Phase I Clinical Trial of Evaluating [^{68}Ga] Ga-NOTA-SNA002 for the Safety Tolerance, Radiation Absorbed Dose and Dosimetry in Patients with Solid Tumor

SN-SNA002-2023-001

Clinical Protocol

Version: V4.0, June.24, 2024

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LIST OF ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Science
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
CMS	Centers for Medicare and Medicaid Services
CRF	Case Report Form
CRO	Contract Research Organization
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
FFR	Federal Financial Report
GCP	Good Clinical Practice
IB	Investigator's rochure
ICH	International Conference on Harmonisation
IND	Investigational New Drug Application
IRB	Investigational Review Board
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SOC	System Organ Class
SOP	Standard Operating Procedure
US	United States

STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with Good Clinical Practice (GCP) as required by the following (use applicable regulations depending on study location and sponsor requirements; examples follow):

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)
- ICH E6

All key personnel (all individuals responsible for the design and conduct of this trial) have completed Human Subjects Protection Training.

I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Principal Investigator: _____

Signed: _____Date: _____

PROTOCOL SUMMARY

Title	Phase I Clinical Trial of Evaluating [^{68}Ga] Ga-NOTA-SNA002 for the Safety Tolerance, Radiation Absorbed Dose and Dosimetry in Patients With Solid Tumor.
Proposed Indication	[^{68}Ga] Ga-NOTA-SNA002, as a radiodiagnostic drug, is suitable for detecting PD-L1 positive lesions in solid tumor patients in combination with PET imaging.
Clinical Trial Phase	Phase 1
Study Drugs	SNA002 is a diagnostic recombinant [^{68}Ga]-NOTA-PD-L1 single domain antibody (M18B) injection for intravenous use.
Sponsor	SmartNuclide Biopharma Co., Ltd.
Objective	To determine the safety, pharmacokinetics (PK), biodistribution, dosimetry, and tumor targeting potential of SNA002.
Study Population	Patient 18-75 years of age, male or female, with solid tumors
Number of Patients Planned	The study plans to recruit approximately 12-28 patients. The actual sample size will be dependent upon meeting the dose escalation criteria.
Objectives	**Primary objectives** To evaluate the safety and tolerability of single doses of SNA002 administered intravenously in patients with solid tumors To assess the biodistribution of SNA002 in patients with solid tumors **Secondary objectives** To assess the radiation dosimetry of SNA002 in patients with solid tumors To assess the radiation dose of SNA002 in the blood of patients with solid tumors To assess the PET imaging characteristics of SNA002 in patients with solid tumor To identify the optimal dose To identify optimal image timing window **Exploratory objectives** To explore the correlation between the PET imaging characteristics of SNA002 and PD-L1 binding and the histological PD-L1 expression patterns. To explore the positive and negative predictive efficacy of [^{68}Ga] Ga-NOTA-SNA002.
Endpoint	**Primary Endpoints** Incidence of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) Dosimetry and biodistribution **Secondary Endpoints** Radiation dosimetry of SNA002 Radiation expoure: detecting radioactivity in the blood Recommended diagnostic dose of SNA002 Optimal imaging window SUV_{max} (Standardized uptake value), SUV_{mean}, tumor to background ratio, and tumor to blood ratio. PK parameters of SNA002: Including but not limited to maximum serum concentration (C_{max}), time to reach maximum serum concentration (T_{max}), and area under the serum concentration versus time curve from time zero to time ($AUC_{0-\tau}$), and terminal half-life ($T_{1/2}$). Immunogenicity: incidence of anti-drug antibodies
Study Design	**Overall Study Design** This is an open-label, dose escalation study to evaluate the safety, PK, biodistribution, dosimetry, and tumor targeting potential of SNA002 in patients with solid tumors. This study will consist of Screening Period, Baseline Period, Study Period and Safety Follow-up Period. A signed and dated informed consent form will be obtained before any study-related procedures are performed. Collect CT/MRI/PET/CT results from subjects within one month before screening to obtain baseline tumor assessment. Eligible patients will be enrolled at least two days before the administration of study drug. The radiation dose for all dose groups at the time of administration should be ranged from 37 to 200MBq.Four dose levels of NOTA-SNA002 are planned: 0.1mg, 0.3mg, 0.5mgand 0.9mg. The final drug product administered to the patient is [^{68}Ga]Ga-NOTA-SNA002. Three to seven patients will be sequentially enrolled into each dose cohort. Patients will be administered a single dose of SNA002 over 1 minute as an intravenous bolus. Patients will be observed for 6±1h and 24±6h post infusion for infusion-related and other adverse reactions. In the first cohort of patients, whole body imaging will be acquired using PET/CT at 15±5 minutes, 60±10 minutes and 120±20 minutes post-injection. Before each imaging, the patients need to empty bladder as much as possible. Total-body PET-CT scans can be performed on 1-2 subjects in a certain dose group or each dose group, covering at least one of the aforementioned time points.In the subsequent cohorts,

the imaging schedule may be modified based on the imaging data from the first cohort of patients.

The optimal time point for PET scanning will be determined based on the analysis of the tumor to background ratio and tumor to blood pool ratio at different timepoints. Tumor to background ratio is defined as the ratio between tumor tracer uptake and the radioactivity on the opposite site or gluteus maximus, etc. The first PET scan will be performed in combination with a low-dose CT scan for attenuation correction and anatomic reference. An independent radiology review committee (IRC), consisting of principal investigator and nuclear medicine physicians, will be established to evaluate all imaging data.

If there is no radioactivity or a small amount of radioactivity in the target lesion as evaluated by the IRC, and the safety criteria are met, the dose will be escalated per the escalation guidelines. If the tumor to background ratio is high per the IRC, three patients will be enrolled at the next higher level and the IRC will determine whether dose escalation should stop based on the imaging data from these three patients. Blood samples will be collected from a peripheral vein to evaluate ADA, PK and the radioactivity in the circulation.

- The time points for blood sample collection are as follows: within 30 minutes before injection of SNA002, at 2±1 minutes, 5±1 minutes, 10±1 minutes, 30±2 minutes, 50±5 minutes, 100±5 minutes and 150±10 minutes post injection.All blood samples are sent to the central laboratory for PK analysis. Radioactivity in the blood sample (whole blood and serum)will be obtained using a γ-well-type detector and measured activity concentrations will be converted to percentage injected activity/L.
- Urine sample will be collected to evaluate the renal excretion of radioactivity before injection, at 90±30 minutes, 180±30 minutes and 300±30 minutes post injection. Counts in aliquots of serum or urine will be obtained using a γ-well-type detector and measured activity concentrations will be converted to percentage injected activity/L.

Blood samples will be taken 30 minutes before administration, on D6±1d and D28±2d, and will be sent to the central laboratory for ADA analysis. Patients were discharged from the study after blood samples were collected on D28±2d.Following the last PET scan, tumor biopsies or operation (if surgery is available) will be obtained. The investigator will determine the number and location of lesions for biopsy for each patient in consultation with the surgeon or interventional radiologist; these should be easily accessible and have positive or negative tracer uptake. Biopsy sites should not exceed 5 for each patient and ideally include both negative lesions and positive lesions. If taken an operation on tumor, the IRC will observe IHC result of tumor and PET scan.

The study will be end for patient after completing blood collection on D28±2d.

Region-of-Interest Definition

Regions of interest (ROIs) will be used to determined SNA002 uptake in different organs. Organs with tracer uptake will be drawn using PMOD software based on the PET image, including all activities on the PET images that are contributing to the organ. For organs without tracer uptake, organ delineation will be based on CT data.

To calculate the biodistribution and dosimetry in normal organs with tracer uptake, a semiautomatic (region grow) method will be used to delineate the ROI on the PET images. For normal organs without tracer uptake, the ROI will be delineated based on CT scan.

Dosimetry

Time–activity curves were derived from volumes of interest for each source organ (i.e., brain, heart, lungs, liver, spleen, kidneys, and thyroid) delineated on the whole-body images using PMOD.

To define volumes of interest (VOIs) the dynamic study was loaded with all or some frames averaged, depending on the evaluated organ. VOIs were defined manually for heart, liver, gallbladder, kidneys with all frames averaged.

Using the PMOD software the VOIs consisted of regions of interest (ROIs) which were defined at the outer contour of the organ. In this way (decay-corrected) TACs of the organs'average radioactivity concentrations and their volumes were obtained.

An example, FYI: Source Organs: For dosimetric calculations, the following source organs were included: kidneys, red marrow, cortical bone mineral surface, trabecular bone mineral surface, urinary bladder content, and remainder body. Red marrow activity uptake was estimated from venous blood sampling.

Dose Levels (mg)	Number of patients
0.1	3-7

0.3	3-7
0.5	3-7
0.9	3-7

Dose escalation criteria

Since SNA002 contains a PD-L1 nanobody that cannot block the binding of PD-1 to its ligands and the dose of PD-L1 antibody is extremely low, the main safety risk is likely to be occurrence of infusion-related reactions (IRRs), which are medically manageable.The dose escalation criteria will include image quality criteria and safety criteria (e.g., serious adverse events, Grade 2 or higher adverse events) as described below.

PD-L1 expression will be measured using immunohistochemistry [(IHC); 22C3-IHC assay] by obtaining at least one biopsy of a target lesion that is amenable to aspiration biopsy on Day 2. IHC results will be reviewed by the IRC.The correspondence between the IHC assay results and the PET imaging results will be evaluated by the IRC.

Dose-Escalation Rules

The dose escalation is determined through both imaging results and safety results:

1) **Imaging:**If the first three positive tumor lesions in a certain dose group judged by the IRC to having a high image quality (such as T/B >1.5, etc.), it can be decided from the imaging perspective to increase to the next dose group after continuing to enroll 3-4 cases in this dose group, or directly increase to the next dose group for further exploration;
   - →If the quality of the first 3 cases in the subsequent dose group is comparable to that in the previous dose group, the IRC shall discuss whether to discontinue further enrollment from a imaging perspective (e.g. The image quality of the first 3 cases in the 0.3mg dose group is similar to that in the 0.1mg dose group, then stop recruting, and the 0.1mg dose was identified as the optimal image dose.
   - →If the quality of the first 3 cases in the posterior dose group is higher than that in the prior, another 3 to 4 cases will be enrolled. After the completion of the posterior dose group, the IRC will discuss and decide whether this group should not be explored from the imaging aspect (e.g, The image quality of the first 3 cases in the 0.3mg dose group is higher than that in the 0.1mg dose group, then 3-4 cases continued to be enrolled in the 0.3mg dose group, and the subsequent dose exploration was not carried out, the 0.3mg dose was identified as the optimal image dose).
2) If the first three positive tumor lesions in a certain dose group judged by the IRC to present poor imaging quality (such as T/B ≤ 1) or nonvisualization (functional imaging without nuclides), the decision of stopping enroll in this dose group can be made from an imaging perspective, and the dose group can directly increase to the next or second dose group (for example, if the imaging quality of the 0.1mg dose group is poor in three consecutive cases, the dose group can increase to the 0.3mg or 0.5mg dose group);
3) If the last dose group shows nonvisualization of the positive tumor lesions determined by the IRC in the first three cases, discussion will be conducted to determine whether to adjust the subsequent dose from the imaging perspective to explore or terminate the entire clinical trial.
4) After the dose escalation of all dose groups is completed, the imaging expert committee and the principal investigator will decide whether to continue enrolling 3-4 subjects in a certain initially identified optimal dose group for further exploration.

Security:

The principal investigator determines whether to increase the dose from the perspective of safety. Dose escalation should be stopped if one of the principles happen：① If at least half of subjects in a dose group experience CTCAE grade 2 (or moderate) or above adverse reactions; ②or at least 1/3 subjects experience CTCAE grade 3 (or severe) or above adverse reactions; ③ or one serious adverse reaction in certain group.

The dose escalation will be determined by the principal investigator based on both imaging and safety results.

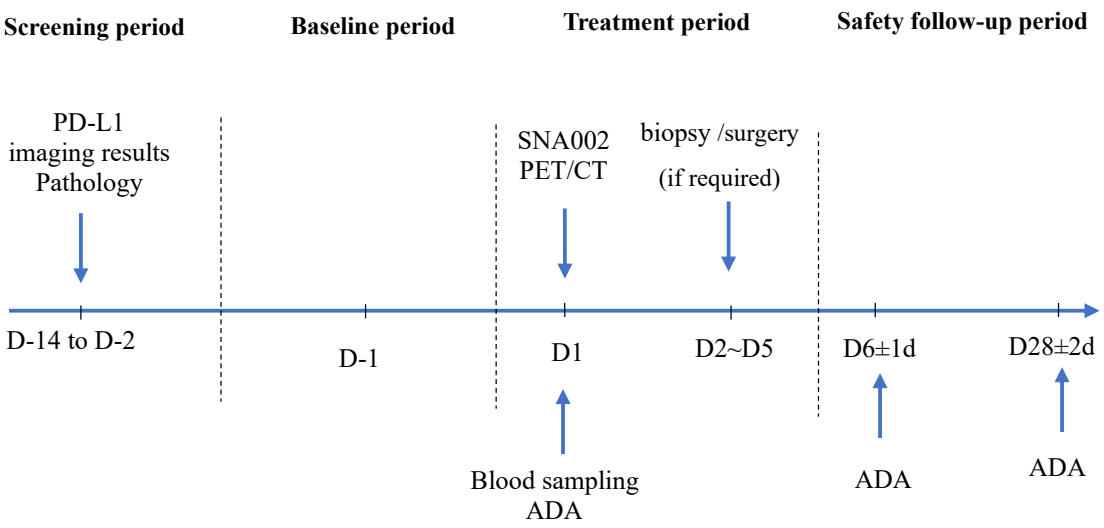
During the clinical trial, based on the principle of subject protection, the dose group can be rapidly escalated to the subsequent dose group if nonvisualization or the above safety events happens after only one subject is enrolled at the investigator's discretion.

