eligible for and continuing to Cycle 2);

  Note: Patients will not take the thyroid-blocking drugs at this visit but will be instructed to take them 24 hours prior to their next visit (ie, 24 hours prior to study drug administration).
- Perform urine hCG testing in all female patients of childbearing potential (ie, ovulating, premenopausal, and not surgically sterile);
- Collect blood to evaluate serum for ADAs and to measure exploratory biomarkers (from patients who have consented to the procedure);
- Assess AEs;
- Measure weight;
- Perform physical examination;
- Measure vital signs;
- Perform clinical laboratory tests;

  Note: Clinical laboratory tests should be performed prior to any imaging.
- Perform triplicate 12-lead ECGs;
- Perform echocardiogram;

  Note: LVEF may alternatively be measured using a multigated acquisition scan.
- Perform urinalysis for kidney biomarkers and for microscopic evaluation of sediment; and
- Perform imaging to evaluate disease status (EOT Visit only).

  Note: Diagnostic CT scan will be performed in all patients. Brain MRI will only be performed in patients with known brain metastases.

  Note: If the patient is continuing to Cycle 2, imaging to evaluate disease status will not be performed.

6.3.3 Cycle 2 of the Dose Expansion Phase

6.3.3.1 Visit 11 (Cycle 2 eligibility assessment)

See the list of procedures for Visit 11 (Week 11) in Cycle 1 of the dose expansion phase in Section 6.3.2.9.

6.3.3.2 Visit 12 (Week 0)

Dose 1 of Cycle 2 will be administered at Visit 12. Visit 12 will occur at approximately 2 weeks after Visit 11. The following procedures will be performed at Visit 12 (Week 0):

- Admit to radioactive unit for hospitalization prior to study drug administration;

  Note: Patients will be admitted during each IV administration for a total of 48 hours. This hospitalization can be shortened if ^{131}I decay and the patient's clearance allow discharge according to the applicable local regulations on radioactive compound exposure.

  Note: Before the patient is released, a leaflet containing information on radioprotection rules and general precautions after radiation treatment will be distributed (see Appendix F).
- Confirm the ingestion of thyroid-blocking drugs at least 24 hours prior to study drug administration;
- Deliver and confirm the ingestion of thyroid-blocking drugs 1 hour prior to study drug administration;
- Deliver and confirm the ingestion of thyroid-blocking drugs 24 and 48 hours after study drug administration;

  Note: If the patient is discharged prior to 48 hours, deliver the thyroid-blocking drugs for 48 hours at 24 hours. Patients will still take the thyroid-blocking drugs 48 hours after study drug administration.
- Perform urine hCG testing in all female patients of childbearing potential (ie, ovulating, premenopausal, and not surgically sterile) prior to study drug administration;
- Assess AEs;
- Perform physical examination prior to study drug administration and at 24 hours after study drug administration;
- Measure vital signs prior to study drug administration and 30 minutes, 5 hours, 24 hours, and 48 hours after study drug administration;
- Administer anti-emetic, anti-histamine, and anti-pyretic premedication therapy approximately 30 minutes prior to the start of the amino acid infusion, according to the site's standard operating procedures;
- Administer saline 0.9% infusion, starting 30 minutes prior to study drug administration and continuing for up to 3 hours after, at a rate of 200 to 300 mL/hour;
- Administer an amino acid solution beginning 30 minutes prior to study drug administration and ending 3 hours after study drug administration at a rate of 250 to 500 mL/hour;

- Administer study drug via slow IV infusion, ie, administer using a shielded infusion device over approximately 3 to 30 minutes, depending on the volume to be injected; and
- Perform a planar WB scan 24 (±4) hours after study drug administration. The planar WB scan done at this visit will also serve as the PD distribution scan.

6.3.3.3 Visit 13 (Week 1)

The following procedures will be performed at Visit 13 (Week 1):

- Collect blood to evaluate serum for ADAs and to measure exploratory biomarkers (from patients who have consented to the procedure);
- Assess AEs;
- Perform physical examination;
- Measure vital signs;
- Perform clinical laboratory tests;
- Perform triplicate 12-lead ECGs; and
- Perform urinalysis for kidney biomarkers and for microscopic evaluation of sediment.

6.3.3.4 Visit 14 (Week 2)

The following procedures will be performed at Visit 14 (Week 2):

- Assess AEs;
- Perform physical examination;
- Measure vital signs; and
- Perform clinical laboratory tests.

6.3.3.5 Visit 15 (Week 3)

The following procedures will be performed at Visit 15 (Week 3):

- Record prior and concomitant medications, including information on any thyroid-blocking drugs;
- Deliver thyroid-blocking drugs for next visit;

  Note: Patients will not take the thyroid-blocking drugs at this visit but will be instructed to take them 24 hours prior to their next visit (ie, 24 hours prior to study drug administration).
- Assess AEs;
- Perform physical examination;
- Measure vital signs;
- Perform clinical laboratory tests;
- Perform triplicate 12-lead ECGs; and
- Perform urinalysis for kidney biomarkers and for microscopic evaluation of sediment.

6.3.3.6 Visit 16 (Week 4)

Dose 2 of Cycle 2 will be administered at Visit 16 (Week 4). The following procedures will be performed at Visit 16 (Week 4):

- Admit to radioactive unit for hospitalization prior to study drug administration;

  Note: Patients will be admitted during each IV administration for a total of 48 hours. This hospitalization can be shortened if ^{131}I decay and the patient's clearance allow discharge according to the applicable local regulations on radioactive compound exposure.

  Note: Before the patient is released, a leaflet containing information on radioprotection rules and general precautions after radiation treatment will be distributed (see Appendix F).
- Confirm the ingestion of thyroid-blocking drugs at least 24 hours prior to study drug administration;
- Deliver and confirm the ingestion of thyroid-blocking drugs 1 hour prior to study drug administration;
- Deliver and confirm the ingestion of thyroid-blocking drugs at least 24 and 48 hours after study drug administration;

  Note: If the patient is discharged prior to 48 hours, deliver the thyroid-blocking drugs for 48 hours at 24 hours. Patients will still take the thyroid-blocking drugs 48 hours after study drug administration.
- Perform urine hCG testing in all female patients of childbearing potential (ie, ovulating, premenopausal, and not surgically sterile) prior to study drug administration;
- Collect blood to evaluate serum for ADAs and to measure exploratory biomarkers (from patients who have consented to the procedure) prior to study drug administration;
- Assess AEs;
- Perform physical examination prior to study drug administration and at 24 hours after study drug administration;
- Measure vital signs prior to study drug administration and 30 minutes, 5 hours, 24 hours, and 48 hours after study drug administration;
- Perform clinical laboratory tests prior to study drug administration;
- Administer anti-emetic, anti-histamine, and anti-pyretic premedication therapy approximately 30 minutes prior to the start of the amino acid infusion, according to the site's standard operating procedures;
- Administer saline 0.9% infusion, starting 30 minutes prior to study drug administration and continuing for up to 3 hours after, at a rate of 200 to 300 mL/hour;
- Administer an amino acid solution beginning 30 minutes prior to study drug administration and ending 3 hours after study drug administration at a rate of 250 to 500 mL/hour;

- Administer study drug via slow IV infusion, ie, administer using a shielded infusion device over approximately 3 to 30 minutes, depending on the volume to be injected; and
- Perform a planar WB scan 24 (±4) hours after study drug administration.

6.3.3.7 Visit 17 (Week 5)

The following procedures will be performed at Visit 17 (Week 5):

- Assess AEs;
- Perform physical examination;
- Measure vital signs;
- Perform clinical laboratory tests;
- Perform triplicate 12-lead ECGs; and
- Perform urinalysis for kidney biomarkers and for microscopic evaluation of sediment.

6.3.3.8 Visit 18 (Week 6)

The following procedures will be performed at Visit 18 (Week 6):

- Assess AEs;
- Perform physical examination;
- Measure vital signs; and
- Perform clinical laboratory tests.

6.3.3.9 Visit 19 (Week 8)

The following procedures will be performed at Visit 19 (Week 8):

- Collect blood to evaluate serum for ADAs and to measure exploratory biomarkers (from patients who have consented to the procedure);
- Assess AEs;
- Perform physical examination;
- Measure vital signs;
- Perform clinical laboratory tests;

  Note: Clinical laboratory tests should be performed prior to any imaging.
- Perform triplicate 12-lead ECGs;
- Perform urinalysis for kidney biomarkers and for microscopic evaluation of sediment;
- Assess performance status using the ECOG PS; and
- Perform imaging to evaluate disease status.

  Note: Diagnostic CT scan will be performed in all patients. Brain MRI will only be performed in patients with known brain metastases.

6.3.3.10 Visit 20 (Week 11): End of Treatment Visit

The following procedures will be performed at Visit 20 (Week 11/EOT Visit):

- Record prior and concomitant medications, including information on any thyroid-blocking drugs;
- Perform urine hCG testing in all female patients of childbearing potential (ie, ovulating, premenopausal, and not surgically sterile);
- Collect blood to evaluate serum for ADAs and to measure exploratory biomarkers (from patients who have consented to the procedure);
- Assess AEs;
- Measure weight;
- Perform physical examination;
- Measure vital signs;
- Perform clinical laboratory tests;

  Note: Clinical laboratory tests should be performed prior to any imaging.
- Perform triplicate 12-lead ECGs;
- Perform echocardiogram;

  Note: LVEF may alternatively be measured using a multigated acquisition scan.
- Perform urinalysis for kidney biomarkers and for microscopic evaluation of sediment; and
- Perform imaging to evaluate disease status.

  Note: Diagnostic CT scan will be performed in all patients. Brain MRI will only be performed in patients with known brain metastases.

6.4 Early Termination Visit and Withdrawal Procedures

For patients who receive at least 1 dose of study drug, but are withdrawn from the study prior to completion, all assessments scheduled for the last visit in the cycle (ie, Week 11) should be performed at an ET Visit.

Patients will continue into the long-term follow-up period after ET or withdrawal so that post-treatment therapy can be monitored.

6.5 Long-Term Follow-Up Period and End of Study

A long-term follow-up period will start after the EOT/ET Visit. Follow-up will continue for a maximum of 12 months. All patients without disease progression will be monitored every 8 weeks to evaluate PFS for a maximum of 12 months or until disease progression, death, or consent is withdrawn, whichever occurs first.

The bi-monthly visits will consist of imaging to evaluate disease status, performance status evaluation using ECOG PS, and assessment for any post-investigational treatment. Other changes in medical history or concomitant medications and AEs will be assessed. Imaging to evaluate

disease status will begin 8 weeks after the last diagnostic CT scan or brain MRI performed during the study treatment period. Diagnostic CT scan will be performed in all patients. Brain MRI will only be performed in patients with known brain metastases. Patients with extracranial lesions will be evaluated for progression using RECIST version 1.1. Patients with brain metastases without extracranial lesions will be evaluated for progression using RANO-BM. Patients with extracranial lesions and brain metastases will be evaluated for progression using both RECIST version 1.1 (extracranial lesions) and RANO-BM (brain metastases). Additional details are provided in the Imaging Review Charter. As long as there is no disease progression, imaging to evaluate disease status will be performed every 8 weeks.

For patients with disease progression or starting alternative anticancer therapy, imaging to evaluate disease status will be performed according to the local site standard of care. Review of images at this point will be done locally and not by the central imaging core laboratory. Additionally, those patients will no longer be followed every 8 weeks, but every 12 weeks, to assess survival, disease status, and post-progression therapy. Follow-up contacts (by clinic visits or telephone call) will be performed every 12 weeks until death, lost to follow-up, study end (12 months post-last patient EOT/ET Visit), or study termination by the Sponsor, whichever occurs first.

7 EFFICACY AND DOSIMETRY VARIABLES

7.1 Primary Efficacy Variables

The primary efficacy endpoints are as follows:

- Proportion of patients achieving an objective response (CR or PR) with the use of CAM-H2 as measured by RECIST version 1.1 (all patients with extracranial lesions) or as measured by RANO-BM (patients with brain metastases without extracranial lesions); and
- CBR of CAM-H2 using the equation CBR = CR + PR + SD, as measured by RECIST version 1.1 (all patients with extracranial lesions) or as measured by RANO-BM (patients with brain metastases without extracranial lesions).

7.2 Secondary Efficacy Variables

The secondary efficacy endpoints are as follows:

- PFS for patients receiving CAM-H2;
- DoR in patients receiving CAM-H2;
- PFS in patients with brain metastases receiving CAM-H2;
- OS for patients receiving CAM-H2; and
- Proportion of patients on CAM-H2 who develop ADAs.

7.3 Dosimetry Variables

The dosimetry endpoint consists of dosimetry for CAM-H2 via SPECT/CT and planar WB scans. Endpoints will include the biodistribution and PD profile of CAM-H2 dosimetry results for target lesions based on region of interest.

7.4 Efficacy Assessments

7.4.1 Objective Response

The proportion of patients achieving an objective response will be measured using RECIST version 1.1 (see Appendix D) or RANO-BM (see Appendix E). All patients with extracranial lesions will be evaluated for progression using RECIST version 1.1. Patients without extracranial lesions will be evaluated for progression using RANO-BM.

7.4.2 Clinical Benefit Rate

The CBR will be measured using the equation CBR = CR + PR + SD, as measured by both RECIST version 1.1 (see Appendix D) and RANO-BM (see Appendix E). All patients with extracranial lesions will be evaluated for progression using RECIST version 1.1. Patients without extracranial lesions will be evaluated for progression using RANO-BM.

7.4.3 Additional Clinical Measurements of Efficacy

In addition to objective response and CBR, the clinical measurements of efficacy evaluated will include PFS, DoR, and OS.

7.4.4 Anti-Drug Antibodies

Blood samples for ADAs will be collected per the laboratory manual instructions. ADAs will be measured during the study via serum sampling using a validated method.

7.4.5 Exploratory Biomarkers

Blood samples for exploratory biomarkers will be collected from patients who have consented to the procedure. The samples will be collected per the laboratory manual instructions and stored at the central laboratory for future analyses. The analyses of these exploratory biomarkers will be performed outside of the scope of this study protocol and will be reported separately.