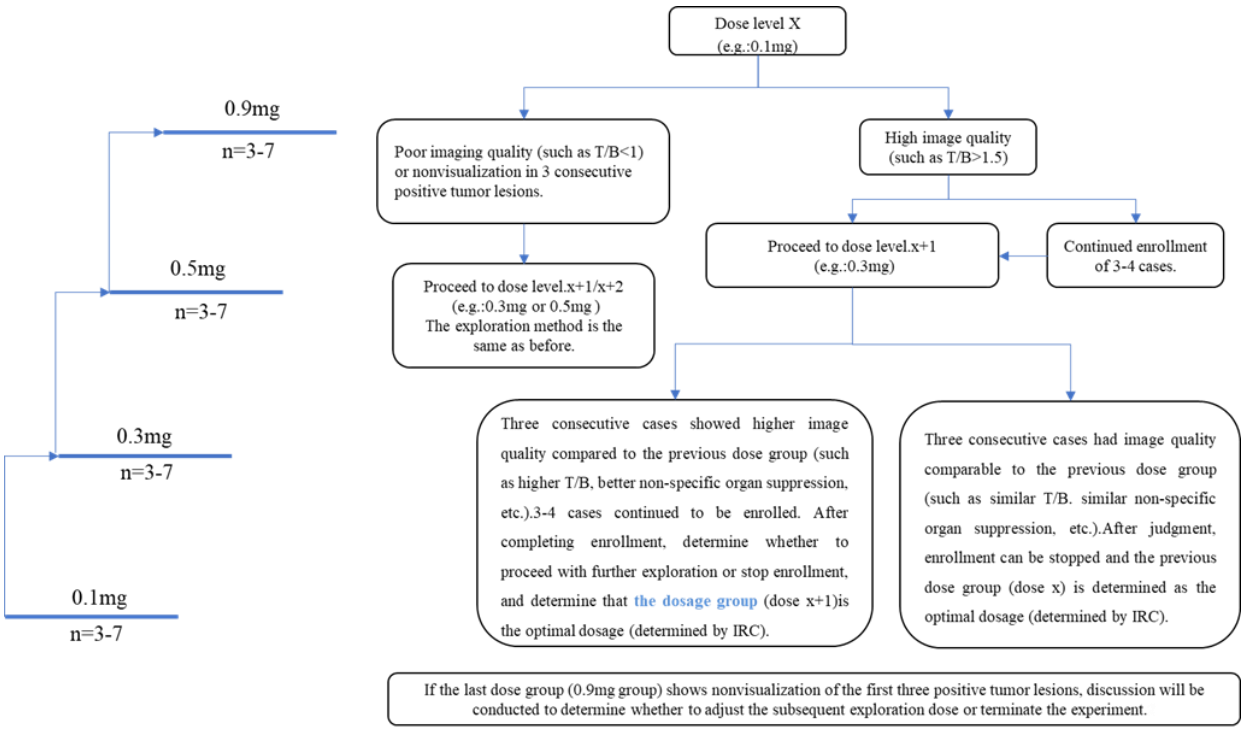
Dose Selection Rationale

SNA002 does not bind to mouse, rat and dog PD-L1. Therefore, cynomolgus monkey was chosen in biodistribution studies and repeat-dose general toxicity studies. ^{68}Ga-NOTA-SNA002 can specifically bind to PD-L1 proteins of primates, and the radioactivity uptake is

	low in other organs except for the excretion organs (kidneys and bladder). The estimated absorbed dose (effective dose) converted from cynomolgus monkeys to adult male or female is 0.022-0.023mSv/MBq, which shows good radiation safety. The recommended dose of ^{68}Ga-NOTA-SNA002 for clinical trials is 185 MBq (5mCi), which generates an effective dose of about 4.1 mSv indicating safe use of ^{68}Ga-NOTA-SNA002 for clinical diagnostics. A NOAEL approach based on the pivotal monkey 2-week study toxicity findings was used to determine the maximum recommended starting dose (MRSD) for the first in human study. In the 2-week monkey study, the potential infusion reaction is the only toxicity observed after 3 repeated iv doses. the dose of 1.5 mg/kg (mean AUC 0-t = 20700 ng•h /mL; mean C_{max} = 32000ng/mL) and 0.5mg/kg (mean AUC_{0-t} = 5060 ng•h /mL; mean C_{max} = 10500ng/mL) was considered the NOAEL for males and females, respectively. Since the molecular weight of ^{68}Ga-NOTA-SNA002 is less than 100KD, The HED is 0.48 mg/kg (male) and 0.16 mag/kg (female) based on body surface. The MRSD is considered to be 0.048 mg/kg (male) and 0.016 mg/kg (female) (1/10 of NOAEL). The highest dose that nonclinical can cover is considered to be 0.24 mg/kg (male) and 0.08 mg/kg (female) (1/2 of NOAEL). The proposed human dose ranges are from 0.00167 mg/kg (0.1mg flat dose) starting dose to the highest ascending dose 0.01503mg/kg (0.9mg flat dose). The starting dose is 28.74- and 9.58-fold lower than the MRSD for males and females, respectively. The highest ascending 0.01503 mg/kg is covered by nonclinical data (½ of the NOAEL). Therefore, the proposed clinical mass dose range of 0.00167mg/kg to 0.01503mg/kg is not expected to pose a significant risk to patient safety.
Duration of Study Participation	Patients will be administered a single dose of SNA002. The duration of study participation will be approximately 42 days, including a screening period up to 14 days and a follow-up period up to 28 days (patients who experience AEs will be followed until resolution).

SCHEMATIC OF STUDY DESIGN





After the dose escalation of all dose groups is completed, the imaging expert committee and the principal investigator will decide whether to enroll another 3 or 4 patients in the identified optimal dose group.

1 Key Roles

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2 Introduction

2.1 Background Information

Epidemiology

Cancer is the second leading cause of death worldwide, accounting for about 1 in every 6 deaths. In 2018, there were an estimated 17.0 million cases of cancer diagnosed and 9.6 million cancer deaths around the world (WHO, 2018). By 2040, the global burden is expected to reach 27.5 million new cancer cases and 16.3 million cancer deaths (American Cancer Society, 2018). To date, the conventional therapies for patients with advanced solid tumors include palliative surgery, chemotherapy, radiotherapy, and more recently immunotherapy has been added to the repertoire.[1].

Table 1 First five incidence and Mortality of Common Cancers in China and America in 2020 (approximate)

China	**Incidence**	Lung (820,000)	Colon (550,000)	Gastric (480,000)	Breast (420,000)	Liver (410,000)
	Mortality	Lung (710,000)	Liver (390,000)	Gastric (370,000)	Esophagus (300,000)	Colon (280,000)
American	**Incidence**	Breast (280,000)	Lung (250,000)	Prostate (240,000)	Colon (170,000)	Bladder (90,000)
	Mortality	Lung (160,000)	Colon (60,000)	Breast (50,000)	Pancreatic (50,000)	Prostate (40,000)

PD-L1 is expressed in many cancers, including bladder, breast, colon, cervical, pancreatic, gastric, and non-small cell lung cancer (NSCLC) as well as melanoma and malignant glioma (Freeman et al 2000).

There are currently 6 PD-(L)1 monoclonal antibodies approved for various cancers in the U.S. Some indications are limited to tumors that are known to express PD-(L)1 while others include

patients regardless of tumor PD-(L)1 expression status. Approximately 20-40% of cancer patients derive clinical benefit from PD-(L)1-targeting mAbs. The efficacy of these mAbs can vary greatly (16–100%) among individual patients. In addition, some studies have reported substantially improved efficacy when used for the treatment of tumors with high PD-(L)1 expression (Walker et al., 2016. Guo et al., 2020. Bensch et al.,2018) . Screening patients for PD-(L)1 expression may be helpful in guiding treatment decisions for patients with certain tumor types at initial diagnosis or at recurrence.

Nuclear medicine and molecular tracing technologies are effective measures for the early diagnosis of solid tumors and extent of disease. The use of radioactive molecular probes allows detection and evaluation of PD-1 and PD-L1 expression in solid tumors, distant metastases, and throughout the body. Unlike immunohistochemistry (IHC) methods for establishing PD-(L)1 expression, radiolabeled PD-(L)1 antibodies offer a noninvasive method (i.e., no biopsy required) of assessing PD-(L)1 expression status and can measure changes in expression during treatment. This technique may therefore serve as an improved strategy for screening and selection of PD-(L)1 responders, optimization of anti-PD-(L)1 regimens, and evaluation of patient prognosis.

Similar products in development

There is currently no PD-L1 imaging agent available in any country. However, several radiolabeledPD-L1 mABs are undergoing clinical evaluation, and these are listed below.

Table 2 List of PD-L1 imaging drug

Product	Study site	Phase	Molecular Type	Molecular Size	Labeled nuclide	Half-life of nuclide	Optimum development time
^{89}Zr-atezolizumab	University Medical Center Groningen	Phase I	Macromolecule monoclonal antibody	150 kDa	^{89}Zr	78.4 h	7 d
^{18}F-BMS-986192	Cancer Center Amsterdam	-	adnectin	10 kDa	^{18}F	109.8 min	70-90 min
^{99}mTc-NM-01	Shanghai General Hospital	Phase I	Single-domain antibody	15 kDa	^{99}mTc	6 h	2 h
^{89}Zr-KN035	The First Affiliated Hospital of Soochow University	Phase I	Single-domain antibody	80 kDa	^{89}Zr	78.4 h	-
RGEN3504	Regeneron Pharmaceuticals Inc.	Phase I	-	-	^{89}Zr	78.4 h	-
^{89}Zr-avelumab	Radboud University Nijmegen	Phase I	Macromolecule monoclonal antibody	150 kDa	^{89}Zr	78.4 h	-
^{89}Zr-durvalumab	Radboud University Nijmegen	Phase I	Macromolecule monoclonal antibody	150 kDa	^{89}Zr	78.4 h	-

2.1.1 ^{89}Zr-atezolizumab

^{89}Zr-atezolizumab is a macromolecule monoclonal antibody with a molecular weight of about 150

kDa. Its optimum development time is on D4–D7 after administration, and the maximum SUV_{max} of the tumor is about 10. However, tumor SUV_{max} is between 5 and 10 on D0–D4 after administration. PET imaging shows that the uptake of 89Zr-atezolizumab is low in brain, subcutaneous tissues, muscle, and lungs, but high in liver and intestinal tract.

A study by de Vries et al. (van de Donk et al., 2020) examined the application of 89Zr-atezolizumab in the evaluation of PD-L1 treatment efficacy in 25 patients with advanced or distant metastatic NSCLC, bladder cancer, or triple negative breast cancer. Twenty-two patients received 37 MBq ^{89}Zr-atezolizumab (1 mg atezolizumab) intravenously and were examined by PET imaging at 1 hour, 2 days, 4 days and 7 days after administration. Tumor SUV_{max} and target to background ratios in the lungs and bone metastases were stable on D7, and SUV_{max} was comparable on D4 and D7. High uptake of the imaging agent was observed in the tumor region, and the geometric mean of SUV_{max} was 10.4 (1.6–46.1). IHC staining of tumor biopsy specimens (IHC kit SP142) showed that higher PD-L1 score was associated with higher 89Zr-atezolizumab uptake in the tumor region (IHC scores of 0, 1, and 2 corresponded to a mean tumor SUV_{max} of 9.2, 10.1, and 17.1, respectively). The mean SUV_{max} of patients was significantly correlated with progression-free survival (PFS) and overall survival (OS). Only one drug-related adverse event (AE), mild pruritis, was observed among the 22 patients (van de Donk et al., 2020).

2.1.2 ^{18}F-BMS-986192

^{18}F-BMS-986192 is a small molecule adnectin-based imaging agent with a molecular weight of about 10 kDa. PET imaging at 70–90 min after administration showed that the mean tumor SUV_{max} was 2.9 in patients with < 50% PD-L1 expression, and 8.2 in patients with > 50% PD-L1 expression. High uptake was observed in the bladder, kidneys, spleen, and liver, and low uptake was observed in bone marrow, lungs, and brain.

Niemeijer et al. (Niemeijer et al., 2018) investigated ^{18}F-BMS-986192 to assess PD-L1 expression in 13 advanced NSCLC patients receiving nivolumab. One patient received 65.5 Mbq ^{18}F-BMS-986192, while the other 12 patients received 3 ± 10% MBq/kg ^{18}F-BMS-986192. Using the SUV value at 70–90 min after injection as a semi-quantitative readout, the SUV_{peak} of ^{18}F-BMS-986192 in the metastatic brain lesion was only 0.2–0.9, which may be attributed to the reduced permeability of imaging agent through the blood-brain barrier. Excluding the SUV of brain metastasis, IHC showed that the SUV_{peak} in patients with < 50% PD-L1 expression was lower (2.9) than that of patients with ≥ 50% PD-L1 expression (8.2). After 3 months of nivolumab therapy, tumor SUV_{peak} was also lower in non-responders (median 3.2) as compared to responders (median 6.5). No grade 3 or greater drug-related AEs were observed among the 13 patients (Niemeijer et al., 2018).

2.1.3 ^{99m}Tc-NM-01

Xing et al. (Xing et al., 2019) reported on ^{99m}Tc-NM-01 use for the assessment of PD-L1 expression in 16 patients with NSCLC. The 16 patients received 3.8–10.4 MBq/kg of ^{99m}Tc-NM-01 (either 100 or 400 μg of NM-01) intravenously and underwent PET imaging at 10 min, 1 h, 2 h, 3 h, and 24 h after administration. PET imaging results at 2 h after administration showed that the tumor-to-lung (TL) and tumor-to-blood pool (TBP) ratios were higher at 2 h (2.69 and 2.22, respectively) than at 1 h after administration (2.22 and 1.79, respectively). The results of tumor IHC staining were consistent with the PET imaging, showing that the 2 h TBP was lower in patients with ≤1% PD-L1 expression (1.89) than in patients with ≥ 1% PD-L1 expression (2.49). No drug-related AEs were observed in all patients during the 7-day follow-up period (Xing et al., 2019). No imaging agent-related AEs were observed in all patients during the 7-day follow-up period. In addition, the symptoms of advanced NSCLC, such as coughing, dyspnea, and fatigue, were not exacerbated by the administration of the imaging agent.

Unmet clinical needs

As nuclear medicine enters into the molecular era, the application of molecular imaging probes has become a topic of active research. PET not only allows early identification and diagnosis of tumors, but also provides systemic imaging of advanced and metastatic tumors. The PD-1/PD-L1 signaling pathway has become one of the key targets of cancer immunotherapy in recent years. PD-1/PD-L1expression levels in tumors may correlate with treatment response and affect prognosis. The development of a PD-1/PD-L1-based radioactive molecular probe is not only important for improved tumor diagnosis effectiveness, but it also offers a potential tool for noninvasive evaluation of tumor PD-1 and PD-L1 expression at diagnosis and during therapy. This may guide treatment regimen optimization and inform prognosis.

2.2 Potential Risks and Benefits

Table 3 SNA002 benefit and risk assessment

	Evidence and uncertainty	**Conclusion and reason**
Analysis of current status	- China has the highest numbers of new cancer cases and cancer deaths in the world. - The top 10 most prevalent malignant solid tumors are lung cancer, gastric cancer, colorectal cancer, liver cancer, breast cancer, oesophageal cancer, thyroid cancer, cervical cancer, brain tumor, and pancreatic cancer, which altogether account for 76.6% of total cancers. - Cancer incidence is rising at a rate of 3.9% annually. - PD-1 is an important immune checkpoint. Studies have found that many tumors can express PD-L1, which can specifically bind to PD-1 on tumor-specific CD8+ T cell surface to suppress their immune response and thereby achieve immune evasion. - Blocking PD-1/PD-L1 signaling pathway can treat tumors. - There are currently several marketed PD-1/PD-L1 drugs that are used for the treatment of NSCLC, metastatic melanoma, and bladder cancer. - The efficacy of mAbs varies greatly (16–100%) among individual cancer patients.	It has significant implications in the screening of immunotherapy responders- Patients who respond to immunotherapy can be effectively identified using the nuclear medicine and molecular tracing. - Molecular imaging with such purpose has already become the hot topic of study.

	- They have up to 90% efficacy in PD-1/PD-L1-positive patients.	
Current treatment methods	- IHC is still the only method for the detection of PD-1 and PD-L1 expression. - This method has several limitations: (1) IHC is an invasive method that requires the acquisition of tissue specimens and the preparation of tissue sections for pathological examination. biopsy cannot be performed on some tumors. (2) IHC results only reflect the PD-1 and PD-L1 expression in the pathological sections and cannot show the PD-1 and PD-L1 expression in distant metastases and throughout the body. (3) IHC detection is complicated and cannot be used for the monitoring of PD-1 and PD-L1 expression during the course of treatment and prognosis. (4) The detected levels of PD-1/PD-L1 expression are easily influenced by previous treatments of the patients.	- IHC is currently the only detection method. - Immunohistochemistry has drawbacks such as invasive examination, inability to dynamically express overall PD-L1 levels, and high heterogeneity.
Expected benefits	- Radionuclide labeling of immunotherapeutic drug molecules and real-time and in vivo detection using molecular imaging methods can provide new strategies for patient screening, efficacy detection, treatment regimen optimization, and prognosis evaluation. - Netspot and Detectnet for neuroendocrine tumor imaging have been approved by the FDA for marketing. - SNA002 has a good ability to bind to PD-L1 receptor and can be used as an in vivo radiodiagnostic agent after coupling with the multifunctional chelator p-SCN-Bn-NOTA and labeling with ^{68}Ga to achieve in vivo localization of PD-L1-positive expressing lesions in solid tumor patients and is suitable for PET scanning. - [^{68}Ga]Ga-NOTA-SNA002 combined with PET detection of PD-L1-positive tumors can effectively predict the efficacy and outcome of patients, and help to develop individualized treatment plans.	- Nuclear medicine molecular tracer technology can provide a new strategy for screening patients who respond to PD-l/PD-L1 immunotherapy, optimizing tumor anti-PD-1/anti-PD-L1 treatment regimens, and evaluating prognosis. - Current evidence demonstrates that SNA002 is favorable for the screening of PD-1/PD-L1-positive subjects and is therefore urgently needed in clinical setting
Risks	- Radiation exposure is the main risk of this product - The radioactive element used in this product is ^{68}Ga and its dose is about 5 mCi. - Although SNA002 is a nano-molecule with extremely low immunogenicity, clinical trial observations are still needed to ascertain its potential risks.	- The risk of radiation exposure is small and within the acceptable range.

Conclusion: The main risk (primarily radiation exposure) of the SNA002-based PET imaging diagnostic method is low. This method can noninvasively detect and evaluate PD-1 and PD-L1 expression in tumors, identify the temporospatial heterogenity in tumors, simplify the complexity and reduce the time and cost of IHC detection, effectively improve the diagnosis and detection rates of tumor, provide new strategies for positive patient screening, treatment regimen optimization, and prognosis evaluation, and bring new insights to the clinical diagnosis and treatment of cancer.

3 Objectives and Purpose

Primary objectives

- To evaluate the safety and tolerability of single doses of SNA002 administered intravenously in patients with solid tumors
- To assess the biodistribution of SNA002 in patients with solid tumors

Secondary objectives

- To assess the radiation dosimetry of SNA002 in patients with solid tumors
- To assess the radiation dose of SNA002 in the blood of patients with solid tumors
- To explore the PET imaging characteristics of SNA002 in patients with solid tumor
- To identify the optimal dose
- To identify optimal image timing window

Exploratory objectives

- To explore the correlation between SNA002 uptake in tumor lesions and PD-L1 expression as determined by immunohistochemistry.
- To explore the positive and negative predictive efficacy of [^{68}Ga] Ga-NOTA-SNA002.

4 Study Design and Endpoints

4.1 Description of the Study Design

This is an open-label, single center, dose escalation study to evaluate the safety, PK, biodistribution, dosimetry, and tumor targeting potential of ^{68}Ga-NOTA-SNA002 in patients with solid tumors.

4.2 Study endpoints

Primary Endpoints

- Incidence of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs)
- Dosimetry and biodistribution

Secondary Endpoints

- Radiation dosimetry of SNA002
- Radiation expoure：detecting radioactivity in the blood
- Recommended diagnostic dose of SNA002
- Optimal imaging window
- SUV_{max} (Standardized uptake value), SUV_{mean}, tumor to background ratio, and tumor to blood ratio.
- PK parameters of SNA002: Including but not limited to maximum serum concentration (C_{max}), time to reach maximum serum concentration (T_{max}), and area under the serum concentration versus time curve from time zero to time ($AUC_{0-\tau}$), and terminal half-life ($T_{1/2}$).
- Immunogenicity: incidence of anti-drug antibodies

5 Study Enrollment and Withdrawal

5.1 Inclusion criteria

Patients must meet all the following criteria to be eligible for participation in this study:

1) Male or female patients, 18-75 years of age, inclusive.
2) Willing and able to provide signed and dated informed consent prior to any study-related procedures and willing and able to comply with all study procedures.

3) Histologically or cytologically confirmed solid tumors including but not limited to non-small cell lung cancer, breast cancer, esophageal cancer, head and neck carcinoma, ovary cancer and melanoma (with or without metastasis); Patients are allowed to enter the study at first diagnosis, at relapse or under treatment.
4) Obtain pathological results within one year.
5) Patients with the imaging results showing at least 1 tumor lesion that can be sampled by biopsy (enhanced CT, enhanced MRI or ^{18}F-FDG PET/CT results are acceptable).
6) ECOG PS 0-2 (See Appendix 1 for details).
7) Adequate hepatic function as evidenced by meeting all the following requirements:
   a) Total bilirubin (TBIL) ≤2.5 × ULN.
   b) Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤3 × ULN.
8) Serum creatinine < 1.5 x ULN and blood urea nitrogen (BUN) ≤ 1.5 × ULN.
9) Adequate hematological function defined as:
   a) White blood cell 3.0-10.0 × 10^9/L in prior to study entry
   b) Absolute neutrophil count 1.5-7.0 × 10^9/L without growth factor support in prior to study entry
   c) Hemoglobin ≥ 90g/L without transfusion in prior to study entry
   d) Platelet count 75-300× 10^9/L without transfusion in prior to study entry
10) Coagulation tests, defined by the following:
   a) Activated partial thromboplastin time (PTT) ≤1.5 × ULN
   b) International normalized ratio (INR) ≤1.5 × ULN.
11) Blood pressure value < grade 1 hypertension (including patients with a history of hypertension whose systolic blood pressure is < 140 mmHg and diastolic blood pressure is < 90 mmHg after exercise or drug treatment).
12) Baseline heart rate 60-100/minute (inclusive)

5.2 Exclusion criteria

Patients who meet any of the following criteria cannot be enrolled:

1) Patients are unable to conduct visits or undergo relevant examinations, surgeries, or biopsies in accordance with the provisions of this clinical trial protocol.
2) Extremely poor nutritional status, BMI<18.5, unable to tolerate the test subjects.
3) Patients with known or suspected evidence of active autoimmune diseases (diagnosed as vitiligo, diabetes, residual hypothyroidism due to autoimmune diseases requiring hormone replacement therapy only, autoimmunological disease such as psoriasis that does not require systemic treatment), Or diseases that are not expected to recur in the absence of external triggers are allowed to be included in the study).

4) Patients receiving high-dose hormones, such as hydrocortisone exceeding 20mg or prednisone 5mg in the morning, and hydrocortisone exceeding 10mg or prednisone 2.5mg at night;
5) Patients with symptomatic brain metastases.
6) Patients with known to be severely allergic to [^{68}Ga]Ga-NOTA-SNA002, similar drugs or excipients.
7) With severe illnesses or other malignant tumors (excluding those who have recovered one year ago or do not require additional treatment).
8) Active severe infections (excluding chronic bronchitis clinical remission).
9) Serum virology check: One of hepatitis B virus surface antigen, hepatitis C virus antibody, and syphilis-specific antibody results is positive or the human immunodeficiency virus antibody cannot be confirmed negative.
10) Total protein <50g/L or albumin<30g/L at screening
11) Unable to provide pathological results of biopsy samples;
12) History of other severe diseases: ① cardiovascular disease, such as acute myocardial infarction/myocardial infarction within 1 year, acute myocarditis, acute pancarditis, acute heart failure, chronic heart failure NYHA heart function class ≥ II (see Appendix 2 for details), CCS class II or higher stable angina pectoris (see Appendix 3 for details), unstable angina pectoris, rheumatic heart disease, malignant arrhythmia [ventricular tachycardia/ventricular fibrillation, frequent ventricular premature beats (more than 5 beats in one minute), II/III degree atrioventricular block, rapid atrial fibrillation/atrial flutter (ventricular rate > 110 beats/min)]. ② brain disease, such as cerebral hemorrhage/cerebral infarction (excluding lacunar infarction), history of epilepsy, pituitary/hypothalamic lesions. ③ lung disease (except lung cancer patients), such as asthma, acute obstructive pulmonary infection, acute bronchitis or acute tracheobronchitis. ④ liver disease (except liver cancer patients), such as cirrhosis (child-pugh score more than 7 points) (see Appendix 4 for details), etc.
13) Participants in any other clinical trial within 3 months before screening (excluding participants who only participated in the screening of this clinical trial and have not used the investigational drug).
14) Drug/alcohol abuse, severe mental disorders.
15) Patients have received high-dose radiation therapy or annual radiation dose>50mSv within 1 year (inquire about their previous radiation therapy and radiation examination within 1 year, and record them in the screening medical record).
16) Patients with claustrophobia, emotional lability, acute persistent spasms, or inability to keep their arms supine for 15 to 30 minutes.

17) Female subjects who are pregnant or lactating, or female subjects who have had unprotected sex within 2 weeks before screening, or with positive blood pregnancy test; male subjects (or their partners) or female subjects who have fertility plan or sperm or egg donors throughout the trial and within 6 months after the end of the study, and are unwilling to take contraceptive measures during the trial and within 6 months after the end of the study.
18) Women of childbearing age do not use sufficient non hormonal contraceptive methods.
19) Any condition that the investigator or primary physician believes may not be appropriate for participating the study.