7.4.6 Dosimetry Study Procedures

For the dosimetry study, defined critical organs (ie, the kidneys and liver) and target lesions (ie, lesions representative of the extent of disease and deemed avid at the discretion of the central reviewer, based on qualitative visual assessment) will be delineated on planar WB scans and/or SPECT/CT scans. Further details are provided in the Imaging Review Charter.

The percentage of injected activity (%IA) will be calculated in each set of images as the ratio between the measured activity in the lesion and the total injected activity as a function of time to derive the absorbed dose. Organ time-activity curves will be generated by plotting %IA versus time to derive the absorbed dose.

Tumor dosimetry in tumor lesions will be calculated based on the consecutive SPECT/CT and/or planar WB scans during Cycle 1 of the dose escalation phase.

8 SAFETY ASSESSMENTS

Safety and tolerability will be assessed during the study and will include the following:

- Incidence and severity of treatment-emergent adverse events (TEAEs);
- MTD of CAM-H2;
- DLT rate of CAM-H2;
- RDP2 for CAM-H2;
- Physical examinations, including full neurologic examinations, as well as assessments of general appearance, skin, eyes, ears, nose, throat, neck, lymph nodes, chest, heart (including auscultation for heart sounds and murmurs), abdomen, extremities, and musculoskeletal systems;
- Vital signs, including systolic and diastolic blood pressure, heart rate, respiratory rate, and temperature;
- Clinical laboratory tests including thyroid panel (thyroid-stimulating hormone [TSH], free T4, and free T3), hematology assessments (white blood cell [WBC] count and differential, hemoglobin, hematocrit, and platelet count), coagulation parameters (activated partial thromboplastin time, INR, and prothrombin time), and chemistry assessments (fasting glucose or glycated hemoglobin, creatinine, blood urea nitrogen, sodium, potassium, calcium, chloride, phosphorus, bicarbonate, AST, ALT, gamma-glutamyl transferase [GGT], alkaline phosphatase, total bilirubin [or fraction of direct bilirubin if >1.5 × ULN], albumin, total protein, lactate dehydrogenase [LDH], creatine kinase (CK) [or fraction of creatine kinase-myocardial band (CK-MB) if >1.5 × ULN], and cystatin-C);
- Urinalysis for kidney biomarkers (including kidney injury molecule-1 [KIM-1], neutrophil gelatinase-associated lipocalin [NGAL], microalbumin, creatinine, and albumin/creatinine ratio) and for microscopic evaluation of sediment (including cylinders, erythrocytes, and leukocytes);
- Pregnancy test (including serum and urine testing);
- Dosimetry results with regard to estimated absorbed dose to the most exposed organs (ie, the kidneys and liver); and
- Concomitant medications.

8.1 Adverse Events

An AE is defined as any untoward medical occurrence in a clinical investigation patient administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and/or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not related to the investigational medicinal product. All AEs, including observed or volunteered problems, complaints, or symptoms, are to be recorded on the appropriate eCRF.

AEs, which include clinical laboratory test variables, will be monitored and documented from the time of informed consent. Patients should be instructed to report any AE that they experience to

the Investigator, whether or not they think the event is due to study treatment. Beginning at screening, Investigators should make an assessment for AEs at each visit and record the event on the appropriate AE eCRF.

Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the Investigator and recorded on the eCRF. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the Investigator, it should be recorded as a separate AE on the eCRF. Additionally, the condition that led to a medical or surgical procedure (eg, surgery, endoscopy, tooth extraction, or transfusion) should be recorded as an AE, not the procedure itself.

Any medical condition already present at screening should be recorded as medical history and not be reported as an AE unless the medical condition or signs or symptoms present at screening changes in severity, frequency, or seriousness at any time during the study. In this case, it should be reported as an AE.

Clinically significant abnormal laboratory or other examination (eg, ECG) findings that are detected during the study or are present at screening and significantly worsen during the study should be reported as AEs, as described below. The Investigator will exercise his or her medical and scientific judgement in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant. Clinically significant abnormal laboratory values occurring during the clinical study will be followed until repeat tests return to normal, stabilize, or are no longer clinically significant. Abnormal test results that are determined to be an error should not be reported as an AE. Laboratory abnormalities or other abnormal clinical findings (eg, ECG abnormalities) should be reported as an AE if any of the following are applicable:

- If an intervention is required as a result of the abnormality;
- If action taken with the study drug is required as a result of the abnormality; or
- Based on the clinical judgement of the Investigator.

8.1.1 Adverse (Drug) Reaction

All noxious and unintended responses to a medicinal product related to any dose should be considered an adverse drug reaction. “Responses” to a medicinal product means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility (ie, the relationship cannot be ruled out).

8.1.2 Unexpected Adverse Drug Reaction

An Unexpected Adverse Drug Reaction is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information.

8.1.3 Assessment of Adverse Events by the Investigator

The Investigator will assess the severity (intensity) of each AE as mild, moderate, or severe, and will also categorize each AE as to its potential relationship to study drug using the categories of Yes or No.

Assessment of severity

The severity of all AEs should be graded according to the CTCAE version 5.0. For those AE terms not listed in the CTCAE, the following grading system should be used:

- CTCAE Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated;
- CTCAE Grade 2: Moderate; minimal local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living;
- CTCAE Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living;
- CTCAE Grade 4: Life-threatening consequences; urgent intervention indicated; and
- CTCAE Grade 5: Death related to the AE.

Causality assessment

The relationship of an AE to the administration of the study drug is to be assessed according to the following definitions:

No (unrelated, not related, unlikely to be related) – The time course between the administration of study drug and the occurrence or worsening of the AE rules out a causal relationship and another cause (concomitant drugs, therapies, complications, etc) is suspected.

Yes (possibly, probably, or definitely related) – The time course between the administration of study drug and the occurrence or worsening of the AE is consistent with a causal relationship and no other cause (concomitant drugs, therapies, complications, etc) can be identified.

The definition implies a reasonable possibility of a causal relationship between the event and the study drug. This means that there are facts (evidence) or arguments to suggest a causal relationship.

The following factors should also be considered:

- The temporal sequence from study drug administration;

  The event should occur after the study drug is given. The length of time from study drug exposure to event should be evaluated in the clinical context of the event.

- Underlying, concomitant, intercurrent diseases;

  Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the patient may have.

- Concomitant drug;

  The other drugs the patient is taking or the treatment the patient receives should be examined to determine whether any of them might be recognized to cause the event in question.

- Known response pattern for this class of study drug;

  Clinical and/or preclinical data may indicate whether a particular response is likely to be a class effect.

- Exposure to physical and/or mental stresses; and

  The exposure to stress might induce adverse changes in the recipient and provide a logical and better explanation for the event.

- The pharmacology and pharmacokinetics of the study drug.

  The known pharmacologic properties (absorption, distribution, metabolism, and excretion) of the study drug should be considered.

8.1.4 Adverse Events of Special Interest

The Investigator will monitor each patient for clinical and laboratory evidence for adverse events of special interest (AESIs), including renal failure and myelodysplastic syndrome, during the patient's participation in this study.

The Investigator will assess and record any additional information on the AESI in detail on an AE form which must be submitted within 24 hours of awareness of the event.

During the course of the study, additional AESIs may be identified by the Sponsor.

AESIs must be recorded in the eCRF.

8.2 Serious Adverse Events

An AE or adverse reaction is considered serious if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death;
- A life-threatening AE;

  Note: An AE or adverse reaction is considered "life-threatening" if, in view of either the Investigator or Sponsor, its occurrence places the patient at immediate risk of death. It does not include an event that, had it occurred in a more severe form, might have caused death.

- Requires hospitalization or prolongation of existing hospitalizations;

  Note: Any hospital admission with at least 1 overnight stay will be considered an inpatient hospitalization. An emergency room or urgent care visit without hospital admission will not be recorded as an SAE under this criterion, nor will hospitalization for a procedure scheduled or planned before signing of informed consent, or elective treatment of a pre-existing condition that did not worsen from baseline. However, unexpected complications and/or prolongation of hospitalization that occur during elective surgery should be recorded as AEs and assessed for seriousness. Admission to the hospital for social or situational reasons (ie, no place to stay, live too far away to come for hospital visits, respite care) will not be considered inpatient hospitalizations.

- A persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions;

- A congenital anomaly/birth defect; or
- An important medical event.

  Note: Important medical events that do not meet any of the above criteria may be considered an SAE when, based upon appropriate medical judgement, they may jeopardize the patient and may require medical or surgical intervention to prevent 1 of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalizations, or the development of drug dependency.

  Note: Events of progression of a patient's underlying cancer, as well as events clearly related to the progression of a patient's cancer (signs/symptoms of progression) should not be reported as an SAE unless the outcome is fatal during the study or within the safety reporting period. If the event has a fatal outcome during that timeframe, the event of Progression of "Type of Cancer" must be recorded as an SAE with CTCAE Grade 5 (fatal) outcome indicated. Diagnosis of progression of disease or hospitalization due to signs and symptoms of disease progression alone should not be reported as an SAE.

8.3 Serious Adverse Event Reporting − Procedures for Investigators

Initial reports

All SAEs occurring from the time of informed consent until 30 days following the last administration of study drug must be reported to Medpace Clinical Safety within 24 hours of the knowledge of the occurrence. After the reporting window, any SAE that the Investigator considers related to the study drug must be reported to the Medpace Clinical Safety or the Sponsor/designee. All SAEs related to the study drug and/or study procedures, as determined by the Investigator, must also be reported to Medpace Clinical Safety within 24 hours of the knowledge of the occurrence.

To report the SAE, complete the SAE form electronically in the electronic data capture (EDC) system for the study. When the form is completed, Medpace Safety personnel will be notified electronically by the EDC system and will retrieve the form. If the event meets serious criteria and it is not possible to access the EDC system, send an email to Medpace Safety at Medpace-safetynotification@medpace.com or call the Medpace SAE reporting line (telephone number listed below), and fax/email the completed paper SAE form to Medpace (contact information listed in Section 8.6) within 24 hours of awareness. When the EDC system becomes available, the SAE information must be entered within 24 hours of the system becoming available.

Follow-up reports

The Investigator must continue to follow the patient until the SAE has subsided or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment), or the patient dies.

Within 24 hours of receipt of follow-up information, the Investigator must update the SAE form electronically in the EDC system for the study and submit any supporting documentation (eg, patient discharge summary or autopsy reports) to Medpace Clinical Safety via fax or email. If it is not possible to access the EDC system, refer to the procedures outlined above for initial reporting of SAEs.

8.4 Pregnancy Reporting

If a patient becomes pregnant during the study or within the Safety Follow-Up Period defined in the protocol, the Investigator is to stop dosing with study drug(s) immediately and the patient should be withdrawn from the study. ET Visit procedures should be implemented at that time.

A pregnancy is not considered to be an AE or SAE; however, it must be reported to Medpace Clinical Safety within 24 hours of knowledge of the event. Medpace Clinical Safety will then provide the Investigator/site the Exposure In Utero (EIU) form for completion. The Investigator/site must complete the EIU form and fax/email it back to Medpace Clinical Safety.

If the female partner of a male patient becomes pregnant while the patient is receiving study drug or within the Safety Follow-Up Period defined in the protocol, the Investigator should notify Medpace Clinical Safety as described above.

The pregnancy should be followed until the outcome of the pregnancy, whenever possible. Once the outcome of the pregnancy is known, the EIU form should be completed and faxed/emailed to Medpace Clinical Safety. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (ie, postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting an SAE.

8.5 Expedited Reporting

The Sponsor/designee will report all relevant information about suspected unexpected serious adverse reactions (SUSARs) that are fatal or life-threatening as soon as possible to the United States Food and Drug Administration (FDA), applicable competent authorities in all the Member States concerned, and to the Central Ethics Committee, and in any case no later than 7 days after knowledge by the Sponsor/designee of such a case. Relevant follow-up information will subsequently be communicated within an additional 8 days.

All other SUSARs will be reported to the FDA, the applicable competent authorities concerned, and the Central Ethics Committee concerned as soon as possible but within a maximum of 15 days of first knowledge by the Sponsor/designee.

The Sponsor/designee will also report any additional expedited safety reports required in accordance with the timelines outlined in country-specific legislation.

The Sponsor/designee will also inform all Investigators as required per local regulation.

The requirements above refer to the requirements relating to investigational medicinal product.

Expedited reporting of SUSARs related to comparators is also required in line with the requirements above. Expedited reporting of SUSARs related to non-investigational medicinal products (NIMPs) and any other NIMPs is not required. Listings of cases related to NIMPs will be included in the Development Safety Update Report.

8.6 Special Situation Reports

Special situation reports include reports of overdose, misuse, abuse, medication error, and reports of adverse reactions associated with product complaints.

- **Overdose:** Refers to the administration of a quantity of a medicinal product given per administration or cumulatively (accidentally or intentionally), which is above the maximum recommended dose according to the protocol. Clinical judgement should always be applied. In cases of a discrepancy in the drug accountability, overdose will be established only when it is clear that the patient has taken additional dose(s) or the Investigator has reason to suspect that the patient has taken additional dose(s).
- **Misuse:** Refers to situations where the medicinal product is intentionally and inappropriately used in a way that is not in accordance with the protocol instructions or local prescribing information and may be accompanied by harmful physical and/or psychological effects.
- **Abuse:** Is defined as persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.
- **Medication error:** Is any unintentional error in the prescribing, dispensing, or administration of a medicinal product by a healthcare professional, patient, or consumer, respectively. The administration or consumption of the unassigned treatment and administration of an expired product are always reportable as medication errors, cases of patients missing doses of study drug are not considered reportable as medication error.
- **Product complaint:** Is defined as any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug or device after it is released for distribution. A special situations form will only be completed if a complaint is associated with an adverse drug reaction.

All special situation events as described above must be reported on the Special Situations Report form and faxed/emailed to Medpace Clinical Safety (contact information listed below) within 24 hours of knowledge of the event. All AEs associated with these Special Situation reports should be reported as AEs or SAEs as well as recorded on the AE eCRF and/or the SAE report form. Details of the symptoms and signs, clinical management, and outcome should be provided, when available.