5.3 Withdrawal or Termination

5.3.1 Reasons for Withdrawal or Termination

The investigator can decide to require an enrolled subject to withdraw from the study if one of the following situations is observed and makes the subject unsuitable for continued participation:

- The investigator determines that the volunteer must stop participation due to medical and ethical concerns.
- The investigator determines that the subject is no longer suitable for continued participation due to SAEs.
- The investigator determines that withdrawal is most beneficial for the subject.
- The subject has poor compliance and is unable to abide with the protocol specifications.

5.3.2 Handling of Participant Withdrawals or Termination

The subject has the right to withdraw during any stage of the study as specified by the ICF.

Regardless of the reason for withdrawal, the reason for subject withdrawal should be recorded and all observations should be completed and reported as detailed as possible.

5.4 Premature Termination or Suspension of Study

According to CTCAE (5.0), the clinical trial should be terminated if over one half of the subjects have grade 2 or greater investigational drug-related AEs or if one case of investigational drug-related SAE is observed.

- Major errors are identified in the clinical trial protocol during the trial, which render drug evaluation difficult.
- Termination requested by the sponsor under the premise that the interests and safety of the subjects are fully guaranteed.
- Trial termination ordered by the NMPA or Ethics Committee due to some tests.
- Inability to recruit patients.
- Lack of imaging even after dose adjustment.

Regardless of whether the trial is terminated by the sponsor or the investigator,

- The investigator should return all investigational drugs, eCRF and relevant trial materials to

the sponsor.

- The sponsor or the investigator should provide a written statement on the reason for early trial termination and inform all principal investigators related to this trial, the Ethics Committee, and NMPA as soon as possible. In addition, all subjects should be informed of the termination of the trial.

5.5 Criteria for Discontinuation from Study

- Patient withdraws consent; no further data will be collected or analyzed in such patients after the date of withdrawal.
- Patient completes all protocol-required procedures and follow-ups through the end of study
- Investigator's discretion.
- Non-compliance with the protocol.
- End of the study.
- Death.

6 Study Agent

6.1 Study Agent and Control Description

6.1.1 Acquisition

Protein part of study agent used in the test is provided by Suzhou SmartNuclide Biopharmaceutical Co., Ltd. The complete drug is configurated with $^{68}Ge/^{68}Ga$ generator at GMP environment in nuclear department or shipped to the site after it was configured at the drug dispensing center generator and received by personnel authorized by the principal investigators.

There is no control product in the test.

6.1.2 Formulation, Appearance, Packaging, and Labeling

Investigational drug: Nota ^{68}Ga-labeled recombinant anti-PD-L1 single domain antibody injection (^{68}Ga-NOTA-SNA002). The main active ingredient of this injection is a nanobody protein with a molecular weight of about 14 kDa. This antibody can bind well to PD-L1 without affecting the process of PD-1/PD-L1-mediated immunosuppression and can effectively locate tumor tissues.

^{68}Ga is a positron-emitting radionuclide generated by the $^{68}Ge/^{68}Ga$ generator with a half-life of 68 min and an electron decay rate of 89%. ^{68}Ga is suitable for the labeling of small molecule drugs that can rapidly distribute and reach the targets in vivo, and the labeling method is easy, mild, and rapid.

The radiation dose for all dose groups at the time of administration should be ranged from 37 to 200MBq.

Upon completion of the test drug configuration, the lead canister used shall be equipped with an external label for the test drug. Aside from the name of the drug, the external label of drug should also include the words "for clinical trials only", as well as the usage and dosage, active ingredient

manufacturing number, radiolabeling, calibration time, expiry date(at least displayed to minutes), storage conditions, and precautions, etc. Since SNA002 is a radiopharmaceutical, the external label should also have a radiopharmaceutical label. The study drug will be supplied in an open-label manner. An example of the external label design is shown below:

Clinical Study NO: SN-SNA002-2023-001

[^{68}Ga]Ga-NOTA-SNA002 (for clinical trials only)

Subject enrollment number:_____
[TIndication]: [^{68}Ga] Ga-NOTA-SNA002, as a radiodiagnostic drug, is suitable for detecting PD-L1 positive lesions in solid tumor patients in combination with PET imaging.
[Route of administration]: Slow intravenous administr ation, time of injection should be no less than 1 min
[Dosage]: mg
[Volume]: ml
[Activity]:_____MBq
[Calibrated time]:_____MM____DD____YYYY____HH____MM
[Active ingredient manufacturing batch number]: _____
[Expiry date]:_____MM____DD____YYYY____HH____MM
[Storage]: Store at room temp erature in a lead container
[Precautions]: Radioactive substances
Caution: New Drug - Limited by Federal (or United States) law to investigational use.

Figure 1 An example of drug label

[^{68}Ga] Ga-NOTA-SNA002 is a radiopharmaceutical, and the drug dish should be equipped with an inner label, which can be slightly introduced, but the drug name and dose should still be labeled. The handwriting of the inner label shall be clearly visible, and it shall be ensured that the injector can still identify it through the drug dish shield. If it cannot be guaranteed, the inner label shall be pasted on the outer side of the drug dish shield.

[^{68}Ga]Ga-NOTA-SNA002 (for clinical trials only)

[Route of administration]: Slow intravenous administr ation, time of injection should be no less than 1 min
[Dosage]:_____mg
[Volume]:_____ml
[Activity]:_____MBq
[Calibrated time]: MM DD YYYY HH MM, Within 4 hours from the expiration date to the administration time
[Active ingredient manufacturing batch number]: _____

Figure 2 An example of drug inner label

6.1.3 Product Storage and Stability

The study site should establish a stringent drug management system (designated personnel, designated cabinet, and locked storage) for the management and distribution of the investigational drug, and establish a registration system. The study site should ensure that the storage temperature of the investigational drug is in accordance with specifications and record the storage temperature. If the storage conditions are found to be out of the specified range, the use of the investigational

drug should be immediately ceased and the investigational drug should be independently stored in a dedicated drug disposal lead container. The investigator and the sponsor will discuss and decide whether the investigational drug is still suitable for use based on the actual situation.

The investigational drug should be stored independently in a sealed lead container. The surface radiation of the lead container should be accordance with relevant specifications. Disposed or excess investigational drugs should be placed in a dedicated drug disposal lead container for at least 10 half-lives and then disposed according to conventional medical waste disposal procedures. The management and use of ^{68}Ga-NOTA-SNA002 are conducted in accordance with the "SOP for Radiopharmaceutical Management" of the study site.

6.1.4 Preparation

Before use, add 3.2 mL of 0.25 M sodium acetate solution and 0.1 mL of 2 mg/mL cold SNA002 protein sequentially and mix well in a sterile vial. Add a total of 5 mL 0.1 M sterile ^{68}Ga washing solution to the vial. Subsequently change the pH of the reaction system to 4.0–4.5. Heat the solution in a metal bath at 37 °C for 20 min to generate the SNA002 injection. The detailed preparation procedures are shown in the "Standard Operating Procedure for the Synthesis of SNA002 Injection".

The complete drug is configurated with ^{68}Ge/^{68}Ga generator at GMP environment in nuclear department or shipped to the site after it was configured at the drug dispensing center generator and received by personnel authorized by the principal investigators. Details of the standard synthesis procedures are shown in the "Standard Operating Procedures for the Synthesis of ^{68}Ga-NOTA-SNA002 Injection".

The investigational drug should be used in 4 hours.

6.1.5 Dosing and Administration

Dose of investigational drug: This trial will include 3–4 dose groups, namely the 0.1 mg, 0.3 mg, 0.5 mg and 0.9 mg dose groups. The dose of protein should be adjusted according to the imaging results of the previous dose group during the trial. The radiation dose for all dose groups at the time of administration should be ranged from 37 to 200MBq.

6.1.6 Route of Administration

Administration method: aspirate [^{68}Ga]Ga-NOTA-SNA002 using a syringe and slowly administer by intravenous injection. The injection time should be no less than 1 min. An indwelling needle should be inserted into the subject before intravenous push. followed by extubation after bolus injection of 10 to 20 ml of normal saline, and clinical routine radiation protection treatment was performed on the indwelling needle and syringe. Subjects were instructed to drink no less than 500 mL of water well for hydration multiple times prior to dosing. Subjects should drink and excrete multiple times after dosing to reduce radiation exposure.

6.1.7 Starting Dose and Dose Escalation Schedule

6.1.7.1 Starting Dose

SNA002 does not bind to mouse, rat and dog PD-L1. Therefore, cynomolgus monkey was chosen in biodistribution studies and repeat-dose general toxicity studies. ^{68}Ga-NOTA-SNA002 can specifically bind to PD-L1 proteins of primates, and the radioactivity uptake is low in other organs except for the excretion organs (kidneys and bladder). The estimated absorbed dose (effective dose) converted from cynomolgus monkeys to adult male or female is 0.022-0.023mSv/MBq, which shows good radiation safety. The recommended dose of ^{68}Ga-NOTA-SNA002 for clinical trials is 185 MBq (5mCi), which generates an effective dose of about 4.1 mSv indicating safe use of ^{68}Ga-NOTA-SNA002 for clinical diagnostics. A NOAEL approach based on the pivotal monkey 2-week study toxicity findings was used to determine the maximum recommended starting dose (MRSD) for the first in human study. In the 2-week monkey study, the potential infusion reaction is the only toxicity observed after 3 repeated iv doses. the dose of 1.5 mg/kg (mean AUC $_{0\text{-}t}$ = 20700 ng•h /mL; mean C_{max} = 32000ng/mL) and 0.5mg/kg (mean AUC $_{0\text{-}t}$ = 5060 ng•h /mL; mean C_{max} = 10500ng/mL) was considered the NOAEL for males and females, respectively. Since the molecular weight of ^{68}Ga-NOTA-SNA002 is less than 100KD, The HED is 0.48 mg/kg (male) and 0.16 mag/kg (female) based on body surface. The MRSD is considered to be 0.048 mg/kg (male) and 0.016 mg/kg (female) (1/10 of NOAEL). The highest dose that nonclinical can cover is considered to be 0.24 mg/kg (male) and 0.08 mg/kg (female) (1/2 of NOAEL). The proposed human dose ranges are from 0.00167 mg/kg (0.1mg flat dose) starting dose to the highest ascending dose 0.01503mg/kg (0.9mg flat dose). The starting dose is 28.74- and 9.58-fold lower than the MRSD for males and females, respectively. The highest ascending 0.01503 mg/kg is covered by nonclinical data (½ of the NOAEL). Therefore, the proposed clinical mass dose range of 0.00167mg/kg to 0.01503mg/kg is not expected to pose a significant risk to patient safety.

6.1.7.2 Dose Escalation Schedule

The dose escalation is determined through both imaging results and safety results:

Imaging:

The Imaging Reviewer Committee consisted of the principal investigator and nuclear medicine physicians.

1) If the first three positive tumor lesions in a certain dose group judged by the IRC having a high image quality (such as T/B >1.5, etc.), it can be decided from the imaging perspective to increase to the next dose group after continuing to enroll 3-4 cases in this dose group, or directly increase to the next dose group for further exploration;

   →If the quality of the first 3 cases in the subsequent dose group is comparable to that in the previous dose group, the IRC shall discuss whether to discontinue further enrollment from a

imaging perspective (e.g. The image quality of the first 3 cases in the 0.3mg dose group is similar to that in the 0.1mg dose group, then stop recruiting, and the 0.1mg dose was identified as the optimal image dose.

•→If the quality of the first 3 cases in the posterior dose group is higher than prior, another 3 to 4 cases will be enrolled. After the completion of the posterior dose group, the IRC will discuss and decide whether this group should not be explored from the imaging aspect (e.g. The image quality of the first 3 cases in the 0.3mg dose group is higher than that in the 0.1mg dose group, then 3-4 cases , and the subsequent dose exploration was not carried out, and the 0.3mg dose was identified as the optimal image dose).

2) If the first three positive tumor lesions in a certain dose group judged by IRC present poor imaging quality (such as T/B ≤ 1) or nonvisualization (functional imaging without nuclides), the decision of stopping enroll in this dose group can be made from an imaging perspective, and the dose group can directly increase to the next or second dose group (for example, if the imaging quality of the 0.1mg dose group is poor in three consecutive cases, the dose group can increase to the 0.3mg or 0.5mg dose group);
3) If the last dose group shows nonvisualization of the positive tumor lesions determined by the IRC in the first three cases, discussion will be conducted to determine whether to adjust the subsequent dose from the imaging perspective or terminate the entire clinical trial.
4) After the dose escalation of all dose groups is completed, the imaging expert committee and the principal investigator will decide whether to continue enrolling 3-4 subjects in a certain initially identified optimal dose group for further exploration.

Security:

The principal investigator determines whether to increase the dose from the perspective of safety. Dose escalation should be stopped if one of the principles happen:① at least half of subjects in a dose group experience CTCAE grade 2 (or moderate) or above adverse reactions;② or at least 1/3 subjects experience CTCAE grade 3 (or severe) or above adverse reactions;③ or one serious adverse reaction in certain group.

The dose escalation will be determined by the principal investigator based on both imaging and safety results. During the clinical trial, based on the principle of subject protection, the dose group can be rapidly escalated to the subsequent dose group if nonvisualization or the above safety events happens after only one subject enrolled according to the investigator's discretion.

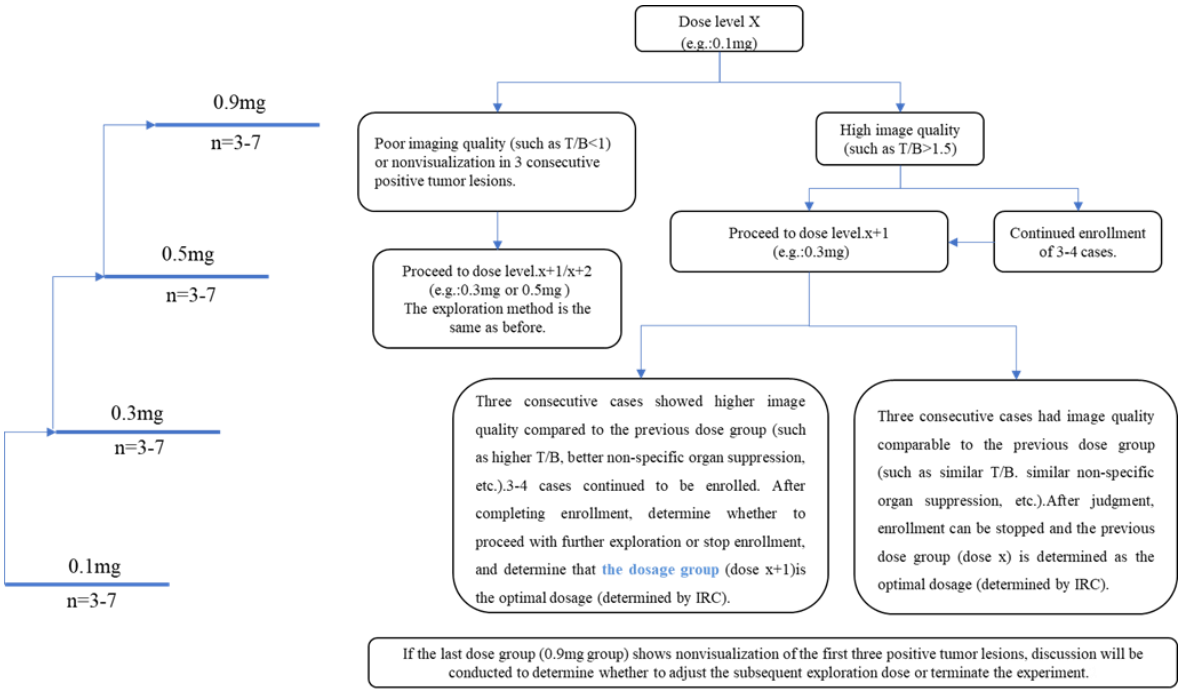

Figure 3 Dose escalation

After the dose escalation of all dose groups is completed, the imaging expert committee and the principal investigator will decide whether to enroll another 3 or 4 patients in the identified optimal dose group.

6.1.8 Dose Adjustments/Modifications/Delays

If no activities in lesions on 0.9mg group, IRC will deside whether to promote higher dose level or not.

6.1.9 Duration of Therapy

Patients will be administered a single dose of SNA002. The duration of study participation will be approximately 42 days, including a screening period up to 14 days and a follow-up period up to 28 days (patients who experience AEs will be followed until resolution).

6.1.10 Tracking of Dose

SNA002 will only be intravenous injected once in the trial.

6.2 Study Agent Accountability Procedures

The complete drug is configurated with $^{68}Ge/^{68}Ga$ generator at GMP environment in nuclear department or shipped to the site after it was configured at the drug dispensing center generator and received by personnel authorized by the principal investigators.

7 Study Procedures and Schedule

7.1 Study Procedures/Evaluations

- Medical history: including personal history, past history, allergy history, and cancer history
- Medication history: including cancer medication history.

- Physical examination: including height, weight, head, chest, neck, face, abdomen, limbs, skin, lymph, nervous system.
- Radiographic: Pet-ct needed in independent SOP.

7.2 Laboratory Procedures/Evaluations

7.2.1 Clinical Laboratory Evaluations

Blood biochemistry	Blood routine	Electrolyte	Urine routine	Coagulation function	Thyroid function	Serum virology
Total protein Albumin Total bilirubin Alanine aminotransferase Aspartate aminotransferase alkaline phosphatase Glucose Creatinine Blood urea nitrogen	Red blood cell count White blood cell count Hemoglobin Platelet count Neutrophil count Lymphocyte count Monocyte count	Potassium Sodium Calcium	Bacterial count Glucose Red blood cells White blood cells	Prothrombin time Thrombin time Fibrinogen	Thyroid function Triiodothyronine Thyroxine	Hepatitis B Hepatitis C Syphilis-specific HIV antibody

7.2.2 Other Assays or Procedures

Anti-SNA002 antibody： Blood samples are collected within 30 min before drug administration and on D6±1d，D28±2d during the safety follow-up. All blood samples are tested in the central laboratory.

Radiation exposure of subjects: The radiation exposure is calculated using OLINDA software. Radioactivity uptake of each organ are input into EXM. Double exponential fitting is performed for each organ. Then OLINDA calculates the decomposition of the drug in each source organ and the radiation doses of all target organs. The organs covered in the fitting calculation include but are not confined to brain, chest, bladder, lungs, liver, kidneys, spleen, gastrointestinal tract, and thyroid glands.

7.2.3 Specimen Preparation, Handling, and Storage

See details in central laboratory manual.

7.2.4 Specimen Shipment

Transport under cold chain conditions. See details in central laboratory manual.

7.3 Study Schedule

7.3.1 Screening

D - 14 to D - 2

1) Sign the ICF.
2) PD-L1 immunohistochemistry results.
3) Collect demographic data.

4) Inquire and record medical history (including personal history, past history, allergy history, and cancer history).
5) Tumor stage.
6) Pathological test results within 1 year before screening.
7) Vital signs.
8) Physical examination.
9) 12-lead ECG.
10) Cardiac function score: scored according to NYHA standards
11) ECOG score.
12) Chest x-ray (not required if chest CT results are available).
13) Enhanced CT/enhanced MRI/PET-CT (results of examinations conducted at the study site or other tertiary hospitals within 30 days prior to enrollment are acceptable).
14) Laboratory tests: blood routine, blood biochemistry, electrolyte, coagulation function, urine routine, serum virology, thyroid function tests, and serum pregnancy test (only for female subjects of childbearing age). Serum virology can accept results within 28 days before screening, while other laboratory tests can accept results within 7 days before screening.
15) Review compliance with inclusion/exclusion criteria.
16) Record concomitant medications.

7.3.2 Baseline Period

D-1

1) Review compliance with inclusion/exclusion criteria for the second time
2) Enrollment (Subjects can be enrolled in the relevant department due to primary tumor before D-1 and after D1 and complete the trial period during hospitalization) .
3) Record concomitant medications.

7.3.3 Study Period

D1

1) Following successful enrollment at screening, intravenous catheter (for blood sampling) will be placed in regular locations (eg, superficial veins of the upper extremities, superficial veins of the lower extremities, etc.)
2) ADA: Collect blood samples within 30 min prior to administration for the detection of anti-SNA002 antibody in the central laboratory.
3) Administration drug: another indwelling needle (used for administration) was placed on the contralateral side of the blood collection vein, [^{68}Ga] Ga-NOTA-SNA002 was slowly injected intravenously, the injection time was not less than 1 min, and extubation was performed after another 10 ~ 20 ml of normal saline was injected, and radiation protection treatment was

performed on the indwelling needle and syringe, and the whole process followed the aseptic operating principles of clinical diagnosis and treatment. Before administration, subject should drink no less than 500 mL of water for hydration.

4) Blood sampling: Blood sampling time points are shown in the table below. ^{68}Ga in the blood samples and centrifugated serum samples are measured using a γ counter within 30 minutes after collectionand should be centrifuged within 10 minutes after measuring and the samples are sent to the central laboratory for SNA002 detection.

Blood sampling time (D1)							
Within 30 min before administration	2min (±1min)	5min (±1min)	10min (±1min)	30min (±2min)	50min (±5min)	100min (±5min)	150min (±10min)

5) Systemic PET/CT: Perform whole-body PET-CT scans on subjects after 15± 5 minutes, 60± 10 minutes, and 120± 20 minutes of administration. Panoramic PET-CT scans performed after dosing were acceptable for 1 to 2 subjects in a dose group or each dose group and were required to cover at least one of these time points.

6) Urine sampling: Urine samples are collected at 90 ± 30 min, 180 ± 30 min, and 300 ± 30 min after administration, and 68Ga in urine samples are measured using a γ counter.

7) Measurement of radiation dose: Surrounding radiation dose is measured at 4 ± 0.5 h after administration.

8) Develop a plan for obtaining target lesion specimens (if applicable): Determine whether to collect tissue specimens after administration based on specific circumstances. If the subject has obtained a biopsy specimen within 2 weeks prior to enrollment and has obtained/can undergo immunohistochemical PD-L1 detection results (such as PD-L1 immunohistochemical detection of pathological tissues in different directions of the lesion collected through bronchoscopy within 2 weeks prior to enrollment), and no treatment has been given, no further biopsy is required. Otherwise, pathological specimens need to be collected in this clinical study. The collection method can accept biopsy or surgical resection of specimens, which is determined by the investigators based on the subject's situation.

   (note: the investigators can arrange for the subjects to enter a safe follow-up period after the subjects complete the tissue specimen collection (D2) or surgical specimen collection (D2-D5) during the trial period, or after the subjects who do not need to collect tissue specimens again complete all operations in D1, in order to shorten the waiting time for subsequent treatment from an ethical perspective).

9) Vital signs: Vital signs are evaluated at 6 ± 1 h after administration on D1.

10) Examination of injection site: observe injection site for redness, swelling, heat, pain, itching and other symptoms 6 ± 1h after administration.

11) Record concomitant medications.

12) Record AEs.

D2 to D5

1) Target lesion specimen acquisition: Biopsy specimens can include endoscopic (such as gastroscopy, fiberoptic bronchoscopy, laparoscopy, etc.) and puncture biopsy specimens, which are generally conducted in D2. The preferred specimen for collection is the primary tumor lesion or metastatic lesion with the highest SUVmax; The collection principle is to collect at least one biopsy sample from the target tumor lesions that can be collected, and the maximum number of samples for the same patient is 5. Ideally, biopsies should be performed on both positive and negative lesions of the same patient under PET imaging. The location of specimen collection and the selected collection method will be determined by the investigators based on previous imaging results and the PET results of this experiment. Perform PD-L1 immunohistochemical detection after obtaining target tissue samples.
2) If surgical resection is performed, it can be performed on the D2 to D5. Immunotherapy, chemotherapy, or radiation therapy should not be performed on the primary tumor disease during the injection of experimental drugs until the surgery period.
3) Vital signs: Vital signs are evaluated at 6 ± 2 h after paracentesis (if performed).
4) Physical examination: evaluated at 6 ± 2h after biopsy (if performed).
5) PD-L1 IHC examination: The collected specimens will be sent to the pathology department to make pathological sections as required, and immediately sent by the cold chain transportation company (Shanghai Shengsheng Logistics Co., Ltd.) to an independent third-party central pathology laboratory (Beijing Geenga Medical Laboratory Co., Ltd.) for PD-L1 immunohistochemical examination. The requirements for specimen preparation transported to the central pathology laboratory can be found in the manual of the central pathology laboratory.
6) Examination of injection site: observe injection site for redness, swelling, heat, pain, itching and other symptoms 24 ± 6h after administration on D1.
7) Record concomitant medications.
8) Record AEs.

7.3.4 Safety Follow-up Period

D6 toD28

1) Anti-SNA002 antibody: Blood samples are collected on D6±1d, D28±2d and sent to the central laboratory for detection.
2) Laboratory examination: blood routine, blood biochemistry, coagulation, and electrolyte tests were conducted on D6 ± 1d.

3) 12-lead ECG: detected on D6 ± 1d.
4) Distribute diary cards during the safe follow-up period of D6 ± 1 days (if the subjects discharge immediately after biopsy, the diary cards will be distributed on the day of discharge; if the subjects are not hospitalized, the diary cards will be issued after completing the D1 examination), and collect the diary card on D28 ± 2 days.
5) Record AEs: all adverse events should be recorded in the diary cards (if the subjects continue to be hospitalized, adverse events will be recorded in the hospitalization medical record).
6) Record concomitant medications: all concomitant medications should be recorded in the diary card (if the subjects continue to be hospitalized, concomitant medications related to primary tumor treatment can be recorded in the hospitalization doctor's order, and medications taken on their own or for long-term underlying diseases can be recorded in the diary cards).
7) Trial completion: the study will be completion for subject after the relevant procedures on D28 ± 2d. Subject should be permitted to undergo relevant chemotherapy, radiotherapy and/or immunotherapy for the primary disease during the safe follow-up period.

7.3.5 Early Termination Visit

1) Vital signs.
2) 12-lead ECG (If the subject withdraws after D6 and has already undergone examination in D6, it can be unnecesary).
3) Laboratory examination: Conduct blood routine, blood biochemistry, coagulation, and electrolyte tests (if the subject withdraws after D6 and has undergone laboratory examination on D6, it may not be conducted again).
4) Anti-SNA002 antibody: sent to an independent third-party central laboratory for testing;
5) Record AEs.
6) Record all concomitant medications.