Safety Contact Information: Medpace Clinical Safety
Medpace SAE reporting line – United States:
Telephone: +1-800-730-5779, dial 3 or +1-513-579-9911, dial 3
Fax: +1-866-336-5320 or +1-513-570-5196
Email: medpace-safetynotification@medpace.com

8.7 Clinical Laboratory Tests

Clinical laboratory tests, performed at the times specified in Appendix A, will consist of the following:

- Thyroid panel (TSH, free T4, and free T3);
- Hematology assessments (WBC count and differential, hemoglobin, hematocrit, and platelet count);

- Coagulation parameters (activated partial thromboplastin time, INR, and prothrombin time); and
- Chemistry assessments (fasting glucose or glycated hemoglobin, creatinine, blood urea nitrogen, sodium, potassium, calcium, chloride, phosphorus, bicarbonate, AST, ALT, GGT, alkaline phosphatase, total bilirubin [or fraction of direct bilirubin if >1.5 × ULN], albumin, total protein, LDH, CK [or fraction of CK-MB if >1.5 × ULN]; and cystatin-C).

Urinalysis, performed at the times specified in Appendix A, will evaluate the following kidney biomarkers: KIM-1, NGAL, microalbumin, creatinine, and albumin/creatinine ratio and will evaluate microscopic evaluation of sediment, including cylinders, erythrocytes, and leukocytes.

Pregnancy tests, both urine and serum, will also be performed.

All standard blood and urine tests will be performed by a clinical reference laboratory. Laboratory certification and normal reference ranges for all laboratories used during the study will be on file with the Sponsor prior to study initiation.

The Investigator must review and sign all laboratory test reports. Abnormal screening laboratory rests may be repeated at the discretion of the Investigator. The Investigator is expected to review all clinical laboratory results within a reasonable period of time.

The specific analytes to be measured are listed in Appendix B.

8.8 Vital Signs

Vital signs will include systolic and diastolic blood pressure, heart rate, respiratory rate, and temperature.

Vital signs will be measured at study visits and time points specified in Appendix A using a standardized process. Prior to measuring vital signs, the patient should be sitting for a minimum of 5 minutes with back supported, feet flat on the floor, and measurement arm supported so that the midpoint of the manometer cuff is at heart level.

An automated blood pressure device with digital read-out and an appropriately sized cuff with the bladder centered over the brachial artery should be used for vital sign measurement.

The arm used for the measurement should be recorded. Whenever possible, the same arm should be used for all vital sign assessments throughout the study.

Blood pressure should be recorded to the nearest whole number on an automated device.

Unscheduled vital signs will be collected at any time during the study that a patient experiences any symptoms suggestive of hemodynamic instability.

8.9 Electrocardiograms

Twelve-lead ECGs will be performed in triplicate approximately 1 minute apart after the patient has been resting in the supine position for at least 10 minutes. Each ECG will include all 12 standard leads and will be recorded at a paper speed of 25 mm/sec. The ECG will be performed at times specified in Appendix A. ECGs will be analyzed locally. The following ECG parameters will be recorded:

- PR interval;
- QRS interval;
- Heart rate;
- RR interval;
- QT interval;
- Corrected QT interval (QTc); and
- QTc using Fridericia's correction.

All ECGs must be evaluated by a qualified Investigator for the presence of abnormalities.

8.10 Physical Examinations

A physical examination will include a full neurologic examination, as well as an assessment of general appearance, skin, eyes, ears, nose, throat, neck, lymph nodes, chest, heart (including auscultation for heart sounds and murmurs), abdomen, extremities, and musculoskeletal systems. A physical examination will be performed at the times specified in Appendix A.

9 STATISTICS

9.1 Analysis Populations

The Safety Analysis Set (SAF) will include all patients who receive at least 1 dose of study drug. The SAF will be used for the summary of patient characteristics and safety analyses.

The Full Analysis Set (FAS) will include all patients who receive at least 1 dose of study drug. The FAS is identical to the SAF. The FAS will be used primarily for the analysis of tumor response and other efficacy-related data.

9.2 Statistical Methods

9.2.1 Analysis of Efficacy

Efficacy analyses will be performed on the FAS. Overall response rate (ORR) will be assessed for each patient as well as the CBR, DoR, and PFS. A water-plot analysis of breast cancer and gastric/GEJ cancer populations will be done. Response magnitude, including CR and near-CR (defined as a >90% confirmed tumor volume reduction) will also be considered.

The primary and secondary efficacy variables are described in Sections 7.1 and 7.2, respectively.

9.2.2 Analysis of Dosimetry

Dosimetry for CAM-H2 via SPECT/CT and planar WB scans will be assessed as described in Section 7.4.6.

All dosimetry evaluations will be done using the OLINDA/EXM or equivalent software. Total dose estimates and the dose estimate for the organs with the highest dose (most likely the kidneys or liver) will be reported using classical descriptive statistics for continuous variables (N, mean, median, standard deviation, minimum, and maximum).

9.2.3 Analysis of Safety

Safety analyses will be performed on the SAF. Descriptive statistics will be used for all safety parameters.

Safety and tolerability will be assessed during the study and will include the incidence and severity of TEAEs, MTD of CAM-H2, DLT rate of CAM-H2, RDP2 for CAM-H2, physical examinations, vital signs, clinical laboratory tests, urinalysis, dosimetry results, and concomitant medications as described in Section 8.

AEs will be coded using the most current version of the Medical Dictionary for Regulatory Activities. TEAEs will be summarized by system organ class and preferred term. TEAEs will be further classified by maximum severity and relationship to treatment. A list of SAEs, AEs leading to withdrawal from the study, and AEs leading to death will be provided.

Summary statistics for laboratory values will be provided at baseline, post-baseline, and for changes from baseline to post-baseline by treatment. Vital signs and ECG parameters will be summarized similarly. The occurrence of laboratory abnormalities will be summarized by treatment. Physical examination data will be listed.

Concomitant medications will be coded using the most current version of the WHO Drug Dictionary. Concomitant medication data will be summarized by treatment. Concomitant medication data and prior medications will be listed.

9.2.4 Sample Size Determination

The proposed study is a dose escalation (Phase 1) study with an expansion cohort reaching into dose expansion (Phase 2). No formal sample size calculation was performed for dose escalation (Phase 1) of the study. A maximum of 18 patients are planned for dose escalation.

No formal sample size calculation was performed for dose expansion (Phase 2). However, a planned sample size of 52 patients is deemed sufficient to obtain an initial estimate of response rates to formally power a subsequent Phase 2/3 study.

For each indication (ie, breast, gastric, or GEJ cancer), an interim evaluation of efficacy will be conducted when approximately 50% of patients complete Cycle 1 at the recommended dose for expansion based on objective responses determined from RECIST 1.1 or RANO-BM. One analysis will be performed for patients with breast cancer, and another analysis will be performed for patients with gastric or GEJ cancer. If the ORR is <10% for a specific indication (ie, breast or gastric/GEJ), the study will be terminated for that particular indication.

The Statistical Analysis Plan will provide more details on the exact statistical approach.

10 DATA MANAGEMENT AND RECORD KEEPING

10.1 Data Management

10.1.1 Data Handling

Data will be recorded at the site on eCRFs and reviewed by the clinical research associate (CRA) during monitoring visits. The CRAs will verify data recorded in the EDC system with source documents. All corrections or changes made to any study data must be appropriately tracked in an audit trail in the EDC system. An eCRF will be considered complete when all missing, incorrect, and/or inconsistent data have been accounted for.

10.1.2 Computer Systems

Data will be processed using a validated computer system conforming to regulatory requirements.

10.1.3 Data Entry

Data must be recorded using the EDC system as the study is in progress. All site personnel must log into the system using their secure user name and password in order to enter, review, or correct study data. These procedures must comply with Title 21 of the Code of Federal Regulations (21 CFR Part 11) and other appropriate international regulations. All passwords will be strictly confidential.

10.1.4 Medical Information Coding

For medical information, the following thesauri will be used:

- Medical Dictionary for Regulatory Activities (most current version) for medical history and AEs; and
- WHO Drug Dictionary for prior and concomitant medications.

10.1.5 Data Validation

Validation checks programmed within the EDC system, as well as supplemental validation performed via review of the downloaded data, will be applied to the data in order to ensure accurate, consistent, and reliable data. Data identified as erroneous, or data that are missing, will be referred to the site for resolution through data queries.

The eCRFs must be reviewed and electronically signed by the Investigator.

10.2 Record Keeping

Records of patients, source documents, monitoring visit logs, eCRFs, inventory of study drug, regulatory documents, and other Sponsor correspondence pertaining to the study must be kept in the appropriate study files at the site. Source data are defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the evaluation and reconstruction of the clinical study. Source data are contained in source documents (original records or certified copies). These records will be retained in a secure file for the period as set forth in the Clinical Study Agreement. Prior to transfer or

destruction of these records, the Sponsor must be notified in writing and be given the opportunity to further store such records.

10.3 Study End

The study end is defined as 12 months after the last patient's EOT/ET Visit.

11 INVESTIGATOR REQUIREMENTS AND QUALITY CONTROL

11.1 Ethical Conduct of the Study

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve human patients. Compliance with this standard provides public assurance that the rights, safety, and wellbeing of study patients are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical study data are credible.

11.2 Institutional Review Board/Independent Ethics Committee

The Institutional Review Board (IRB) or Independent Ethics Committee (IEC) will review all appropriate study documentation in order to safeguard the rights, safety, and well-being of patients. The study will only be conducted at sites where IRB/IEC approval has been obtained. The protocol, Investigator's Brochure, ICF, advertisements (if applicable), written information given to the patients, safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC by the Investigator.

Federal regulations and International Council for Harmonisation (ICH) Guidelines require that approval be obtained from an IRB/IEC prior to participation of patients in research studies. Prior to study onset, the protocol, any protocol amendments, ICFs, advertisements to be used for patient recruitment, and any other written information regarding this study to be provided to a patient or patient's legal guardian must be approved by the IRB/IEC.

No drug will be released to the site for dosing until written IRB/IEC authorization has been received by the Sponsor.

It is the responsibility of the Sponsor or their designee (ie, Medpace) to obtain the approval of the responsible ethics committees according to the national regulations.

The study will only start in the respective sites once the respective committee's written approval has been given.

11.3 Informed Consent

The ICF and any changes to the ICF made during the course of the study must be agreed to by the Sponsor or designee and the IRB/IEC prior to its use and must be in compliance with all ICH GCP, local regulatory requirements, and legal requirements.

The Investigator must ensure that each study patient is fully informed about the nature and objectives of the study and possible risks associated with participation and must ensure that the patient has been informed of his/her rights to privacy. The Investigator will obtain written informed consent from each patient before any study-specific activity is performed and should document in the source documentation that consent was obtained prior to enrollment in the study. The original signed copy of the ICF must be maintained by the Investigator and is subject to inspection by a representative of the Sponsor, their representatives, auditors, the IRB/IEC and/or regulatory agencies. A copy of the signed ICF will be given to the patient.

11.4 Subject Card

On enrollment in the study, the patient will receive a subject card to be carried at all times. The subject card will state that the patient is participating in a clinical research study, with a radio-pharmaceutical study treatment, number of treatment packs received, and contact details in case of an SAE. The subject card will also outline any local guidelines or restrictions put in place in order to minimize radiation exposure to third parties.

11.5 Study Monitoring Requirements

It is the responsibility of the Investigator to ensure that the study is conducted in accordance with the protocol, Declaration of Helsinki, ICH GCP, Directive 2001/20/European Commission, and applicable regulatory requirements, and that valid data are entered into the eCRFs.

To achieve this objective, the CRA's duties are to aid the Investigator and, at the same time, the Sponsor in the maintenance of complete, legible, well-organized and easily retrievable data. Before the enrollment of any patient in this study, the Sponsor or their designee will review with the Investigator and site personnel the following documents: protocol, Investigator's Brochure, eCRFs and procedures for their completion, informed consent process, and the procedure for reporting SAEs.

The Investigator will permit the Sponsor or their designee to monitor the study as frequently as deemed necessary to determine that data recording and protocol adherence are satisfactory. During the monitoring visits, information recorded on the eCRFs will be verified against source documents and requests for clarification or correction may be made. After the eCRF data are entered by the site, the CRA will review the data for safety information, completeness, accuracy, and logical consistency. Computer programs that identify data inconsistencies may be used to help monitor the clinical study. If necessary, requests for clarification or correction will be sent to Investigators. The Investigator and his/her staff will be expected to cooperate with the CRA and provide any missing information, whenever possible.

All monitoring activities will be reported and archived. In addition, monitoring visits will be documented at the site by signature and date on the study-specific monitoring log.

11.6 Disclosure of Data

The collection and processing of personal data from patients enrolled in the study will be limited to those data that are necessary to investigate the safety, quality, and utility of the investigational medicinal product used in the study. These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place.

Sponsor personnel whose responsibilities require access to personal data need to agree to keep the identity of the study patients confidential. During the informed consent process the patients will be informed that, if they participate in this study, the Investigator may be required to allow direct access to patients' original medical records for study-related monitoring, audit, IEC/IRB review and regulatory inspection. The patients will also be informed of possible transfer of the collected personal data to other entities and to other countries and that should such transfer take place, the Sponsor will ensure that technical and organizational measures are put in place to protect the data.

Data generated by this study must be available for inspection by the FDA, the Sponsor or their designee, applicable foreign health authorities, and the IRB/IEC as appropriate. Patients or their legal representatives may request their medical information be given to their personal physician or other appropriate medical personnel responsible for their welfare.

Patient medical information obtained during the study is confidential and disclosure to third parties other than those noted above is prohibited.

11.7 Retention of Records

To enable evaluations and/or audits from regulatory authorities or the Sponsor, the Investigator will keep records, including the identity of all participating patients (sufficient information to link records, eg, eCRFs and hospital records), all original signed ICFs, copies of all eCRFs, SAE forms, source documents, and detailed records of treatment disposition. The records should be retained by the Investigator according to specifications in the ICH guidelines, local regulations, or as specified in the Clinical Study Agreement, whichever is longer. The Investigator must obtain written permission from the Sponsor before disposing of any records, even if retention requirements have been met.

If the Investigator relocates, retires, or for any reason withdraws from the study, the Sponsor should be prospectively notified. The study records must be transferred to an acceptable designee, such as another Investigator, another institution, or to the Sponsor.