7.3.6 Unscheduled visits

Unscheduled visits will be conducted if clinically required during the trial. During unscheduled visits, relevant clinical test, laboratory test, concurrent medication and AE data will be collected from the original medical records and CRFs if necessary.

7.3.7 Schedule of Events Table

Table 4 Schedule of Events Table

Study Period/Visits	Screening Period	Baseline Period	Study Period (5 days)		Safety Follow-up Period（D6-28）		Premature Withdrawal [18]
Study Day (s)	D-14~-2	D-1	D1	D2~D5	D6±1d	D28±2d	
Informed consent	x						
Inclusion/exclusion criteria	x	x					

Study Period/Visits		Screening Period	Baseline Period	Study Period (5 days)		Safety Follow-up Period（D6-28）		Premature Withdrawal [18]
Study Day (s)		D-14~-2	D-1	D1	D2~D5	D6±1d	D28±2d	
Demographics		x						
Physical examination		x			x			
Vital signs[1]		x		x	x			x
Medical history:	Personal history	x						
	Past history	x						
	Allergy history	x						
	Tumor History	x						
Tumor stage		x						
Pathological examination[2]		x						
Laboratory examination[3]	Blood routine	x				x		x
	Blood Biochemistry	x				x		x
	Electrolyte	x				x		x
	Thyroid Function	x						
	Coagulation Function	x				x		x
	Urinalysis	x						
	Blood Pregnancy (If Needed)	x						
	Serum Virology	x						
12-lead ECG		x				x		x
Cardiac function score		x						
Physical condition score		x						
Chest X-ray (can be ignored if there is chest CT)[4]		x						
CT/MRI/PET-CT[5]		x						
Administration								
[^{68}Ga]Ga-NOTA-SNA002 administration[6]				x				
Biological Samples, Imaging, Safety Data, Specimen Collection								
Blood sampling[7]				x				
Urine sampling[8]				x				
Ada[9]				x		x	x	x
Pet-ct[10]				x				
Measurement of radiation dose[11]				x				
Formulate a Plan for Obtaining Target Lesion Specimens （ If Performed）[12]				x				
Collection of tissue samples from target lesions（if performed）[13]					x			
Pd-l1 immunohistochemical examination[14]		x			x			
Other								
Examination of injection site[15]				x	x			
Enrollment[16]			x					
Out of group							x	
Concomitant medications[17]		x	x	x	x	x		x

Study Period/Visits	Screening Period	Baseline Period	Study Period (5 days)		Safety Follow-up Period（D6-28）		Premature Withdrawal [18]
Study Day (s)	D-14~-2	D-1	D1	D2~D5	D6±1d	D28±2d	
Ae[18]			x	x	x		x
Distribute/recycle journal cards					x		

1. Vital Signs: tested during the screening period, 6 ± 1 hours after D1 administration, and 6 ± 2 hours after D2 biopsy (if performed).
2. Pathological Examination: if the pathological examination results within one year before screening are obtained, and the subject receives biopsy samples within two weeks before enrollment and has not undergone chemotherapy, radiotherapy, or immunotherapy until enrollment, biopsy may not be performed after administration in this clinical trial.
3. Laboratory examination: Subjects should obtain blood routine (red blood cell count, white blood cell count, hemoglobin, platelet count, neutrophil count, lymphocyte count, monocyte count), blood biochemistry (total protein, albumin, total bilirubin, alanine aminotransferase, aspartate aminotransferase alkaline phosphatase, glucose, creatinine, blood urea nitrogen), electrolyte (potassium, sodium, calcium), thyroid function (thyroid function, triiodothyronine, thyroxine), coagulation function (prothrombin time, thrombin time, fibrinogen), urine routine (bacterial count, glucose, red blood cells, white blood cells), serum virological (hepatitis B virus surface antigen, hepatitis C virus antibody, syphilis specific antibody, human immunodeficiency virus antibody). During the safe follow-up period D6, retest blood routine, blood biochemistry, electrolytes, and coagulation series (note: serum virology can accept results within 28 days before screening, while other laboratory tests can accept results within 7 days before screening).
4. Chest X-Ray: if there is chest CT, it can be ignored.
5. CT/MRI/PET-CT: imaging within one month prior to screening can be acceptable at the research center or other tertiary hospitals.
6. [^{68}Ga]Ga-NOTA-SNA002 Administration: slowly inject [^{68}Ga] Ga-NOTA-SNA002 intravenously on D1 for at least 1 minute. Before injection, the subjects should drink sufficient water to ensure proper hydration, and the amount of water consumed should not be less than 500mL. After administration, regular drinking and excretion should be carried out to reduce radiation exposure.
7. Blood Sampling: collected within 30 minutes before administration, 2 minutes (± 1 minute), 5 minutes (± 1 minute), 10 minutes (± 1 minute), 30 minutes (± 2 minute), 50 minutes (± 5 minute), 100 minutes (± 5 minute), and 150 minutes (± 10 minute) after administration. Each blood sample should be tested for whole blood radiation dose within 30 minutes after collection, and centrifuged within 10 minutes after measuring whole blood radiation dose. Serum radiation dose should be tested within 5 minutes after centrifugation. After testing, the separated serum samples are divided into cryopreservation tubes, frozen (-60 ℃~-90 ℃), and regularly sent to the central laboratory for SNA002 protein content determination.
8. Urine will be pooled for renal radiotracer clearance before drug administration, 90±30 minutes, 180±30 minutes and 300±30 minutes post injection.
9. ADA: blood samples were collected within 30 minutes before administration, on D6 ± 1d and D28 ± 2d during the safe follow-up period. All blood samples were tested in an independent third-party central laboratory.
10. Systemic PET-CT: Three systemic PET CT scans are performed at 15±5 minutes, 60±10 minutes, and 120±20 minutes after administration. Panoramic PET-CT scans performed after dosing were acceptable for 1 to 2 subjects in a dose group or each dose group and were required to cover at least one of these time points.
11. Measurement of Radiation Dose: measure the surrounding radiation dose at 4 ± 0.5 hours after administration.
12. PD-L1 Immunohistochemical Examination and Formulate a Plan for Obtaining Target Lesion Specimens（If Performed）: Obtain the PD-L1 immunohistochemical results of the subjects at the study site during the screening period. This experiment determines whether to collect tissue specimens after administration based

on specific circumstances. If the subject has obtained a biopsy specimen within 2 weeks before enrollment and has not undergone any treatment, there is no need to perform another biopsy, otherwise the specimen needs to be collected again. Researchers need to determine the method of specimen collection based on the subject's situation, and can accept surgical resection of tumor tissue or biopsy for sampling. Surgical resection can be performed after 1 day of drug administration (i.e. after D2, surgical resection is generally performed between D2 and D5). Immunotherapy, chemotherapy, or radiation therapy should not be performed on the primary tumor disease during the period from drug administration to surgery. Biopsy sampling can include endoscopic (such as gastroscopy, fiberoptic bronchoscopy, laparoscopy, etc.) sampling and puncture biopsy sampling, generally conducted in D2. The preferred specimen for collection is the primary tumor tissue or metastatic lesion with the highest SUVmax. The collection principle is to collect at least one biopsy sample from the target tumor lesions that can be collected, and the maximum number of samples for the same patient should not exceed 5. Ideally, biopsies should be performed separately for positive and negative lesions under PET imaging in the same patient. The location of specimen collection and the selected collection method are determined by the researcher based on previous imaging results and PET results of this experiment. After obtaining target tissue samples, PD-L1 immunohistochemistry was performed at the research center.

13. Collection of Tissue Samples from Target Lesions（If Performed）:Specimens collected according to established target lesion specimen acquisition protocol from D2 to D5.
14. Examination of Injection Site: observe injection site for redness, swelling, heat, pain, itching and other symptoms 6± 1h and 24 ± 6h after administration.
15. Enrollment: The subjects were enrolled after reviewing the inclusion and exclusion criteria on D-1 again, and were hospitalized in the department of primary tumor due to primary tumor before D-1 and after D1. After the end of the trial period of this clinical trial, the possible continued hospitalization of the subjects was not affected.(Note: Researchers can arrange for subjects to enter a safe follow-up period based on their condition, after completing the collection of tissue specimens (D2) or surgical specimens (D2-D5) during the trial period, or after completing various operations in D1 for subjects who do not need to collect new tissue specimens, to shorten the waiting time for subsequent treatment from an ethical perspective.)
16. Concomitant Medications: Starting from the signing of the informed consent form, record the daily concomitant medication until the end of the trial. (For subjects who are no longer hospitalized, the safe follow-up period will be recorded in the diary card; if they continue to be hospitalized, the combination medication will be reflected in the hospitalization doctor's order, and drugs taken on their own or for underlying diseases for a long time can be recorded in the diary card).
17. AE: Record any AE observed by the subjects after administration until the end of the experiment. (For subjects who are no longer hospitalized, the safe follow-up period shall be recorded in the diary card; if hospitalization continues, adverse events shall be recorded in the hospitalization medical record).
18. Premature Withdrawal: For subjects who withdraw prematurely, laboratory tests such as vital signs, 12-lead ECG, blood routine, blood biochemistry, coagulation and electrolytes should be performed (if the subject withdraws after D6,and laboratory tests and 12-lead ECG have been performed on D6, they can no longer be performed), anti-SNA002 anti-drug antibody tests should be performed, and adverse events and concomitant medications of the subjects should be recorded.

7.4 Justification for Sensitive Procedures

Not applicable.

7.5 Precautionary Medications, Treatments, and Procedures

Prophylactic medications such as antihistamines (diphenhydramine or similar drugs) and antipyretics (acetaminophen or similar drugs) are permitted within 30–60 min prior to intravenous injection of SNA002.

For subjects who require glucocorticoid therapy for immune-related AEs, high-dose systemic glucocorticoids should be avoided, such as a single dose of > 200 mg hydrocortisone or > 50 mg

prednisone.

7.6 Prohibited Medications, Treatments, and Procedures

Except for the investigational drug, all systemic immunotherapies (e.g., Anti-PD-1/PD-L1 drugs or immunoreceptor inhibitors) are prohibited during the trial. If such therapies are used, the subject must withdraw from the study and the investigator will evaluate the impact of the concomitant medication on the investigational drug.

Immunostimulatory Chinese herbal medicines (e.g., mistletoe extract) or those known to interfere with important organ functions (e.g., hypericin) are prohibited during the trial.

7.7 Rophylactic Medications, Treatments, and Procedures

Not applicable.

7.8 Rescue Medications, Treatments, and Procedures

Not applicable.

7.9 Participant Access to Study Agent at Study Closure

Not applicable.

8 Assessment of Safety

8.1 Specification of Safety Parameters

8.1.1 Definition of Adverse Events (AE)

Adverse event (AE) refers to all adverse medical events that are observed in the subjects after receiving the investigational drug. These events may manifest as symptoms, signs, diseases or abnormal laboratory test results, but may not have a causal relationship with the investigational drug.

8.1.2 Definition of Serious Adverse Events (SAE)

Serious adverse event (SAE) refers to adverse medical events that lead to death, life-threatening results, permanent or serious disability or loss of function, or hospitalization or prolonged hospitalization in the subjects after receiving the investigational drug or congenital abnormalities or birth defects.

8.1.3 Definition Of Unanticipated Problems (UP)

OHRP considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and

- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

This study will use the OHRP definition of UP.

Suspected unexpected serious adverse reaction (SUSAR) refers to suspected and unexpected serious medical events with clinical manifestations and severity that are not listed in the existing data or information, such as the investigator's brochure, package inserts of the marketed drugs, or summary of product characteristics.

8.2 Classification Of an Adverse Event

8.2.1 Severity Of Event

- **Mild** – No clinical symptoms or mild clinical symptoms; only clinical or laboratory abnormalities; no treatment required.
- **Moderate** – Requiring minimal, local, or non-invasive treatment; The daily activities of using tools that are appropriate for age are limited, and the daily activities of using tools include cooking, shopping, making phone calls, etc.
- **Severe** –Illness or medically severe symptoms but not immediately life-threatening; Causing hospitalization or prolonged length of stay; Causing disability; Restricted daily self-care. Self care in daily life refers to bathing, dressing, undressing, eating, going to the bathroom, taking medication, etc., not being bedridden.
- Endangering life and requiring emergency treatment.
- Deaths related to AE.

8.2.2 RELATIONSHIP TO STUDY AGENT

Correlation determination can be done using the five point method: relevant, highly likely related, possibly related, possibly unrelated, or unrelated. Dichotomy can also be used: relevant or unrelated (those that are relevant, highly likely related, or possibly related can be classified as "relevant" according to the dichotomy method; those that are unrelated or potentially unrelated can be classified as "unrelated" according to the dichotomy method).