11.8 Publication Policy

Following completion of the study, the data may be considered for publication in a scientific journal or for reporting at a scientific meeting. Each Investigator is obligated to keep data pertaining to the study confidential. The Investigator must consult with the Sponsor before any study data are submitted for publication. The Sponsor reserves the right to deny publication rights until mutual agreement on the content, format, interpretation of data in the manuscript, and journal selected for publication are achieved.

11.9 Financial Disclosure

Investigators are required to provide financial disclosure information to the Sponsor to permit the Sponsor to fulfill its obligations under 21 CFR Part 54. In addition, Investigators must commit to promptly updating this information if any relevant changes occur during the study and for a period of 1 year after the completion of the study.

11.10 Insurance and Indemnity

In accordance with the relevant national regulations, the Sponsor has taken out patient liability insurance for all patients who have given their consent to the clinical study. This coverage is designed for the event that a fatality, physical injury, or damage to health occurs during the clinical study’s execution.

11.11 Legal Aspects

The clinical study is submitted to the relevant national competent authorities in all participating countries to achieve a clinical trial authorization (CTA).

The study will commence (ie, initiation of sites) when the CTA and favorable Ethics opinion have been received.

12 STUDY ADMINISTRATIVE INFORMATION

12.1 Protocol Amendments

Any amendments to the study protocol will be communicated to the Investigators by Medpace or the Sponsor. All protocol amendments will undergo the same review and approval process as the original protocol. A protocol amendment may be implemented after it has been approved by the IRB/IEC unless immediate implementation of the change is necessary for patient safety. In this case, the situation must be documented and reported to the IRB/IEC within 5 working days.

13 REFERENCES

1. Iqbal N, Iqbal N. Human epidermal growth factor receptor 2 (HER2) in cancers: overexpression and therapeutic implications. *Mol Biol Int*. 2014:852748
2. Breast Cancer. World Cancer Research Fund Web site. Published 2018. Accessed January 15, 2020.
3. Ross JS, Slodkowska EA, Symmans WF, et al. The HER-2 receptor and breast cancer: ten years of targeted anti-HER-2 therapy and personalized medicine. *Oncologist*. 2009;14(4):320-368.
4. Slamon DJ, Clark GM, Wong SG, et al. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. *Science*. 1987;235(4785):177-182.
5. Larionov AA. Current therapies for human epidermal growth factor receptor 2-positive metastatic breast cancer patients. *Front Oncol*. 2018;8:89.
6. Koo T, Kim IA. Brain metastasis in human epidermal growth factor receptor 2-positive breast cancer: from biology to treatment. *Radiat Oncol J*. 2016;34(1):1-9.
7. AlMazmomy AM, Al-Hayani MM, Alomari M, et al. The use of epidermal growth factor receptor type 2-targeting tyrosine kinase inhibitors in the management of epidermal growth factor receptor type 2-positive gastric cancer: a narrative review. *Cureus*. 2019;11(12):e6295.
8. Cavanna L, Seghini P, Di Nunzio C, et al. Gastric cancer with brain metastasis and the role of human epidermal growth factor 2 status. *Oncol Lett*. 2018;15(4):5787-5791.
9. Bang YJ, Van Cutsem E, Feyereislova A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. *Lancet*. 2010;376(9742):687-697.
10. Vaneycken I, Devoogdt N, Van Gassen N, et al. Preclinical screening of anti-HER2 nanobodies for molecular imaging of breast cancer. *FASEB J*. 2011;25(7):2433-2446.
11. Emami B, Lyman J, Brown A, et al. Tolerance of normal tissue to therapeutic irradiation. *Int J Radiat Oncol Biol Phys*. 1991;21(1):109-122.
12. CKD-EPI creatinine equation (2009). National Kidney Foundation. https://www.kidney.org/content/ckd-epi-creatinine-equation-2009. Accessed 22 September 2021.
13. American Thyroid Association Taskforce On Radioiodine Safety, Sisson JC, Freitas J, et al. Radiation safety in the treatment of patients with thyroid diseases by radioiodine ^{131}I: practice recommendations of the American Thyroid Association [published correction appears in *Thyroid*. 2011;21(6):689]. *Thyroid*. 2011;21(4):335-346.

APPENDIX A: SCHEDULE OF PROCEDURES

Table 7. Schedule of Procedures: Dose Escalation Phase, Cycle 1

Study Period	Screening[a]		Treatment Period Cycle 1																		LT FU[e]
			Dose 1							Safety FU			Dose 2							Safety FU				
Week	W-4 to W-1		W0							W1	W2	W3	W4							W5	W6	W8	W11[d] (EOT/Cycle 2 Eligibility Assessment)	
Days Relative to Dose Administration	D-28 to D0		D1 to D3							D8	D15	D22	D1[c] to D3							D8	D15	D29	D50	
Visit Number	V1	V2[b]	V3							V4	V5	V6	V7							V8	V9	V10	V11	
Visit Window (Days)	-	-	±3							±1	±3	±3	±3							±3	±3	+7	±7	
			Pre	0 m	30 m	3 h	5 h	24 h	48 h				Pre	0 m	30 m	3 h	5 h	24 h	48 h					
Informed consent	X																							
I/E criteria	X																							
Demographics and medical history[f]	X																						X	X
Prior and con meds[g]	X											X											X	X
Delivery of thyroid-blocking drugs[h]		X	X					X[i]	X			X	X					X[i]	X				X[j]	
Confirmation of ingestion of thyroid-blocking drugs[k]			X					X	X				X					X	X					
Pregnancy evaluation[l]	X	X	X										X										X	

Footnotes at end of table.

Table 7. Schedule of Procedures: Dose Escalation Phase, Cycle 1 (Continued)

Study Period	Screening[a]		Treatment Period Cycle 1																				LT FU[e]
			Dose 1							Safety FU			Dose 2							Safety FU				
Week	W-4 to W-1		W0							W1	W2	W3	W4							W5	W6	W8	W11[d] (EOT/Cycle 2 Eligibility Assessment)	
Days Relative to Dose Administration	D-28 to D0		D1 to D3							D8	D15	D22	D1[c] to D3							D8	D15	D29	D50	
Visit Number	V1	V2[b]	V3							V4	V5	V6	V7							V8	V9	V10	V11	
Visit Window (Days)	-	-	±3							±1	±3	±3	±3							±3	±3	+7	±7	
			Pre	0 m	30 m	3 h	5 h	24 h	48 h				Pre	0 m	30 m	3 h	5 h	24 h	48 h					
Blood sample for ADAs and exploratory biomarkers[m]		X											X										X	
Safety assessments																								
AEs	X----------																						X	X
Weight and height[n]	X																						X	
Physical examination[o]	X		X					X		X	X	X	X					X		X	X	X	X	
Vital signs[p]	X		X		X		X	X	X	X	X	X	X		X		X	X	X	X	X	X	X	
Clinical laboratory tests[q]	X	X						X		X	X	X	X					X		X	X	X	X	
Triplicate 12-lead ECGs	X		X						X	X	X	X	X						X		X		X	
Echo (LVEF)[r]	X																						X	
Urinalysis[s]	X	X						X		X	X	X	X					X		X	X	X	X	
ECOG PS	X																					X		X

Footnotes at end of table.

Table 7. Schedule of Procedures: Dose Escalation Phase, Cycle 1 (Continued)

Study Period	Screening[a]		Treatment Period Cycle 1																		LT FU[e]
			Dose 1							Safety FU			Dose 2							Safety FU				
Week	W-4 to W-1		W0							W1	W2	W3	W4							W5	W6	W8	W11[d] (EOT/Cycle 2 Eligibility Assessment)	
Days Relative to Dose Administration	D-28 to D0		D1 to D3							D8	D15	D22	D1[c] to D3							D8	D15	D29	D50	
Visit Number	V1	V2[b]	V3							V4	V5	V6	V7							V8	V9	V10	V11	
Visit Window (Days)	-	-	±3							±1	±3	±3	±3							±3	±3	+7	±7	
			Pre	0 m	30 m	3 h	5 h	24 h	48 h				Pre	0 m	30 m	3 h	5 h	24 h	48 h					
CAM-H2 administration procedures																								
Radioactive unit admission[t]			X----------X										X----------X											
Premedication therapy[u]			X										X											
Saline infusion[v]			X----------X										X----------X											
Amino acid infusion[w]			X----------X										X----------X											
Study drug administration[x]				X---X										X----X										

Footnotes at end of table.

Table 7. Schedule of Procedures: Dose Escalation Phase, Cycle 1 (Continued)

Study Period	Screening[a]		Treatment Period Cycle 1																			LT FU[e]
			Dose 1							Safety FU			Dose 2							Safety FU				
Week	W-4 to W-1		W0							W 1	W2	W3	W4							W5	W6	W8	W11[d] (EOT/Cycle 2 Eligibility Assessment)	
Days Relative to Dose Administration	D-28 to D0		D1 to D3							D8	D15	D22	D1[c] to D3							D8	D15	D29	D50	
Visit Number	V1	V2[b]	V3							V4	V5	V6	V7							V8	V9	V10	V11	
Visit Window (Days)	-	-	±3							±1	±3	±3	±3							±3	±3	+7	±7	
			Pre	0 m	30 m	3 h	5 h	24 h	48 h				Pre	0 m	30 m	3 h	5 h	24 h	48 h					
Imaging to evaluate organ/target lesion uptake and dosimetry[y]																								
SPECT/CT scan							X	X	X	X							X	X	X	X[aa]				
Planar WB scan							X[z]	X	X	X							X	X	X	X[aa]				
Imaging to evaluate disease status[bb]																								
Diagnostic CT scan	X																					X	X[cc]	X
Brain MRI[dd]	X																					X	X[cc]	X

a. The screening period may be extended up to an additional 2 weeks upon Sponsor approval in certain exceptional cases (eg, to allow for a repeat blood draw or to assess previously unavailable imaging results) following a discussion between the Principal Investigator, Medical Monitor, and Sponsor. Also, if a patient misses a dose of study drug due to study drug production problems (eg, insufficient activity yield, ^{131}I supply problem), the interval between screening activities (V1 and 2) and first dosing (V3) may be extended up to an additional 2 weeks to allow for the production of a new batch of study drug.

b. V2 should occur preferably within the 14 days prior to study drug administration (V3).

c. Dose 2 will begin 7 days after the end of the Dose 1 Safety FU Period. However, if a patient misses Dose 2 of the study drug during a given cycle due to study drug production problems, the interval between Dose 1 and Dose 2 may be extended up to an additional 2 weeks (ie, Dose 2 may occur up to 6 weeks after Dose 1). Safety FU visits after Dose 2 will be scheduled based on the actual Dose 2 visit date.

d. If the patient has CB and the cumulative kidney dose remains <23 Gy (based on the dosimetry results during Cycle 1), the patient will not undergo an EOT Visit but proceed to the next cycle's eligibility assessment visit (Table 8). If the patient does not have CB, the patient will undergo an EOT Visit and no further treatment will be administered. The patient will enter the LT FU period.

e. An LT FU period will start after the EOT (or ET) Visit. Follow-up will continue for a maximum of 12 months as described in Sections 3.1.3 and 6.5. Imaging to evaluate disease status will begin 8 weeks after the last diagnostic CT scan or brain MRI performed during the study treatment period. As long as there is no disease progression, imaging to evaluate disease status will be performed every 8 weeks. For patients with disease progression or starting alternative anticancer therapy, imaging to evaluate disease status will be performed according to the local site standard of care. Additionally, those patients will no longer be followed every 8 weeks, but every 12 weeks, to assess survival, disease status, and post-progression therapy.
f. Medical history should include confirmation of lesion size.
g. Prior and concomitant meds should include information on any thyroid-blocking drugs.
h. Acceptable thyroid-blocking drugs include potassium iodate capsules, potassium iodide capsules, Lugol's 1% solution, and potassium perchlorate capsules (see Section 5.2.5.1). Patients will not always take the thyroid-blocking drugs (potassium iodide 130 mg daily or equivalent) on the same day that they are delivered, but will take them starting 24 hours before study drug administration, 1 hour before study drug administration, and 24 and 48 hours after study drug administration as indicated.
i. If the patient is discharged prior to 48 hours, deliver the thyroid-blocking drugs for 48 hours at 24 hours. Patients will still take the thyroid-blocking drugs 48 hours after study drug administration.
j. Delivery of thyroid-blocking drugs at this visit will occur only for patients eligible for and continuing to Cycle 2.
k. Confirmation of ingestion of thyroid-blocking drugs will be performed by directly asking the patient and by counting pills left in his/her medication bottle.
l. Serum hCG testing will be performed in all female patients of childbearing potential (ie, ovulating, premenopausal, and not surgically sterile) at V1 and V2. Urine hCG test will be performed at all other visits.
m. Blood samples for exploratory biomarkers will be collected from patients who have consented to the procedure. Blood samples will be collected per the laboratory manual instructions.
n. Height will be measured only at V1.
o. Physical examination will include full neurologic examination, as well as an assessment of general appearance, skin, eyes, ears, nose, throat, neck, lymph nodes, chest, heart (including auscultation for heart sounds and murmurs), abdomen, extremities, and musculoskeletal systems.
p. Vital signs will include systolic and diastolic blood pressure, heart rate, respiratory rate, and temperature.
q. Clinical laboratory tests will include thyroid panel (TSH, free T4, and free T3), hematology assessments (WBC count and differential, hemoglobin, hematocrit, and platelet count), coagulation parameters (activated partial thromboplastin time, INR, and prothrombin time), and chemistry assessments (fasting glucose or glycated hemoglobin, creatinine, blood urea nitrogen, sodium, potassium, calcium, chloride, phosphorus, bicarbonate, AST, ALT, GGT, alkaline phosphatase, total bilirubin [or fraction of direct bilirubin if >1.5 × ULN], albumin, total protein, LDH, CK [or fraction of CK-MB if >1.5 × ULN], and cystatin-C). Clinical laboratory tests should be performed prior to any imaging.
r. LVEF may alternatively be measured using a multigated acquisition scan.
s. Urinalysis will evaluate the following kidney biomarkers: KIM-1, NGAL, microalbumin, creatinine, and albumin/creatinine ratio and will evaluate microscopic evaluation of sediment, including cylinders, erythrocytes, and leukocytes.
t. This hospitalization can be shortened if ^{131}I decay and the patient's clearance allow discharge according to the applicable local regulations on radioactive compound exposure. Before the patient is released, a leaflet containing information on radioprotection rules and general precautions after radiation treatment will be distributed (see Appendix F).
u. Anti-emetic, anti-histamine, and anti-pyretic premedication should be administered approximately 30 minutes before the start of the amino acid infusion, according to the site's standard operating procedures. In the case of severe nausea or vomiting during the study drug or amino acid infusion, additional anti-emetic therapy can be initiated as per local procedures.
v. Saline 0.9% infusion will be initiated 30 minutes prior to study drug administration and continued for up to 3 hours after, at a rate of 200 to 300 mL/hour.
w. Administration of the amino acid solution should be initiated 30 minutes prior to study drug administration, with an infusion rate of 250 to 500 mL/hour. Amino acid solution infusion should be continued for 3 hours after study drug administration. Rates lower than 320 mL/hour are not recommended for commercial solutions. The amino acid solution will be prepared as a compounded product, in compliance with the hospital's sterile medicinal product preparation good practices and according to the composition specified in Table 5.
x. This will be injected via a slow IV infusion. The study drug will be administered using a shielded infusion device over approximately 3 to 30 minutes, depending on the volume to be injected.
y. Acceptable time windows for the imaging to evaluate the organ/target lesion uptake and dosimetry are provided in Table 1.
z. During Dose 1 of the cycle, the first planar WB scan will serve as the PD distribution scan.
aa. Although V8 has a visit window of ±3 days, the SPECT/CT and planar WB scans have a window of ±24 hours.