Table 5 Classification and criteria for determining the correlation between adverse events in clinical drug trials

Five point method	Basis of determination	Dichotomy
Related	- Has a reasonable temporal relationship -Conforming to known drug mechanisms, characteristics, or known adverse reactions -De-excitation positive -No other plausible explanation -Re-excitation positive	relevant
Probably	- Has a reasonable temporal relationship	

Related	-Conforming to known drug mechanisms, characteristics, or known adverse reactions -De-excitation positive -No other plausible explanation -Absence of Re-excitation positive proof.	
Possibly Related	-Has a reasonable temporal relationship -Absence of re-excitation positive proof -Manifested as any of the following situations: ①Conforming to known drug mechanisms, characteristics, or known adverse reactions，de-excitation positive，but other reasonable reasons can also be used for explanation. ② Conforming to known drug mechanisms, characteristics, or known adverse reactions，absence of de-excitation positive proof，and there are no other reasonable reasons to explain. ③Does not conform to the known mechanism of action, properties or known adverse reactions of the drug, de-excitation positive, and there is no other reasonable reason to explain. ④ Does not conform to the known mechanism of action, properties or known adverse reactions of the drug, de-excitation positive,also explained by other plausible reasons. ⑤ Does not conform to the known mechanism of action, , properties or known adverse reactions of the drug,absence of de-excitation positive proof，and no other plausible reason to explain.	
Unlikely to be related	-Has a reasonable temporal relationship -Absence of de-excitation positive proof -Absence of re-excitation positive proof -Manifested as any of the following situations: ① Does not conform to the known mechanism of action, properties or known adverse reactions of the drug, and can be explained by other reasonable reasons. ②Conforming to known drug mechanisms, characteristics, or known adverse reactions，but other reasonable reasons can be used for explanation.	unrelated
Not Related	- (Medically considered) There is no rational time relationship -Does not conform to the known mechanism of action, properties or known adverse reactions of the drug -Absence of de-excitation positive proof -Absence of re-excitation positive proof -Other reasonable reasons can be used to explain	

8.2.3 Expectedness

Sponsor will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study agent

8.3 Time Period and Frequency for Event Assessment and Follow-Up

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate RF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with

the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. UPs will be recorded in the data collection system throughout the study.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization

8.4 Reporting Procedures

8.4.1 Adverse Event Reporting

All AEs occurring after the first dose and before the last follow-up need to be collected and recorded. If an AE occurs after the last follow-up (within one month after the follow-up) and it cannot be determined as unrelated to the investigational drug, then the follow-up should be continued and recorded for this case until symptom disappearance or recovery to the baseline (or even better than the baseline), or disease stability, or the recovery of any laboratory abnormalities to normal or the baseline level, or loss to follow-up. The AE record form should be authentically filled out during the trial, including AE's name, time of occurrence, severity, end time, relevance to the investigational drug, countermeasures, and outcome.

All AEs (including SAEs/SUSARs) occurring during the clinical trial will be graded according to the severity classification system for AEs in Chapter 8.1.3 and then properly handled. Whether there is a causal relationship between an AE and the investigational drug, the investigators should carry out a follow-up of the AE until symptom disappearance or recovery to the baseline (or even better than the baseline), or disease stability, or the recovery of any laboratory abnormalities to normal or the baseline level, or loss to follow-up. For clinically significant laboratory abnormalities of grade 3 or 4, close follow-up and reexamination should be carried out.

During the follow-up of AEs, the cases progressing into SAEs should be reported following the SAE reporting procedures after the investigators are informed of the situation.

The investigators should observe and treat the AEs based on clinical practice and prepare original medical records during the treatment.

8.4.2 Serious Adverse Event Reporting

All SAEs occurring after the first dose and before the last follow-up are collected and recorded. The investigators should carefully fill in the SAE Report Form item by item, and sign and date the report once SAEs occur. The investigators should report the occurrence of SAEs to the sponsor within 24 h after being informed (the requirements on the need to submit the report to the clinical trial institution or the ethics committee vary across the study sites). If a SAE occurs after the last follow-up (within one month after the follow-up) and it cannot be determined as unrelated to the investigational drug, then the follow-up should be continued and recorded for this case until symptom disappearance or recovery to the baseline (or even better than the baseline), or disease stability, or the recovery of any laboratory abnormalities to normal or the baseline level, or loss to follow-up.

8.4.3 Unanticipated Problem Reporting

After receiving safety-related information from any sources, the sponsor should carry out analysis and assessment immediately, including the severity, relevance to the investigational drug, and whether the safety event is expected. The sponsor should immediately report the SUSARs to all participating investigators, clinical trial institution, and ethics committee. In the meantime, the sponsor should report the suspected and unexpected SAEs to the drug administration authorities and the health authorities within the stipulated time. Upon receiving the safety-related information concerning the clinical trial from the sponsor, the investigators should immediately sign and read it and consider whether there is a need to adjust the treatments for subjects. The investigators should communicate with the subjects early if necessary. The SUSARs provided by the sponsor should be reported to the ethics committee as per the requirements developed by the ethics committee within the stipulated time. The day that the sponsor is informed first is denoted as day 0.

The sponsor (or the entrusted CRO) has already built a safety database that conforms to the E2B (R3) standard and implemented management of the safety data. Moreover, relevant terms are coded according to MedDRA (version 23.1 or above).

8.4.4 Events of Special Interest

Not applicable.

8.4.5 Reporting of Pregnancy

The subjects should be told to take strict contraceptive measures during the study before enrollment (including subjects themselves and their partners). If the subjects or their partners get pregnant during the study, the investigators should fill it in the Pregnancy Event Table within 24 h after the confirmation and then submit it to the sponsor. All reporting procedures should conform to the ethical requirements at the study site involved. A pregnancy event is neither an AE nor a

SAE but should be recorded in the CRF as a SAE.

The pregnant subjects should immediately withdraw from the study and the situation should be timely recorded, reported and followed up. If the partners of male subjects get pregnant, the male subjects are not be required to withdraw. However, the pregnant partners of the male subjects should be recorded, reported, and followed up in the same way as with the pregnant female subjects.

The investigators should communicate with the subjects in a scientific and rigorous way about medication. The subjects should be informed of the potential impact and risks of the investigational drug on the pregnant women and fetuses. Whether to terminate or continue the pregnancy is left to the discretion of the subjects and their partners.

If the subjects and their partners decide to continue the pregnancy, they are required to receive follow-up for pregnancy once every there months until one month after the end of pregnancy. Any abnormalities occurred during the pregnancy should be recorded and reported as SAEs. Except for normal delivery and normal newborns, all other pregnancy outcomes are recorded and reported as SAEs.

Any abnormalities of the newborns should be collected and recorded, and those meeting the criteria for SAEs should be handled according to the procedures for SAEs.

8.5 Study Halting Rules

Administration of study agent will be halted when three grade 2 AEs determined to be “probably related” are reported to the IRC. The IRC will notify the study sponsor and investigators immediately when the third grade 2 event is reported, and enrollment screens will stop accepting new study participants.

8.6 Safety Oversight

Safety oversight will be under the direction of a safety committee, composed of individuals with the appropriate expertise, including nuclear medicine expertise, pharmacologist.

9 Clinical Monitoring

9.1 Quality control and quality assurance

- Quality control measures of the laboratory: The laboratory should provide documents such as quality control certificate.
- Investigators participating in the clinical trial must have the professional skills, qualifications, and competence related to clinical trials. They must pass the qualification examinations. Minimum mobility of the investigators is required during the clinical trial.
- Before the clinical trial, the staff participating in the clinical trial should receive training on the protocol, current GCP, and SOP related to the present clinical trial.
- The study site should designate 1-2 imaging instruments for use in the clinical trial. The selected instruments must have a good performance and can completely satisfy the

requirements of the trial. The designated instruments should be attached with relevant certification documents.

- The operating staff of the instruments should be authorized by PI and the authorization remains valid during the clinical trial. Moreover, they should be familiar with the protocol and the standard operating procedure of the imaging instruments.
- The specific procedure and parameters of imaging can be found in the standard operating procedure.
- The drug preparation staff should have the qualifications for radioactive drug preparation. They should be authorized by PI, and the authorization remains valid during the clinical trial.

9.2 Monitoring

The CRA of sponsor will visit the study sites and perform clinical monitoring according to *Good Clinical Practice* and the Project Management Plan. The investigators should proactively cooperate with the CRA. The specific duties of CRA include the following:

- Before the clinical trial, the CRA should confirm that the clinical trial institutions are fully equipped and eligible in the following aspects: staff preparation and training, laboratory tests related to the trial, equipment and their working status, a sufficient sample size, and familiarity with the protocol requirements of the study participants.
- During the clinical trial, the CRA should focus on the implementation of the clinical trial protocol and confirm that ICF has been obtained from all subjects before the screening. The CRA should know of the enrollment rate and the progress of the clinical trial and confirm that the enrolled subjects are eligible.
- The CRA should confirm that all data records and reports are accurate and complete. All eCRFs are correctly input and consistent with the raw data. The CRA should also ensure that all mistakes or omissions are corrected or marked, with investigators' signature and date. The CRA should confirm that the dose modification, therapy change, concomitant medications, loss to follow-up, and omissions in examinations are recorded for each subject. The CRA should confirm that the withdrawal and loss to follow-up are explained in the CRF for each enrolled subject.
- The CRA should confirm that all AEs are recorded and SAEs are reported and recorded within the stipulated time.
- The CRA should confirm whether the investigational drugs are supplied, stored, distributed, and recovered as per relevant laws and regulations and whether the corresponding records are kept.

- The CRA should record clearly and authentically any follow-up visits, tests or examinations that are not conducted by the investigators as required and any mistakes and omissions that are not corrected.
- The CRA should finish the monitoring report after each visit and report the problems to the investigators. The subjects are followed up until symptom disappearance or recovery to the baseline (or even better than the baseline), or disease stability, or the recovery of any laboratory abnormalities to normal or the baseline level, or loss to follow-up.
- During each follow-up, the CRA should check the PET/CT parameters and pay attention to the quality of the imaging instruments and the images.

9.3 Audit and inspection

Upon receiving the notice for audit and inspection, the investigators should inform the sponsor as soon as possible. The source documents of this clinical trial should be available for view by the sponsor's qualified staff or the designated personnel, or the inspector dispatched by the health and drug administration authorities. The above-mentioned personnel may need to verify the CRF or the data in EDC by directly browsing the source documents.

10 Statistical Considerations

10.1 Statistical and Analytical Plans

A formal SAP of this study will be completed prior to database lock and unblinding of the study data.

10.2 Statistical Hypotheses

This clinical trial is an exploratory study, and no hypothesis testing is set up.

10.3 Analysis Datasets

Full analysis set (FAS): Based on the intention-to-treat (ITT) principle, it includes all subjects who are enrolled after passing the screening.

Safety set (SS): It includes all subjects who receive the investigational drug (including the discontinuation after the initial administration) and have at least one safety observation record.

PK Dataset (PKS): All subjects who received the study drug and had at least one blood drug concentration data during the trial period.

10.4 Description of Statistical Methods

10.4.1 General Approach

This study mainly uses descriptive statistics.

In general, measurement data are described in mean, standard deviation, median, quartile, minimum, and maximum. Count data are described in frequency and percentage.

Unless otherwise stated, α is set to 0.05 (two-sided) for type I errors, and β to 0.2 for type II errors. All statistical tests are two-sided. $P \leq 0.05$ is taken to indicate significant difference.

10.4.2 Analysis of The Primary Efficacy Endpoints

Pharmacokinetic evaluation

- Change in whole blood radiation dose: Blood samples are collected on D1 after administration and the ^{68}Ga dose in blood samples is measured using a radiation detector.
- Change in serum radiation dose: Blood samples are collected on D1 after administration and the whole blood samples are treated to obtain serum. The ^{68}Ga dose in serum is measured using a radiation detector.
- SNA002 detection: Blood samples are collected on D1 after administration for the detection of SNA002 in blood samples in the central laboratory.
- Hemodynamic change of SNA002: Imaging results are interpreted and the heart is delineated as ROI. Data collected at various time points are analyzed, and the result is determined according to the concentration–time curve.
- Change in urine sample radiation dose：Urine samples should be collected before and post administration.^{68}Ga dose in urine sample should be measured with γ detector.

Evaluation of imaging features

- Evaluation of PET imaging features of target tumor tissues: In combination with CT, the image results were read, multiple target tumor lesions were selected (no less than 1, ideally, no less than 1 should be selected for both positive and negative imaging foci), the uptake of [^{68}Ga] Ga-NOTA-SNA002 in each target tumor lesion was observed, and the count was recorded, quantization for SUV-based standardized uptake (SUV_{max}, SUV_{mean} etc.).
- Tumor lesion hot spots by PET imaging——target to background ratio: Hot spot and T/B ratio is determined based on the SUV_{mean} (semi-quantitative analysis) of the target lesion and the lesion contralesional side and liver.
- Evaluation of optimal imaging time: The optimal imaging time is determined based on the T/B ratios at different time points.
- Optimal dosage: should be determined according to T/B ratio, detection ability of lesions (primary lesions, metastatic lymph nodes and distant metastases) and normal organs with abundant PD-L1 expression except lesions are fully inhibited.

10.4.3 Analysis of the Secondary Endpoints

Immunogenicity evaluation

- Anti-SNA002 antibody: ADA blood samples are collected before administration and on D6 ± 1d and D28 ± 2d after administration for the detection of anti-SNA002 antibody in the independent third-party central laboratory.

Evaluation of correlation of expression between imaging and IHC

- The IHC analysis is conducted to the collected tumor tissue samples (tested by the independent third party central laboratory) and the results are compared with those of imaging. Take the immunohistochemistry result as the true values (if only baseline immunohistochemistry result is available, the baseline result is the true value; if both baseline and post administration immunohistochemistry results are available, then post administration results are true values) .Sensitivity [true positive/(true positive + false negative)], specificity [true negative/(true negative + false positive)], positive predictive value [true positive/(true positive + false positive)], and negative predictive value [true negative/(true negative + false negative)] are calculated. Explore the correlation between PET imaging features (such as tumor SUVs, tumor/muscle SUVs) and immunohistochemical results.