bb. All patients will undergo pre-treatment imaging for eligibility and baseline at V1 with a diagnostic CT scan for RECIST v1.1 and a brain MRI scan for RANO-BM. Imaging to evaluate disease status after treatment will start 4 weeks after the last CAM-H2 infusion (Dose 2) of the cycle at V10 (Week 8). If a patient cannot receive Dose 2 of a given cycle, his/her imaging to evaluate disease status will start at the theoretical timing for Dose 2 (ie, 4 weeks after Dose 1 of the cycle).
cc. Imaging to evaluate disease status will be done at the EOT Visit only. If the patient is continuing to Cycle 2, imaging to evaluate disease status will not be performed.
dd. Brain MRI will only be performed in patients with known brain metastases.

^{131}I = ^{131}Iodine; ADA = anti-drug antibody; AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CB = clinical benefit; CK = creatine kinase; CK-MB = creatine kinase-myocardial band; con = concomitant; CT = computed tomography; D = Day; ECG = electrocardiogram; Echo = echocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; EOT = End of Treatment; ET = Early Termination; FU = follow-up; GGT = gamma-glutamyl transferase; h = hours; hCG = human chorionic gonadotropin; I/E = inclusion/exclusion; INR = international normalized ratio; IV = intravenous; KIM-1 = kidney injury molecule-1; LDH = lactate dehydrogenase; LT = long-term; LVEF = left ventricular ejection fraction; m = minutes; meds = medications; MRI = magnetic resonance imaging; NGAL = neutrophil gelatinase-associated lipocalin; PD = pharmacodynamic(s); Pre = Pre-Treatment; RANO-BM = Response Assessment in Neuro-Oncology Brain Metastases; RECIST = Response Evaluation Criteria in Solid Tumors; SPECT = single photon emission computed tomography; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone; ULN = upper limit of normal; V = Visit; v = version; W = Week; WB = whole body; WBC = white blood cell.

Table 8. Schedule of Procedures: Dose Escalation Phase, Cycles 2, 3, and 4

Study Period	Cycle Eligibility[a]	Treatment Period Cycles 2, 3, and 4																			LT FU[d]
		Dose 1							Safety FU			Dose 2							Safety FU				
Week	W-2 to W-1	W0							W1	W2	W3	W4							W5	W6	W8	W11[c] (EOT/ Eligibility Assess for Next Cycle)	
Days Relative to Dose Administration	D-14 to D0	D1 to D3							D8	D15	D22	D1[b] to D3							D8	D15	D29	D50	
Visit Number (Cycle 2)	V11	V12							V13	V14	V15	V16							V17	V18	V19	V20	
Visit Number (Cycle 3)	V20	V21							V22	V23	V24	V25							V26	V27	V28	V29	
Visit Number (Cycle 4)	V29	V30							V31	V32	V33	V34							V35	V36	V37	V38	
Visit Window (Days)	-	±3							±1	±3	±3	±3							±3	±3	+7	±7	
		Pre	0 m	30 m	3 h	5 h	24 h	48 h				Pre	0 m	30 m	3 h	5 h	24 h	48 h					
Demographics and medical history	X																					X	X
Prior and con meds[e]	X										X											X	X
Delivery of thyroid-blocking drugs[f]	X	X					X[g]	X			X	X					X[g]	X				X[h]	
Confirmation of ingestion of thyroid-blocking drugs[i]		X					X	X				X					X	X					
Pregnancy evaluation[j]	X	X										X										X	
Blood sample for ADAs and exploratory biomarkers[k]	X											X										X	

Footnotes at end of table.

Table 8. Schedule of Procedures: Dose Escalation Phase, Cycles 2, 3, and 4 (Continued)

Study Period	Cycle Eligibility[a]	Treatment Period Cycles 2, 3, and 4																				LT FU[d]
		Dose 1							Safety FU			Dose 2							Safety FU				
Week	W-2 to W-1	W0							W1	W2	W3	W4							W5	W6	W8	W11[c] (EOT/ Eligibility Assess for Next Cycle)	
Days Relative to Dose Administration	D-14 to D0	D1 to D3							D8	D15	D22	D1[b] to D3							D8	D15	D29	D50	
Visit Number (Cycle 2)	V11	V12							V13	V14	V15	V16							V17	V18	V19	V20	
Visit Number (Cycle 3)	V20	V21							V22	V23	V24	V25							V26	V27	V28	V29	
Visit Number (Cycle 4)	V29	V30							V31	V32	V33	V34							V35	V36	V37	V38	
Visit Window (Days)	-	±3							±1	±3	±3	±3							±3	±3	+7	±7	
		Pre	0 m	30 m	3 h	5 h	24 h	48 h				Pre	0 m	30 m	3 h	5 h	24 h	48 h					
Safety assessments																							
AEs	X----------X																						X
Weight	X																					X	
Physical examination[l]	X	X					X		X	X	X	X					X		X	X	X	X	
Vital signs[m]	X	X		X		X	X	X	X	X	X	X		X		X	X	X	X	X	X	X	
Clinical laboratory tests[n]	X								X	X	X	X							X	X	X	X	
Triplicate 12-lead ECGs	X								X		X								X		X	X	
Echo (LVEF)[o]	X																					X	
Urinalysis[p]	X								X		X								X		X	X	
ECOG PS																					X		X

Footnotes at end of table.

Table 8. Schedule of Procedures: Dose Escalation Phase, Cycles 2, 3, and 4 (Continued)

Study Period	Cycle Eligibility[a]	Treatment Period Cycles 2, 3, and 4																		LT FU[d]
		Dose 1							Safety FU			Dose 2							Safety FU				
Week	W-2 to W-1	W0							W1	W2	W3	W4							W5	W6	W8	W11[c] (EOT/ Eligibility Assess for Next Cycle)	
Days Relative to Dose Administration	D-14 to D0	D1 to D3							D8	D15	D22	D1[b] to D3							D8	D15	D29	D50	
Visit Number (Cycle 2)	V11	V12							V13	V14	V15	V16							V17	V18	V19	V20	
Visit Number (Cycle 3)	V20	V21							V22	V23	V24	V25							V26	V27	V28	V29	
Visit Number (Cycle 4)	V29	V30							V31	V32	V33	V34							V35	V36	V37	V38	
Visit Window (Days)	-	±3							±1	±3	±3	±3							±3	±3	+7	±7	
		Pre	0 m	30 m	3 h	5 h	24 h	48 h				Pre	0 m	30 m	3 h	5 h	24 h	48 h					
CAM-H2 administration procedures																							
Radioactive unit admission[q]		X----------X										X----------X											
Premedication therapy[r]		X										X											
Saline infusion[s]		X----------X										X----------X											
Amino acid infusion[t]		X----------X										X----------X											
Study drug administration[u]			X---X										X---------- X										
Imaging to evaluate organ/target lesion uptake[v]																							
Planar WB scan							X[w]										X						
Imaging to evaluate disease status[x]																							
Diagnostic CT scan																					X	X[z]	X
Brain MRI[y]																					X	X[z]	X

Footnotes on the next page.

a. The eligibility assessment for Cycle 2 is the same visit as the EOT/Cycle eligibility assessment in Cycle 1 of the dose escalation phase. (See Table 7).
b. Dose 2 will begin 1 week (7 days) after the end of Dose 1 Safety FU Period. However, if a patient misses a dose of study drug due to study drug production problems or due to other circumstances (in certain cases), the interval between doses may be extended up to 6 weeks (Cycle 2) or up to 12 weeks (Cycles 3 and 4). Safety FU visits after Dose 2 will be scheduled based on the actual Dose 2 visit date.
c. For Cycles 2 and 3, if the patient has CB and the cumulative kidney dose remains <23 Gy (based on the dosimetry results during Cycle 1), the patient will not undergo an EOT Visit but proceed to the next cycle's (ie, Cycle 3 or Cycle 4) Cycle Eligibility visit. If the patient does not have CB or if this is Cycle 4, the patient will undergo an EOT Visit and no further treatment will be administered. The patient will enter the LT FU period.
d. An LT FU period will start after the EOT (or ET) Visit of the last cycle. Follow-up will continue for a maximum of 12 months as described in Sections 3.1.3 and 6.5. Imaging to evaluate disease status will begin 8 weeks after the last diagnostic CT scan or brain MRI performed during the study treatment period. As long as there is no disease progression, imaging to evaluate disease status will be performed every 8 weeks. For patients with disease progression or starting alternative anticancer therapy, imaging to evaluate disease status will be performed according to the local site standard of care. Additionally, those patients will no longer be followed every 8 weeks, but every 12 weeks, to assess survival, disease status, and post-progression therapy.
e. Prior and concomitant meds should include information on any thyroid-blocking drugs.
f. Acceptable thyroid-blocking drugs include potassium iodate capsules, potassium iodide capsules, Lugol's 1% solution, and potassium perchlorate capsules (see Section 5.2.5.1). Patients will not always take the thyroid-blocking drugs (potassium iodide 130 mg daily or equivalent) on the same day that they are delivered, but will take them starting 24 hours before study drug administration, 1 hour before study drug administration, and up to 48 hours after study drug administration as indicated.
g. If the patient is discharged prior to 48 hours, deliver the thyroid-blocking drugs for 48 hours at 24 hours. Patients will still take the thyroid-blocking drugs 48 hours after study drug administration.
h. Delivery of thyroid-blocking drugs at this visit will occur only for patients eligible for and continuing to another cycle (Cycle 3 or Cycle 4).
i. Confirmation of ingestion of thyroid-blocking drugs will be performed by directly asking the patient and by counting pills left in his/her medication bottle.
j. Urine hCG testing will be performed in all female patients of childbearing potential (ie, ovulating, premenopausal, and not surgically sterile).
k. Blood samples for exploratory biomarkers will be collected from patients who have consented to the procedure. Blood samples will be collected per the laboratory manual instructions.
l. Physical examination will include full neurologic examination, as well as an assessment of general appearance, skin, eyes, ears, nose, throat, neck, lymph nodes, chest, heart (including auscultation for heart sounds and murmurs), abdomen, extremities, and musculoskeletal systems.
m. Vital signs will include systolic and diastolic blood pressure, heart rate, respiratory rate, and temperature.
n. Clinical laboratory tests will include thyroid panel (TSH, free T4, and free T3), hematology assessments (WBC count and differential, hemoglobin, hematocrit, and platelet count), coagulation parameters (activated partial thromboplastin time, INR, and prothrombin time), and chemistry assessments (fasting glucose or glycated hemoglobin, creatinine, blood urea nitrogen, sodium, potassium, calcium, chloride, phosphorus, bicarbonate, AST, ALT, GGT, alkaline phosphatase, total bilirubin [or fraction of direct bilirubin if >1.5 × ULN], albumin, total protein, LDH, CK [or fraction of CK-MB if >1.5 × ULN], and cystatin-C). Clinical laboratory tests should be performed prior to any imaging.
o. LVEF may alternatively be measured using a multigated acquisition scan.
p. Urinalysis will evaluate the following kidney biomarkers: KIM-1, NGAL, microalbumin, creatinine, and albumin/creatinine ratio and will evaluate microscopic evaluation of sediment, including cylinders, erythrocytes, and leukocytes.
q. This hospitalization can be shortened if ^{131}I decay and the patient's clearance allow discharge according to the applicable local regulations on radioactive compound exposure. Before the patient is released, a leaflet containing information on radioprotection rules and general precautions after radiation treatment will be distributed (see Appendix F).
r. Anti-emetic, anti-histamine, and anti-pyretic premedication should be administered approximately 30 minutes prior to the start of the amino acid infusion, according to the site's standard operating procedures. In the case of severe nausea or vomiting during the study drug or amino acid infusion, additional anti-emetic therapy can be initiated as per local procedures.
s. Saline 0.9% infusion will be initiated 30 minutes prior to study drug administration and will continue for up to 3 hours after, at a rate of 200 to 300 mL/hour.
t. Administration of the amino acid solution should be initiated 30 minutes prior to study drug administration, with an infusion rate of 250 to 500 mL/hour. Amino acid solution infusion should be continued for 3 hours after study drug administration. Rates lower than 320 mL/hour are not recommended for commercial solutions. The amino acid solution will be prepared as a compounded product, in compliance with the hospital's sterile medicinal product preparation good practices and according to the composition specified in Table 5.

u. This will be injected via a slow IV infusion. The study drug will be administered using a shielded infusion device over approximately 3 to 30 minutes, depending on the volume to be injected.
v. Acceptable time windows for the imaging to evaluate the organ/target lesion uptake are provided in Table 1.
w. During Dose 1 of the cycle, the planar WB scan will serve as the PD distribution scan.
x. Imaging to evaluate disease status will be performed with a diagnostic CT scan and brain MRI (if indicated). Diagnostic CT scan will be performed in all patients. Imaging to evaluate disease status after treatment will start 4 weeks after the last CAM-H2 infusion (Dose 2) of the cycle at V19 (Week 8). If a patient cannot receive Dose 2 of a given cycle, his/her imaging to evaluate disease status will start at the theoretical timing for Dose 2 (ie, 4 weeks after Dose 1 of the cycle).
y. Brain MRI will only be performed in patients with known brain metastases.
z. Imaging to evaluate disease status will be done at the EOT Visit only. If the patient is continuing to another cycle, imaging to evaluate disease status will not be performed.

^{131}I = ^{131}Iodine; ADA = anti-drug antibody; AE = adverse event; ALT = alanine aminotransferase; Assess = assessment; AST = aspartate aminotransferase; CB = clinical benefit; CK = creatine kinase; CK-MB = creatine kinase-myocardial band; con = concomitant; CT = computed tomography; D = Day; ECG = electrocardiogram; Echo = echocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; EOT = End of Treatment; ET = Early Termination; FU = follow-up; GGT = gamma-glutamyl transferase; h = hours; hCG = human chorionic gonadotropin; INR = international normalized ratio; IV = intravenous; KIM-1 = kidney injury molecule-1; LDH = lactate dehydrogenase; LT = long-term; LVEF = left ventricular ejection fraction; m = minutes; meds = medications; MRI = magnetic resonance imaging; NGAL = neutrophil gelatinase-associated lipocalin; PD = pharmacodynamic; Pre = Pre-Treatment; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone; ULN = upper limit of normal; V = Visit; W = Week; WB = whole body; WBC = white blood cell.

Table 9. Schedule of Procedures: Dose Expansion Phase, Cycle 1

Study Period	Screening[a]		Treatment Period Cycle 1																			LT FU[e]
			Dose 1							Safety FU			Dose 2							Safety FU				
Week	W-4 to W-1		W0							W1	W2	W3	W4							W5	W6	W8	W11[d] (EOT/ Cycle 2 Eligibility Assess)	
Days Relative to Dose Administration	D-28 to D0		D1 to D3							D8	D15	D22	D1[c] to D3							D8	D15	D29	D50	
Visit Number	V1	V2[b]	V3							V4	V5	V6	V7							V8	V9	V10	V11	
Visit Window (Days)	-	-	±3							±1	±3	±3	±3							±3	±3	+7	±7	
			Pre	0 m	30 m	3 h	5 h	24 h	48 h				Pre	0 m	30 m	3 h	5 h	24 h	48 h					
Informed consent	X																							
I/E criteria	X																							
Demographics and medical history[f]	X																						X	X
Prior and con meds[g]	X											X											X	X
Delivery of thyroid-blocking drugs[h]		X	X					X[i]	X			X	X					X[i]	X				X[j]	
Confirmation of ingestion of thyroid-blocking drugs[k]			X					X	X				X					X	X					
Pregnancy evaluation[l]	X	X	X										X										X	
Blood sample for ADAs and exploratory biomarkers[m]		X								X			X									X	X	

Footnotes at end of table.

Table 9. Schedule of Procedures: Dose Expansion Phase, Cycle 1 (Continued)

Study Period	Screening[a]		Treatment Period Cycle 1																				LT FU[e]
			Dose 1							Safety FU			Dose 2							Safety FU				
Week	W-4 to W-1		W0							W1	W2	W3	W4							W5	W6	W8	W11[d] EOT/ Cycle 2 Eligibility Assess	
Days Relative to Dose Administration	D-28 to D0		D1 to D3							D8	D15	D22	D1[c] to D3							D8	D15	D29	D50	
Visit Number	V1	V2[b]	V3							V4	V5	V6	V7							V8	V9	V10	V11	
Visit Window (Days)	-	-	±3							±1	±3	±3	±3							±3	±3	+7	±7	
			Pre	0 m	30 m	3 h	5 h	24 h	48 h				Pre	0 m	30 m	3 h	5 h	24 h	48 h					
Safety assessments																								
AEs	X----------																						X	X
Weight and height[n]	X																						X	
Physical examination[o]	X		X					X		X	X	X	X					X		X	X	X	X	
Vital signs[p]	X		X		X		X	X	X	X	X	X	X		X		X	X	X	X	X	X	X	
Clinical laboratory tests[q]	X	X								X	X	X	X							X	X	X	X	
Triplicate 12-lead ECGs	X									X		X								X		X	X	
Echo (LVEF)[r]	X																						X	
Urinalysis[s]	X	X								X		X								X		X	X	
ECOG PS	X																					X		X
CAM-H2 administration procedures																								
Radioactive unit admission[t]			X----------						X				X----------						X					
Premedication therapy[u]			X										X											

Footnotes at end of table.

Table 9. Schedule of Procedures: Dose Expansion Phase, Cycle 1 (Continued)

Study Period	Screening[a]		Treatment Period Cycle 1																		LT FU[e]
			Dose 1							Safety FU			Dose 2							Safety FU				
Week	W-4 to W-1		W0							W1	W2	W3	W4							W5	W6	W8	W11[d] (EOT/ Cycle 2 Eligibility Assess)	
Days Relative to Dose Administration	D-28 to D0		D1 to D3							D8	D15	D22	D1[c] to D3							D8	D15	D29	D50	
Visit Number	V1	V2[b]	V3							V4	V5	V6	V7							V8	V9	V10	V11	
Visit Window (Days)	-	-	±3							±1	±3	±3	±3							±3	±3	+7	±7	
			Pre	0 m	30 m	3 h	5 h	24 h	48 h				Pre	0 m	30 m	3 h	5 h	24 h	48 h					
CAM-H2 administration procedures (continued)																								
Saline infusion[v]			X----------X										X----------X											
Amino acid infusion[w]			X----------X										X----------X											
Study drug administration[x]				X---X										X---X										
Imaging to evaluate organ/target lesion uptake[y]																								
SPECT/CT scan								X										X						
Planar WB scan								X[z]										X						
Imaging to evaluate disease status[aa]																								
Diagnostic CT	X																					X	X[bb]	X
Brain MRI[cc]	X																					X	X[bb]	X

a. The screening period may be extended up to an additional 2 weeks upon Sponsor approval in certain exceptional cases (eg, to allow for a repeat blood draw or to assess previously unavailable imaging results) following a discussion between the Principal Investigator, Medical Monitor, and Sponsor. Also, if a patient misses a dose of study drug due to study drug production problems (eg, insufficient activity yield, ^{131}I supply problem), the interval between screening activities (V1 and 2) and first dosing (V3) may be extended up to an additional 2 weeks to allow for the production of a new batch of study drug.

b. V2 should occur preferably within the 14 days prior to study drug administration (V3).

c. Dose 2 will begin 7 days after the end of the Dose 1 Safety FU Period. However, if a patient misses Dose 2 of the study drug during a given cycle due to study drug production problems, the interval between Dose 1 and Dose 2 may be extended up to an additional 2 weeks (ie, Dose 2 may occur up to 6 weeks after Dose 1). Safety FU visits after Dose 2 will be scheduled based on the actual Dose 2 visit date.
d. If the patient has CB and the cumulative kidney dose remains <23 Gy (based on the dosimetry results during Cycle 1 of dose escalation), the patient will not undergo an EOT Visit but proceed to the next cycle's eligibility assessment visit (Table 10). If the patient does not have CB, the patient will undergo an EOT Visit and no further treatment will be administered. The patient will enter the LT FU period.
e. An LT FU period will start after the EOT (or ET) Visit. Follow-up will continue for a maximum of 12 months as described in Sections 3.1.3 and 6.5. Imaging to evaluate disease status will begin 8 weeks after the last diagnostic CT scan or brain MRI performed during the study treatment period. As long as there is no disease progression, imaging to evaluate disease status will be performed every 8 weeks. For patients with disease progression or starting alternative anticancer therapy, imaging to evaluate disease status will be performed according to the local site standard of care. Additionally, those patients will no longer be followed every 8 weeks, but every 12 weeks, to assess survival, disease status, and post-progression therapy.
f. Medical history should include confirmation of lesion size.
g. Prior and concomitant meds should include information on any thyroid-blocking drugs.
h. Acceptable thyroid-blocking drugs include potassium iodate capsules, potassium iodide capsules, Lugol's 1% solution, and potassium perchlorate capsules (see Section 5.2.5.1). Patients will not always take the thyroid-blocking drugs (potassium iodide 130 mg daily or equivalent) on the same day that they are delivered, but will take them starting 24 hours before study drug administration, 1 hour before study drug administration, and up to 48 hours after study drug administration as indicated.
i. If the patient is discharged prior to 48 hours, deliver the thyroid-blocking drugs for 48 hours at 24 hours. Patients will still take the thyroid-blocking drugs 48 hours after study drug administration.
j. Delivery of thyroid-blocking drugs at this visit will occur only for patients eligible for and continuing to Cycle 2.
k. Confirmation of ingestion of thyroid-blocking drugs will be performed by directly asking the patient and by counting pills left in his/her medication bottle.
l. Serum hCG testing will be performed in all female patients of childbearing potential (ie, ovulating, premenopausal, and not surgically sterile) at V1 and V2. Urine hCG will be performed at all other visits.
m. Blood samples for exploratory biomarkers will be collected from patients who have consented to the procedure. Blood samples will be collected per the laboratory manual instructions.
n. Height will be measured at V1 only.
o. Physical examination will include full neurologic examination, as well as an assessment of general appearance, skin, eyes, ears, nose, throat, neck, lymph nodes, chest, heart (including auscultation for heart sounds and murmurs), abdomen, extremities, and musculoskeletal systems.
p. Vital signs will include systolic and diastolic blood pressure, heart rate, respiratory rate, and temperature.
q. Clinical laboratory tests will include thyroid panel (TSH, free T4, and free T3), hematology assessments (WBC count and differential, hemoglobin, hematocrit, and platelet count), coagulation parameters (activated partial thromboplastin time, INR, and prothrombin time), and chemistry assessments (fasting glucose or glycated hemoglobin, creatinine, blood urea nitrogen, sodium, potassium, calcium, chloride, phosphorus, bicarbonate, AST, ALT, GGT, alkaline phosphatase, total bilirubin [or fraction of direct bilirubin if >1.5 × ULN], albumin, total protein, LDH, CK [or fraction of CK-MB if >1.5 × ULN], and cystatin-C). Clinical laboratory tests should be performed prior to any imaging.
r. LVEF may alternatively be measured using a multigated acquisition scan.
s. Urinalysis will evaluate the following kidney biomarkers: KIM-1, NGAL, microalbumin, creatinine, and albumin/creatinine ratio and will evaluate microscopic evaluation of sediment, including cylinders, erythrocytes, and leukocytes.
t. This hospitalization can be shortened if ^{131}I decay and the patient's clearance allow discharge according to the applicable local regulations on radioactive compound exposure. Before the patient is released, a leaflet containing information on radioprotection rules and general precautions after radiation treatment will be distributed (see Appendix F).
u. Anti-emetic, anti-histamine, and anti-pyretic premedication should be administered approximately 30 minutes before the start of the amino acid infusion, according to the site's standard operating procedures. In the case of severe nausea or vomiting during the study drug or amino acid infusion, additional anti-emetic therapy can be initiated as per local procedures.
v. Saline 0.9% infusion will be initiated 30 minutes prior to study drug administration and continued for up to 3 hours after, at a rate of 200 to 300 mL/hour.

w. Administration of the amino acid solution should be initiated 30 minutes prior to study drug administration, with an infusion rate of 250 to 500 mL/hour. Amino acid solution infusion should be continued for 3 hours after study drug administration. Rates lower than 320 mL/hour are not recommended for commercial solutions. The amino acid solution will be prepared as a compounded product, in compliance with the hospital's sterile medicinal product preparation good practices and according to the composition specified in Table 5.
x. This will be injected via a slow IV infusion. The study drug will be administered using a shielded infusion device over approximately 3 to 30 minutes, depending on the volume to be injected.
y. Acceptable time windows for the imaging to evaluate the organ/target lesion uptake are provided in Table 2.
z. During Dose 1 of the cycle, the planar WB scan will serve as the PD distribution scan.
aa. All patients will undergo pre-treatment imaging for eligibility and baseline at V1 with a diagnostic CT scan for RECIST v1.1 and a brain MRI scan for RANO-BM. Imaging to evaluate disease status after treatment will start 4 weeks after the last CAM-H2 infusion (Dose 2) of the cycle at V10 (Week 8). If a patient cannot receive Dose 2 of a given cycle, his/her imaging to evaluate disease status will start at the theoretical timing for Dose 2 (ie, 4 weeks after Dose 1 of the cycle).
bb. Imaging to evaluate disease status will be done at the EOT Visit only. If the patient is continuing to Cycle 2, imaging to evaluate disease status will not be performed.
cc. Brain MRI will only be performed in patients with known brain metastases.

^{131}I = ^{131}Iodine; ADA = anti-drug antibody; AE = adverse event; ALT = alanine aminotransferase; Assess = assessment; AST = aspartate aminotransferase; CB = clinical benefit; CK = creatine kinase; CK-MB = creatine kinase-myocardial band; con = concomitant; CT = computed tomography; D = Day; ECG = electrocardiogram; Echo = echocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; EOT = End of Treatment; ET = Early Termination; FU = follow-up; GGT = gamma-glutamyl transferase; h = hours; hCG = human chorionic gonadotropin; I/E = inclusion/exclusion; INR = international normalized ratio; IV = intravenous; KIM-1 = kidney injury molecule-1; LDH = lactate dehydrogenase; LT = long-term; LVEF = left ventricular ejection fraction; m = minutes; meds = medications; MRI = magnetic resonance imaging; NGAL = neutrophil gelatinase-associated lipocalin; PD = pharmacodynamic; Pre = Pre-Treatment; RANO-BM = Response Assessment in Neuro-Oncology Brain Metastases; RECIST = Response Evaluation Criteria in Solid Tumors; SPECT = single photon emission computed tomography; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone; ULN = upper limit of normal; V = visit; v = version; W = Week; WB = whole body; WBC = white blood cell.