10.4.4 Safety Analyses

Safety evaluation indicators

- AE/SAE/SUSARs.
- Vital signs: Blood pressure, pulse, respiration, and body temperature.
- Physical Examination: Assessment of changes in physical examination of subjects before and after drug administration.
- Laboratory tests: Blood routine, blood biochemistry, urine routine, and coagulation function.
- Electrocardiogram: Evaluate changes in subjects' electrocardiogram before and after administration.
- Examination of injection site: Evaluate the condition of the injection site after administration, such as redness, swelling, heat, pain, itching, etc.
- Systemic and organ radiation distribution: Regions of interest (ROI) such as the brain, liver, and heart are delineated based on the iteratively reconstructed PET/CT imaging results to obtain the mean and maximum tumor volume radioactivity at different time points. The radioactive decay of each source organ and the radiation dose of all target organs are calculated.
- Radiation exposure in ambient environment: Radiation exposure in ambient environment measured by a radiation detector.
- Researcher exposure: such as recording exposure through personal radiation dosimeters worn by researchers.

10.4.5 Baseline Descriptive Statistics

Descriptive statistics for demographics and other baseline features is conducted.

For continuous variables, the number of cases, mean, standard deviation, median, quartile, minimum, and maximum are calculated.

For enumeration and ranked data, counts and frequencies are calculated.

10.4.6 Planned Interim Analyses

Not applicable.

10.4.7 Exploratory Analyses

Not applicable.

10.5 Determination of Sample Size

This is an exploratory study and sample size determination is not based on any hypothesis testing. SNA002 is a ^{68}Ga-labeled radiodiagnostic reagent that has no pharmacological or toxicological effects during clinical use. Based on the sample size for ^{68}Ga-NOTA-2Rs15d (a total of 20 subjects, with 5–7 subjects per group) and ^{89}Zr-Df-IAB22M2C (a total of 6 subjects, with 1 subject per group), 12-28 subjects are intended to be enrolled in this trial. Each group is planned to include 3 to 7 subjects, and the number of subjects will be adjusted based on the imaging results. The detailed rules for adjustment are shown in the "General considerations for dose escalation" section. A total of 12-28 subjects will be enrolled into the effective dose group to allow sufficient observation of preliminary safety and common adverse reactions.

11 Source Documents and Access To Source Data/Documents

Source documents are defined as original documents recording observation results and clinical study activities. Source documents include but are not confined to the following: progress notes, electronic data, screening log, and data recorded by automated instruments. For more details, please refer to the source document list. The investigators should maintain all source documents related to the clinical trial. These source documents will be submitted to the authorized staff (see below) for direct review as per ICF:

- Clinical trial team and authorized staff
- Sponsor and its authorized agent
- Ethics committee
- The supervisory bodies and other staff from governmental agencies who are responsible for safeguarding the safety of the subjects

Direct review consists of the inspection, analysis, verification and reproduction of records and reports which are of great significance for evaluating the clinical trial by the supervisory bodies. The source document list can be found in the source document list table.

12 Quality Assurance and Quality Control

- Quality control measures of the laboratory : The laboratory should provide documents such as quality control certificate.
- Investigators participating in the clinical trial must have the professional skills, qualifications, and competence related to clinical trials. They must pass the qualification examinations. Minimum mobility of the investigators is required during the clinical trial.

- Before the clinical trial, the staff participating in the clinical trial should receive training on the protocol, current GCP, and SOP related to the present clinical trial.
- The study site should designate 1-2 imaging instruments for use in the clinical trial. The selected instruments must have a good performance and can completely satisfy the requirements of the trial. The designated instruments should be attached with relevant certification documents.
- The operating staff of the instruments should be authorized by PI and the authorization remains valid during the clinical trial. Moreover, they should be familiar with the protocol and the standard operating procedure of the imaging instruments.
- The specific procedure and parameters of imaging can be found in the standard operating procedure.
- The drug preparation staff should have the qualifications for radioactive drug preparation. They should be authorized by PI, and the authorization remains valid during the clinical trial.

13 Ethics/Protection of Human Subjects

13.1 Ethical Standard

The clinical trial is implemented according to *GCP* (version 2020), *ICH-GCP*, *Declaration of Helsinki*, relevant laws and regulations by NMPA, and the opinions of the ethics committee.

Before the clinical trial, the investigators/study sites should first obtain approval from the ethics committee on investigator's brochure, protocol/protocol revision, paper copies of ICF, and recruitment materials.

13.2 Institutional Review Board

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

13.3 Informed Consent Process

The investigators are responsible for informing the subjects of the study background, pharmacological features of the investigational drug, trial protocol, risks and benefits of participating in the clinical trial. ICF signed by the subjects should be obtained from the subjects before their participation (before the screening examinations). The subjects and the investigators should sign and date the ICF. One signed copy of ICF should be preserved by the investigator and the subject, respectively. The sponsor should timely update ICF in case of any major discoveries. After approval by the ethics committee, the subjects who have not yet completed the clinical trial

should re-sign the revised version.

The signed ICF is in duplicate. One copy is preserved by the subject, and another is kept in the investigator file.

The subjects have the right to know the latest information about the investigational drug and to withdraw from the study at any time. Such decisions will not influence their subsequent diagnosis and treatment or incur discrimination or unfair treatment.

13.4 Participant and Data Confidentiality

The data (including the clinical trial protocol) provided by the sponsor to the investigators are nonpublic information and must be kept confidential.

The sponsor has the right to release and publish the information or data related to the clinical trial or present them to the drug administration agencies. If other individuals or institutions related to the clinical trial want to release or publish the study results or relevant data, they must first obtain the consent from the sponsor. If the investigators' names are to appear in the contents released, published, or advertised by the sponsor, the sponsor should first obtain the consent from the investigators.

13.5 Future Use of Stored Specimens

Data collected for this study will be analyzed and stored at the data manager center. After the study is completed, the de-identified, archived data will be transmitted to and stored at the data manager center, under the supervision of PM, for use by other researchers including those outside of the study. Permission to transmit data to the data manager center will be included in the informed consent.

With the participant's approval and as approved by local IR s, de-identified biological samples will be stored at the biosample manager center with the same goal as the sharing of data with the data manager center.

During the conduct of the study, an individual participant can choose to withdraw consent to have biological specimens stored for future research. However, withdrawal of consent with regard to biosample storage will not be possible after the study is completed.

14 Data Handling and Record Keeping

14.1 Data Collection and Management Responsibilities

EDC software is used for data collection and management in this clinical trial. The system keeps track of all revisions to ensure the traceability of clinical trial data. The data management procedure should conform to GCP, thereby ensuring the authenticity, integrity, and accuracy of clinical trial data.

Table 6 Management Responsibilities

Post	Abbreviation:	Responsibilities
Sub-investigator	Sub-I	1. Input data. 2. Answer queries.
Principal investigator	PI	1. Input data. 2. Answer queries. 3. Approve.
Clinical research associate (CRA)	CRA	1. Verify the consistency of source documents 2. Generate queries.
Project manager	PM	1. Verify the consistency of source documents. 2. Generate queries.
Data management	DM	1. Generate queries. 2. Review the queries. 3. Freeze/restore data. 4. Lock the data.
Medical coding	coder	1. Code. 2. Generate queries.

The investigators or the staff authorized by the investigators will finish on-line data input after the visits.

The investigators should approve the data in eCRF to ensure that the data recorded in eCRF is authentic. Once the data input is completed, any revisions of the data should be accompanied by comments and automatically recorded in the system.The data of plasma concentrations is managed as external data. For requirements on data transmission, refer to the "Protocol on External Data Transmission". DM is responsible for the review and consistency check of external data.

14.2 Study Records Retention

At the end of the clinical trial, the eCRF of each subject is exported to a PDF document and saved to a CD, which is preserved by the clinical trial institution. The eCRF will be preserved until two years after the investigational drug comes to the market.

14.3 Protocol Deviations

PD occurs when the investigators or the subjects do not conform to the protocol, SOP, GCP, and relevant laws and regulations. PD is divided into mild, moderate, and serious by severity.

Mild PD: A situation that deviates from the routine procedure but does not have an adverse impact on subjects or data and where proper measures should be taken to cope with it. It is simply known as a PD.

Moderate PD: A situation that significantly deviates from the principles of scientificity, ethicality and laws, or impairs the commercial reputation and where timely measures should be taken. If left unheeded, a moderate PD may develop into a serious one.

Serious PD: A situation that may threaten the safety of subjects and significantly deviates from the principles of scientificity, ethicality and laws, or impairs the commercial reputation. A serious PD may lead to study data or results unacceptable by the supervisory bodies, and so countermeasures

should be adopted immediately.

Moderate and serious PDs are both critical situations and collectively known as PV. They should be summarized in the clinical study report.

The staff who first know of PDs should report to the CRA after a preliminary assessment of the severity of the PDs.

If the PD is a mild one, the CRA should fill in the PD tracking form. The investigators should receive relevant training to prevent the recurrence of similar PDs. The CRA should collect, summarize, report, and assess PDs occurring during the clinical trial by month. The sponsor should submit them to the ethics committee or the supervisory bodies for review according to the requirements of study sites.

If the PD is a serious one, the CRA should fill in the PD tracking form and immediately submit it to the sponsor. The sponsor should analyze the reasons and develop relevant countermeasures or revisions. After finishing the PD tracking form, the CRA should offer face-to-face training for the investigators. They should also keep track of the PD to prevent recurrence, and submit it to the ethics committee or the supervisory bodies for review according to the requirements of study sites. This serious PD should be timely recorded in the project progress report and sent to all study sites to prevent the recurrence of similar PDs.

At the completion stage, the study director should summarize all PDs and major PDs throughout the clinical trial and analyze their overall features. The director should assess how severe the clinical data are influenced and generate a PD summary report.

14.4 Publication and Data Sharing Policy

The data (including the clinical trial protocol) provided by the sponsor to the investigators are nonpublic information and must be kept confidential.

The sponsor has the right to release and publish the information or data related to the clinical trial or present them to the drug administration agencies. If other individuals or institutions related to the clinical trial want to release or publish the study results or relevant data, they must first obtain the consent from the sponsor. If the investigators' names are to appear in the contents released, published, or advertised by the sponsor, the sponsor should first obtain the consent from the investigators.

15 Study Administration

Not applicable.

16 Conflict Of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and

managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial.

17 Literature References

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[23] ^{68}Ge/^{68}Ga generator @ EMA.

Appendix 1

ECOG score

Grade	Performance status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. up and about more than 50% of waking hours.
3	Capable of only limited selfcare. confined to bed or chair more than 50% of waking hours
4	Completely disabled. cannot carry on any selfcare. totally confined to bed or chair
5	Dead

--Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

Appendix 2

NYHA Functional Classification

The New York Heart Association (NYHA) functional classification criteria categorize functional and therapeutic aspects of physical activity in subjects with cardiac function. Subjects were categorized according to NYHA definitions as follows:

GRADE	PATIENT SYMPTOMS
Grade I (mild)	No limitation of physical activity and no symptoms caused by usual activities.
Grade II (mild)	Slight limitation of physical activity. No discomfort at rest or with light activity.
Grade III (moderate)	Marked limitation of physical activity and no discomfort at rest only.
Grade IV (severe)	Unable to engage in any physical activity, confined to bed or chair; any physical activity causes discomfort or symptoms at rest.

NYHA =New York Heart Association

- Adapted from Criteria Committee of the New York Heart Association. Nomenclature and Criteria for Diagnosis of Cardiac and Macrovascular Diseases, 9th ed. Criteria Committee of the New York Heart Association, 1994:253-6.

Appendix 3

CCS Angina Classification

The Canadian Cardiovascular Society (CCS) classifies angina severity into four classes:

GRADE	PATIENT SYMPTOMS
Grade I	General physical activity (eg, walking and stair climbing) is not restricted, and angina pectoris occurs only when exertion is strong, rapid, or continuous.
Grade II	Mild limitation of general physical activity. Angina pectoris occurs within hours of brisk walking, meals, cold or wind, mental stress, or awakening. In general, walking on flat ground for more than 200 m or climbing more than one floor is limited.
Grade III	General physical activity is significantly limited, and angina pectoris is is caused by walking on a flat ground within 200 m or climbing one floor in general.
Grade IV	Angina pectoris can occur with minimal activity or rest.

-- This table is cited from ACC/AHA/ACP-ASIM Guidelines for the Management of Chronic Stable Angina Pectoris, 1976:54 (3): 522-523.

Appendix 4

Child-pugh score of liver function

PARAMETER	SCORE		
	1	2	3
Hepatic encephalopathy (stage)	NOT		
Ascites	NOT	FEW	MORE
Bilirubin(μmol/L)	<34	34~51	>51
Albumin (g/L)	>35	28~35	<28
Prolonged coagulation time (s)	<4	4~6	>6

Grading: A rating of 5-6 points; A B-level score of 7-9 points; The C-level score is 10-15 points.
- From Internal Medicine 9th ed.

Version	Date	Significant Revisions
V1.0	Sep. 8, 2021	NA