Table 10. Schedule of Procedures: Dose Expansion Phase, Cycle 2

Study Period	Cycle 2 Eligibility[a]	Treatment Period Cycle 2																				LT FU[c]
		Dose 1							Safety FU			Dose 2							Safety FU				
Week	W-2 to W-1	W0							W1	W2	W3	W4							W5	W6	W8	W11 (EOT)	
Days Relative to Dose Administration	D-14 to D0	D1 to D3							D8	D15	D22	D1[b] to D3							D8	D15	D29	D50	
Visit Number	V11	V12							V13	V14	V15	V16							V17	V18	V19	V20	
Visit Window (Days)	-	±3							±1	±3	±3	±3							±3	±3	+7	±7	
		Pre	0 m	30 m	3 h	5 h	24 h	48 h				Pre	0 m	30 m	3 h	5 h	24 h	48 h					
Demographics and medical history	X																						X
Prior and con meds[d]	X										X											X	X
Delivery of thyroid-blocking drugs[e]	X	X					X[f]	X			X	X					X[f]	X					
Confirmation of ingestion of thyroid-blocking drugs[g]		X					X	X				X					X	X					
Pregnancy evaluation[h]	X	X										X										X	
Blood sample for ADAs and exploratory biomarkers[i]	X								X			X									X	X	
Safety assessments																							
AEs	X----------X																						X
Weight	X																					X	
Physical examination[j]	X	X					X		X	X	X	X					X		X	X	X	X	

Footnotes at end of table.

Table 10. Schedule of Procedures: Dose Expansion Phase, Cycle 2 (Continued)

Study Period	Cycle 2 Eligibility[a]	Treatment Period Cycle 2																					LT FU[c]
		Dose 1							Safety FU			Dose 2							Safety FU				
Week	W-2 to W-1	W0							W1	W2	W3	W4							W5	W6	W8	W11 (EOT)	
Days Relative to Dose Administration	D-14 to D0	D1 to D3							D8	D15	D22	D1[b] to D3							D8	D15	D29	D50	
Visit Number	V11	V12							V13	V14	V15	V16							V17	V18	V19	V20	
Visit Window (Days)	-	±3							±1	±3	±3	±3							±3	±3	+7	±7	
		Pre	0 m	30 m	3 h	5 h	24 h	48 h				Pre	0 m	30 m	3 h	5 h	24 h	48 h					
Safety assessments (continued)																							
Vital signs[k]	X	X		X		X	X	X	X	X	X	X		X		X	X	X	X	X	X	X	
Clinical laboratory tests[l]	X								X	X	X	X							X	X	X	X	
Triplicate 12-lead ECGs	X								X		X								X		X	X	
Echo (LVEF)[m]	X																					X	
Urinalysis[n]	X								X		X								X		X	X	
ECOG PS																					X		X
CAM-H2 administration procedures																							
Radioactive unit admission[o]		X----------X										X----------X											
Premedication therapy[p]		X										X											
Saline infusion[q]		X----------X										X----------X											
Amino acid infusion[r]		X----------X										X----------X											
Study drug administration[s]			X---X										X---X										

Footnotes at end of table.

Table 10. Schedule of Procedures: Dose Expansion Phase, Cycle 2 (Continued)

Study Period	Cycle 2 Eligibility[a]	Treatment Period Cycle 2																				LT FU[c]
		Dose 1							Safety FU			Dose 2							Safety FU			
Week	W-2 to W-1	W0							W1	W2	W3	W4							W5	W6	W8	W11 (EOT)	
Days Relative to Dose Administration	D-14 to D0	D1 to D3							D8	D15	D22	D1[b] to D3							D8	D15	D29	D50	
Visit Number	V11	V12							V13	V14	V15	V16							V17	V18	V19	V20	
Visit Window (Days)	-	±3							±1	±3	±3	±3							±3	±3	+7	±7	
		Pre	0 m	30 m	3 h	5 h	24 h	48 h				Pre	0 m	30 m	3 h	5 h	24 h	48 h					
Imaging to evaluate organ/target lesion uptake[t]																							
Planar WB scan							X[u]										X						
Imaging to evaluate disease status[v]																							
Diagnostic CT scan																					X	X	X
Brain MRI[w]																					X	X	X

a. The eligibility assessment visit for Cycle 2 is the same visit as the EOT/Cycle 2 eligibility assessment in Cycle 1 of the dose expansion phase (see Table 9).
b. Dose 2 will begin 7 days after the end of the Dose 1 Safety FU Period. However, if a patient misses Dose 2 of the study drug during a given cycle due to study drug production problems, the interval between Dose 1 and Dose 2 may be extended up to an additional 2 weeks (ie, Dose 2 may occur up to 6 weeks after Dose 1). Safety FU visits after Dose 2 will be scheduled based on the actual Dose 2 visit date.
c. An LT FU period will start after the EOT (or ET) Visit. Follow-up will continue for a maximum of 12 months as described in Sections 3.1.3 and 6.5. Imaging to evaluate disease status will begin 8 weeks after the last diagnostic CT scan or brain MRI performed during the study treatment period. As long as there is no disease progression, imaging to evaluate disease status will be performed every 8 weeks. For patients with disease progression or starting alternative anticancer therapy, imaging to evaluate disease status will be performed according to the local site standard of care. Additionally, those patients will no longer be followed every 8 weeks, but every 12 weeks, to assess survival, disease status, and post-progression therapy.
d. Prior and concomitant meds should include information on any thyroid-blocking drugs.
e. Acceptable thyroid-blocking drugs include potassium iodate capsules, potassium iodide capsules, Lugol's 1% solution, and potassium perchlorate capsules (see Section 5.2.5.1). Patients will not always take the thyroid-blocking drugs (potassium iodide 130 mg daily or equivalent) on the same day that they are delivered, but will take them starting 24 hours before study drug administration, 1 hour before study drug administration, and up to 48 hours after study drug administration as indicated.
f. If the patient is discharged prior to 48 hours, deliver the thyroid-blocking drugs for 48 hours at 24 hours. Patients will still take the thyroid-blocking drugs 48 hours after study drug administration.
g. Confirmation of ingestion of thyroid-blocking drugs will be performed by directly asking the patient and by counting pills left in his/her medication bottle.
h. Urine hCG testing will be performed in all female patients of childbearing potential (ie, ovulating, premenopausal, and not surgically sterile).
i. Blood samples for exploratory biomarkers will be collected from patients who have consented to the procedure. Blood samples will be collected per the laboratory manual instructions.

j. Physical examination will include full neurologic examination, as well as an assessment of general appearance, skin, eyes, ears, nose, throat, neck, lymph nodes, chest, heart (including auscultation for heart sounds and murmurs), abdomen, extremities, and musculoskeletal systems.
k. Vital signs will include systolic and diastolic blood pressure, heart rate, respiratory rate, and temperature.
l. Clinical laboratory tests will include thyroid panel (TSH, free T4, and free T3), hematology assessments (WBC count and differential, hemoglobin, hematocrit, and platelet count), coagulation parameters (activated partial thromboplastin time, INR, and prothrombin time), and chemistry assessments (fasting glucose or glycated hemoglobin, creatinine, blood urea nitrogen, sodium, potassium, calcium, chloride, phosphorus, bicarbonate, AST, ALT, GGT, alkaline phosphatase, total bilirubin [or fraction of direct bilirubin if >1.5 × ULN], albumin, total protein, LDH, CK [or fraction of CK-MB if >1.5 × ULN], and cystatin-C). Clinical laboratory tests should be performed prior to any imaging.
m. LVEF may alternatively be measured using a multigated acquisition scan.
n. Urinalysis will evaluate the following kidney biomarkers: KIM-1, NGAL, microalbumin, creatinine, and albumin/creatinine ratio and will evaluate microscopic evaluation of sediment, including cylinders, erythrocytes, and leukocytes.
o. This hospitalization can be shortened if ^{131}I decay and the patient's clearance allow discharge according to the applicable local regulations on radioactive compound exposure. Before the patient is released, a leaflet containing information on radioprotection rules and general precautions after radiation treatment will be distributed (see Appendix F).
p. Anti-emetic, anti-histamine, and anti-pyretic premedication should be administered approximately 30 minutes prior to the start of the amino acid infusion, according to the site's standard operating procedures. In the case of severe nausea or vomiting during the study drug or amino acid infusion, additional anti-emetic therapy can be initiated as per local procedures.
q. Saline 0.9% infusion will be initiated 30 minutes prior to study drug administration and will continue for up to 3 hours after, at a rate of 200 to 300 mL/hour.
r. Administration of the amino acid solution should be initiated 30 minutes prior to study drug administration, with an infusion rate of 250 to 500 mL/hour. Amino acid solution infusion should be continued for 3 hours after study drug administration. Rates lower than 320 mL/hour are not recommended for commercial solutions. The amino acid solution will be prepared as a compounded product, in compliance with the hospital's sterile medicinal product preparation good practices and according to the composition specified in Table 5.
s. This will be injected via a slow IV infusion. The study drug will be administered using a shielded infusion device over approximately 3 to 30 minutes, depending on the volume to be injected.
t. Acceptable time windows for the imaging to evaluate the organ/target lesion uptake are provided in Table 2.
u. During Dose 1 of the cycle, the planar WB scan will serve as the PD distribution scan.
v. Imaging to evaluate disease status will be performed with a diagnostic CT scan and brain MRI (if indicated). Diagnostic CT scan will be performed in all patients. Imaging to evaluate disease status after treatment will start 4 weeks after the last CAM-H2 infusion (Dose 2) of the cycle at V19 (Week 8). If a patient cannot receive Dose 2 of a given cycle, his/her imaging to evaluate disease status will start at the theoretical timing for Dose 2 (ie, 4 weeks after Dose 1 of the cycle).
w. Brain MRI will only be performed in patients with known brain metastases.

^{131}I =^{131}Iodine; ADA = anti-drug antibody; AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CK = creatine kinase; CK-MB = creatine kinase-myocardial band; con = concomitant; CT = computed tomography; D = Day; ECG = electrocardiogram; Echo = echocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; EOT = End of Treatment; ET = Early Termination; FU = follow-up; GGT = gamma-glutamyl transferase; h = hours; hCG = human chorionic gonadotropin; INR = international normalized ratio; IV = intravenous; KIM-1 = kidney injury molecule-1; LDH = lactate dehydrogenase; LT = long-term; LVEF = left ventricular ejection fraction; m = minutes; meds = medications; MRI = magnetic resonance imaging; NGAL = neutrophil gelatinase-associated lipocalin; PD = pharmacodynamic; Pre = Pre-Treatment; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone; ULN = upper limit of normal; V = Visit; W = Week; WB = whole body; WBC = white blood cell.

APPENDIX B: CLINICAL LABORATORY ANALYTES

Local Laboratory Analytes

Chemistry Panel

Alanine aminotransferase	Albumin
Alkaline phosphatase	Aspartate aminotransferase
Bicarbonate	Blood urea nitrogen
Calcium	Chloride
Creatine kinase [1]	Creatinine
Estimated glomerular filtration rate [2]	Gamma-glutamyl transferase
Glucose (fasting)	Glycated hemoglobin
Lactate dehydrogenase	Phosphorus
Potassium	Sodium
Total bilirubin [3]	Total protein

1. If creatine kinase is >1.5 × upper limit of normal (ULN), then fraction of creatine kinase-myocardial band will be measured.
2. This will be measured using the Chronic Kidney Disease Epidemiology Collaboration equation.
3. If total bilirubin is >1.5 × ULN, then fraction of direct bilirubin will be measured.

Coagulation Parameters

Activated partial thromboplastin time	International normalized ratio
Prothrombin time	

Endocrinology

Free triiodothyronine	Free thyroxine
Human chorionic gonadotropin (hCG) [1]	Thyroid-stimulating hormone

1. Serum or urine hCG testing will be performed in all female patients of childbearing potential (ie, ovulating, premenopausal, and not surgically sterile).

Hematology

Hematocrit	Hemoglobin
Platelets	White blood cell count and differential [1]

1. Manual microscopic review is performed only if white blood cell count and/or differential values are out of reference range.

Urinalysis for microscopic evaluation of sediment

Cylinders	Erythrocytes
Leukocytes	

Optional Tests for Drug-Related Hypersensitivity Reactions

Basophil activation/histamine release test	Complement parameters [1]
Cytokines	Immunoglobulin E
Skin tests	Tryptase

1. Complement parameters will include C3a and C5a.

Central Laboratory Analytes

Additional Chemistry Parameters

Cystatin-C

Urinalysis for kidney biomarkers

Albumin/creatinine ratio	Creatinine
Kidney injury molecule-1	Microalbumin
Neutrophil gelatinase-associated lipocalin	

Other Laboratory Tests

Anti-drug antibodies

APPENDIX C: EASTERN COOPERATIVE ONCOLOGY PERFORMANCE STATUS

Table 11. Eastern Cooperative Oncology Group Performance Status

Grade	Description
0	Fully active, able to carry on all predisease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (eg, light house work, office work).
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry out any self-care. Totally confined to bed or chair.
5	Dead.
Source: Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol*. 1982;5(6):649-655	

APPENDIX D: TUMOR MEASUREMENTS AND THE RESPONSE EVALUATION CRITERIA IN SOLID TUMORS VERSION 1.1

Tumor measurements for Response Criteria in Solid Tumors (RECIST) version 1.1 are to be performed for all patients during screening as follows:

- All patients will undergo pre-treatment imaging for eligibility and baseline at Visit 1 with a diagnostic computed tomography (CT) scan for RECIST version 1.1.

Thereafter, tumor measurements and disease response assessments are to be performed as follows:

- Imaging to evaluate disease status after treatment will start 4 weeks after the last CAM-H2 infusion (Dose 2) of the cycle, at Week 8 (Visit 10 or Visit 19), and every 8 weeks thereafter, as long as there is no disease progression. For patients with disease progression, imaging to evaluate disease status will be performed according to the local site standard of care).

During screening, tumor lesions are to be categorized as measurable versus non-measurable and target versus non-target, as follows:

Measurable versus non-measurable

- Measurable: Measurable disease is defined as:
  - Lesions that can accurately be measured in at least 1 dimension (the longest diameter in the plane of measurement to be recorded) with a size ≥10 mm by CT scan; and
  - Malignant lymph nodes ≥15 mm in short axis when assessed by CT scan. At baseline and in follow-up, only the short axis will be measured and followed.
- Non-measurable: Non-measurable disease is defined as all other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), and truly non-measurable lesions.

Target versus non-target

- Target: Target lesions will include all measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs. Target lesions are to be selected on the basis of their size (ie, those with the longest diameter) and suitability for accurate repeated measurement. Lymph nodes may be selected as target lesions; they must be defined as measurable, and only the short axis of the node will contribute to the baseline sum. All other pathologic nodes with short axis ≥10 mm but <15 mm should be considered non-target lesions; and
- Non-target: All other lesions not classified as target lesions (or sites of disease) are to be identified as non-target lesions and are to be recorded in the electronic case report form. Measurement is not required.

Disease response in target and non-target lesions will be assessed by the Investigator using RECIST version 1.1, according to the categories and criteria described in Table 12 below.

Table 12. Response Evaluation Criteria in Solid Tumors Version 1.1 Guidelines

Disease Response Criteria for Target and Non-Target Lesions	
Evaluation of Target Lesions	
CR	Disappearance of all target lesions. Any pathologic lymph nodes (whether target or non-target lesions) must have a reduction in SAD to less than 10 mm.
PR	At least a 30% decrease in the SOD (LD for non-nodal lesions and SAD for nodal lesions) of target lesions, taking as reference the baseline sum diameters.
SD	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters since the treatment started.
PD	At least 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest sum on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm (Note: the appearance of 1 or more new lesions is also considered progression).
Evaluation of Non-Target Lesions	
CR	Disappearance of all non-target lesions and normalization of tumor marker level.
Non-CR/Non-PD	Persistence of 1 or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits.
PD	Appearance of 1 or more new lesions and/or unequivocal progression of existing non-target lesions.

CR = complete response; LD = longest diameter; PD = progressive disease; PR = partial response; SAD = short axis diameters; SD = stable disease; SOD = sum of the diameters.
Source: Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45(2):228-247

APPENDIX E: BRAIN TUMOR MEASUREMENTS AND RESPONSE ASSESSMENT IN NEURO-ONCOLOGY BRAIN METASTASES

Brain tumor measurements for Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM) are to be performed for patients during screening as follows:

- Patients with known brain metastases will undergo a magnetic resonance imaging scan for RANO-BM at Visit 1.

Thereafter, tumor measurements and disease response assessments are to be performed as follows:

- Imaging to evaluate disease status after treatment will start 4 weeks after the last CAM-H2 infusion (Dose 2) of the cycle, at Week 8 (Visit 10 or Visit 19), and every 8 weeks thereafter, as long as there is no disease progression. For patients with disease progression, imaging to evaluate disease status will be performed according to the local site standard of care.

During screening, tumor lesions are to be categorized as measurable versus non-measurable and target versus non-target, as follows:

Measurable versus non-measurable

- Measurable: Measurable disease is defined as a contrast-enhancing lesion that can be accurately measured in at least 1 dimension, with the following characteristics:
  - Lesion size: ≥10 mm; and
  - Visible on ≥2 or more axial slices, preferably 5 mm or less apart with 0 mm skip (and ideally ≤1.5 mm apart with 0 mm skip).
- Non-measurable: Non-measurable disease includes all other lesions, including small lesions (longest diameter <10 mm), lesions with borders that cannot be reproducibly measured, dural metastases, bony skull metastases, cystic-only lesions, and leptomeningeal disease.

Target versus non-target

- Target: Target lesions will include all measurable lesions, up to a maximum of 5 lesions. When more than 1 measurable lesions in the central nervous system (CNS) is present at baseline, all lesions up to a maximum of 5 CNS lesions should be identified as target lesions and will be recorded and measured at baseline. If a patient has multiple lesions, of which only 1 or 2 are increasing in size, the enlarging lesions should be considered the target lesions and other lesions will be considered non-target lesions;
- A sum of the diameters for all target lesions will be calculated and reported as the baseline sum of longest diameters; and
- Non-target: All other lesions not classified as target lesions are to be identified as non-target lesions. Non-target lesions should be identified and recorded in the electronic case report form at baseline. Measurement is not required.

Disease response in target and non-target lesions will be assessed by the Investigator using RANO-BM, according to the categories and criteria described in Table 13 and Table 14 below.

Table 13. Response Assessment in Neuro-Oncology Brain Metastases

Disease Response Criteria for Target and Non-Target Lesions	
Evaluation of Target Lesions	
CR	Disappearance of all CNS target lesions sustained for at least 4 weeks with no new lesions, no use of corticosteroids, and patient is stable or improved clinically.
PR	At least a 30% decrease in the sum longest diameter or CNS target lesions, taking as reference the baseline sum longest diameter sustained for at least 4 weeks; no new lesions; stable to decreased corticosteroid dose; stable or improved clinically.
SD	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum longest diameter while on study.
PD	At least a 20% increase in the sum longest diameter of CNS target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, at least 1 lesion must increase by an absolute value of 5 mm or more to be considered progression.
Evaluation of Non-Target Lesions	
CR	Disappearance of all enhancing CNS non-target lesions and no new CNS lesions.
Non-CR or Non-PD	Persistence of 1 or more non-target CNS lesion or lesions.
PD	Unequivocal progression of existing enhancing non-target CNS lesions, new lesion(s) (except while on immunotherapy-based treatment*), or unequivocal progression of existing tumor-related non-enhancing (T2/FLAIR) CNS lesions.

*In the case of immunotherapy-based treatment, new lesions alone may not constitute PD.
CNS = central nervous system; CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease; T2-FLAIR = T2-weighted fluid attenuated inversion recovery.
Source: Lin NU, Lee EQ, Aoyama H, et al. Response assessment criteria for brain metastases: proposal from the RANO group. *Lancet Oncol*. 2015;16(6):e270-e278

Table 14. Summary of the Response Criteria for Central Nervous System Metastases Proposed by the Response Assessment in Neuro-Oncology Brain Metastases

	CR	PR	SD	PD
Target lesions	None	≥30% decrease in sum longest distance relative to baseline	<30% decrease relative to baseline but <20% increase in sum longest diameter relative to nadir	≥20% increase in sum longest distance relative to nadir [1]
Non-target lesions	None	Stable or improved	Stable or improved	Unequivocal progressive disease [1]
New lesion(s) [2]	None	None	None	Present [1]
Corticosteroids	None	Stable or decreased	Stable or decreased	NA [3]
Clinical status	Stable or improved	Stable or improved	Stable or improved	Worse [1]
Requirement for response	All	All	All	Any [3]

1. Progression occurs when this criterion is met.
2. A new lesion is one that is not present on prior scans and is visible in a minimum of 2 projections. If a new lesion is equivocal, for example, because of its small size, continued therapy can be considered, and follow-up assessment will clarify if the new lesion is new disease. If repeat scans confirm there is definitely a new lesion, progression should be declared using the date of the initial scan showing the new lesion. For immunotherapy-based approaches, new lesions alone do not define progression.
3. Increase in corticosteroids alone will not be taken into account in determining progression in the absence of persistent clinical deterioration.

CR = complete response; NA = not applicable; PD = progressive disease; PR = partial response; SD = stable disease.
Source: Lin NU, Lee EQ, Aoyama H, et al. Response assessment criteria for brain metastases: proposal from the RANO group. *Lancet Oncol*. 2015;16(6):e270-e278

APPENDIX F: EXAMPLE OF SAFETY INSTRUCTIONS FOR PATIENTS RECEIVING RADIOIODINE TREATMENT

To be given verbally and in writing and edited as appropriate for the patient.

Dear Patient, (name)_____ Date: _____

With regard to your radioiodine therapy, please consider the following:

Step 1: Talk with your doctor or a member of the Radioiodine Treatment Team about the following:

- Why treated women must:
  - Avoid pregnancy for a period of time; and
  - Not breastfeed.
- When treated men can consider fathering a child; and
- Who will give you the radioiodine therapy, and where and when this will happen.

Step 2: Make preparations before treatment and talk with your doctor or a member of the Radioiodine Treatment Team about the following specific items:

- Obtaining the following:
  - Wipes and/or toilet paper that can be flushed down the toilet;
  - Disposable gloves if others will be helping to take care of you; and
  - Heavy duty (doubled if possible), leak proof, specified plastic trash bags for tissues, paper towels, and other things that may be contaminated and trashed.
- For your travel:
  - If you are well enough, it is best to drive yourself;
  - If you ride with someone else, confirm she is not pregnant, and maintain a distance of >3 feet (use the back seat on opposite side of the driver);
  - When and where you can take necessary trips; and
  - When it is safe to use public transportation.
- For home:
  - Living or working with a pregnant woman;
  - Associations with children;
  - Inability to control your urine or bowels;
  - Using special medical equipment, such as catheters, ostomy bags, or anything that could be contaminated by your body fluids;

- Getting sick easily (throw up or get woozy); and
- Not being able to go directly home; arrangements must be made through your treatment team; hotel and motel stays are not recommended.

Step 3: Your doctor or member of the Radioiodine Treatment Team will discuss with you the following items and fill in the number of days related to each:

- Days that you need to stay >3 feet away from your adult family members and caregivers for at least 18 hours a day, and at least 6 feet away as much as possible;
- Days that you need to stay >6 feet away from babies, children younger than 16 years old, and pregnant women;
- Days that you need to stay away from work and close contact with others in public places (movies, shopping, etc); and
- Days that you need to stay away from school or daycare (includes both teachers and students).

Step 4: Recommendations for after therapy include the following:

- At home:
  - Specific recommendations. Ask your doctor for the number of days to:
    - Sleep alone in a bed that is >6 feet away from another person, and, if possible, use a separate bedroom or sleeping room all by yourself;
    - Not kiss anyone;
    - Not have sexual activity;
    - Move your bowels every day and use a laxative if you need help;
    - Empty your bladder (urinate) every hour or so during the day of, and day after your radioiodine treatment; follow your doctor's advice on how much to drink;
    - Use wipes (preferably flushable) to clean the toilet seat after use; men should sit down to urinate and use wipes to remove splatter of urine; wipe yourself dry after urinating so that you do not drip; and
    - For a phone you share with others, after use, wipe off the mouthpiece, or, while using, cover the phone with a plastic bag that, after use, is placed in the specified plastic trash bag.
  - General recommendations, especially for patients sharing a bathroom:
    - Flush the toilet after each time you use it; flush toilet paper and wipes;
    - Always wash your hands well after using the toilet;
    - Rinse the sink and wash your hands after brushing your teeth to wash away the saliva (spit);
    - Do not share your toothbrush, razor, face cloth, towel, food or drinks, spoons, forks, glasses, and dishes;

- Shower every day for at least the first 2 days after your treatment;
- Do not cook for other people. If cooking is necessary, use plastic gloves and dispose of it in the specified plastic trash bag;
- Wash your dishes in a dishwasher or by hand; it is better not to use disposable (throw away) dishes which must be put into a specified plastic trash bag;
- Try to flush any tissues or any other items that contain anything from your body, such as blood, down the toilet; items that cannot be flushed, such as menstrual pads, bandages, paper/plastic dishes, spoons and forks and paper towels, should be put in the specified plastic trash bag;
- Wash your underwear, pajamas, sheets, and any clothes that contain sweat, blood, or urine by themselves; use a standard washing machine; you do not need to use bleach and do not need extra rinses; and
- Have any one who helps you clean up vomit, blood, urine, or stool wear plastic gloves; the gloves should then be put in the specified plastic trash bag.

o Trash recommendations:

- Keep the specified plastic trash bags separate from other trash; keep the bags away from children and animals; and
- A member of your Radioiodine Treatment Team will tell you how and when to get rid of the specified plastic trash bag; you may be asked to bring the bag back to your treatment facility, or, after 80 days, the bag may be removed as other trash bags.

o Pets:

- Usually pets will not receive enough radiation to harm them; however, do not sleep with pets (ask your doctor for how long) since your saliva, perspiration or other secretions may be carried away by the pet.

• Outside the Home:

o Ask Your Doctor or a member of the Radioiodine Treatment Team when:

- It will be safe to eat out, go shopping and attend events such as religious services, parties, and movies;
- You will be able to return to work and to care for or teach others;
- It would be safe to donate blood; and
- Special or longer distance travel is possible (Note: For up to 3 months or more following radioiodine treatment you may set off radiation detectors at national borders, airports, bus and train stations, tunnels, bridges, trash collection sites, and even your place of employment). A member of your Radioiodine Treatment Team will issue you a letter or card describing the therapy and the phone number of a person knowledgeable about your treatment (usually at the treating facility) in case

local law enforcement agents need to check on this information. You should keep the letter or card containing the information with you whenever you are traveling for at least 3 months.

- Emergency care:
  - You will get an information card or letter at the time of your treatment that will show the date, type and amount of radioiodine that you were treated with; carry this card with you at all times for at least 3 months following your treatment; and
  - If you are in a traffic accident or any other medical emergency during the first week after your treatment, you should show this card to the medical people to let them know about the date and dose of your radioiodine treatment.

IMPORTANT INFORMATION FOR PATIENTS ON RISKS OF RADIATION

- Radiation exposure to others should always be As Low As Reasonably Achievable, a goal often abbreviated as ALARA. If you follow the above advice, the radiation from you to others is likely to be less than what they receive from radiation in nature over a year's time; and
- Please phone us if:
  - You have any questions, and particularly if:
    - Any of the above instructions cannot be followed; and/or
    - If you see anything that may have accidentally or unavoidably increased exposure of others to radiation.

We welcome your input on how we can improve our methods and advice to patients.

Phone:_____

Sincerely yours,

_____

Source: American Thyroid Association Taskforce On Radioiodine Safety, Sisson JC, Freitas J, et al. Radiation safety in the treatment of patients with thyroid diseases by radioiodine ^{131}I: practice recommendations of the American Thyroid Association [published correction appears in *Thyroid*. 2011;21(6):689]. *Thyroid*. 2011;21(4):335-346