S1 Table. Protocol synopsis

Title of the study	A phase 1 clinical trial to evaluate the safety, tolerability, and dosimetry of SNU-KB-01 in patients with inoperable, progressive somatostatin receptor-positive, metastatic or locally advanced neuroendocrine tumor
Investigational drug	SNU-KB-01 (^{177}Lu-DOTA-TATE)
Study duration	About 36 months from the date of approval by the Ministry of Food and Drug Safety in Korea and the institutional review board of the Seoul National University Hospital (However, it may be shortened or extended depending on the registration status of the patients.)
Indication	Inoperable, progressive somatostatin receptor-positive, metastatic or locally advanced neuroendocrine tumor.
Objective	**Primary objective:** This study aims to evaluate the safety and tolerability, and to determine the maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D) of SNU-KB-01 in patients with inoperable and progressive neuroendocrine tumor. **Secondary objective:** 1) To evaluate dosimetry of SNU-KB-01 in patients with inoperable and progressive neuroendocrine tumor. 2) To evaluate the efficacy of SNU-KB-01 in patients with inoperable and progressive neuroendocrine tumor. • Tumor response evaluation based on Response Evaluation Criteria in Solid Tumors (RECIST) ver. 1.1 evidenced with computed tomography (CT)/magnetic resonance imaging (MRI) • Progression-free survival (PFS) • Overall survival (OS) • Changes in levels of the biomarkers: chromogranin-A (CgA), 5-Hydroxyindoleacetic acid (5-HIAA) • Frequency of carcinoid syndrome • Quality of life (QOL): European Organization for Research and Treatment of Cancer (EORTC) QLQ-G.I.NET21 questionnaire • Somatostatin receptor imaging (^{111}In-Pentetreotide scan, ^{68}Ga-DOTA-TATE or ^{68}Ga-DOTA-TOC positron emission tomography [PET]/CT)-based treatment response evaluation
Planned	✧ Two dose cohort

number of patients	✧ Maximum 6 patients per cohort (Total maximum 12 patients)
Study design	This is a prospective, open-label, sequential, dose-escalation study, and patients are enrolled according to the rolling six design The US FDA-approved recommended dose of ^{177}Lu-DOTA-TATE (Lutathera) (200 mCi, every 8 weeks, total 4 cycles) is set as the maximum planned dose (MPD) for this study.
Study methods	The purpose of this phase 1 clinical trial is to determine the RP2D of SNU-KB-01 through the evaluation of safety, tolerability, dosimetry, and exploratory efficacy. ✧ Patient enrollment is performed using the rolling six method to quickly search for the MTD and the RP2D. ✧ All matters related to the adequacy of dose-escalation in the dose-escalation cohort, such as dose level and the cycle of administration of the SNU-KB-01, are subject to the decision of the safety review committee. ✧ To prepare for the unexpected adverse reactions, staggered administration is performed in which patients are enrolled at a 1-week interval after administration of the SNU-KB-01 to the first patient in each dose group. 1) Patients have 8 weeks of dose-limiting toxicity (DLT) observation period after the first administration of SNU-KB-01 (In case of delayed administration, a delayed schedule is included for the DLT observation period). 2) Tumor response evaluation is performed 16 weeks after C1D1, and then every 16 weeks based on calendar days. 3) Tests such as CgA, 5-HIAA (5-HIAA is performed when it is necessary at the discretion of the investigator), and laboratory tests are performed every 4 weeks and adverse reactions are monitored (However, tests and adverse reaction evaluation are performed every 2 weeks in cycle 1 to closely monitor the safety.) 4) Renal scan and salivary scan may be performed before administration of SNU-KB-01 at each cycle to evaluate urinary tract obstruction and sialadenitis respectively. (However, these scans can be omitted at the discretion of the investigator if there are no symptoms of salivary gland disease or if the renal function test result is normal.) 5) The following combination treatments are possible during clinical trials. ① Use of diuretics and/or laxatives for easy excretion of SNU-KB-01

	through urine and feces. ② Use of ice packs to reduce radiation exposure of salivary glands up to 4 hours after administration of the SNU-KB-01. ③ Use of prophylactic antiemetics such as Ondansetron. ④ Long-acting somatostatin analog: In the case of long-acting octreotide 20-30 mg (intramuscularly, monthly) and lanreotide 120 mg (deep subcutaneously, monthly), it is possible to administer in combination. During the 4 cycles of the treatment phase, the administration is possible from 4-24 hours after SNU-KB-01 administration, but it is not allowed within 4 weeks before SNU-KB-01 administration. If the 4 cycles of the treatment phase are completed or if the administration of SNU-KB-01 is permanently discontinued, it is possible to resume administration every 4 weeks. ⑤ Short-acting somatostatin analog: It can be administered by subcutaneous injection to relieve carcinoid symptoms such as diarrhea and flushing, but the administration is limited within 24 hours of SNU-KB-01 administration. ✧ Dosimetry evaluation is performed in Cycle 1 of the first dose cohort of SNU-KB-01. Radioactivity is quantified using ^{177}Lu-DOTATATE whole-body planar scans (anterior/posterior view) and single photon emission computed tomography (SPECT)/CT, and the method is as follows. 1) ^{177}Lu-DOTATATE whole-body planar scans and SPECT/CT are performed using a dedicated hybrid SPECT/CT scanner with a medium-energy general-purpose collimator and a 20% energy window width centered symmetrically over the 208-keV photopeak of ^{177}Lu. 2) ^{177}Lu-DOTATATE whole-body planar scans and SPECT/CT are obtained 4 hr (3-5 hr), 24 hr (16-24 hr), 48 hr (40-48 hr), and 120 hr (100-120 hr) after the administration of SNU-KB-01. However, it is possible to omit a one-time point, and in this case, it is additionally acquired at the time of 168 hr (156-168 hr). 3) The whole-body images are acquired on a dual-headed planar imaging with 1,024×256 matrices at a scan speed of 18 cm/min. 4) SPECT/CT images covering at least the liver and kidneys are acquired in step and shoot mode, 120 projections (60 per detector head), 20 sec per projection, and matrix size 128×128.

5) Images are reconstructed using an iterative algorithm (ordered subset expectation maximization, iteration 2, subset 10), and CT images are reconstructed into a 3.75-mm-thick slice.

6) Radiation dosimetry is performed based on the Medical Internal Radiation Dose (MIRD) S-value methodology, and calculated using OLINDA/EXM, ver. 1.1. Kidneys, liver, spleen, and bone marrow are selected as source organs.

Evaluation methods

Dose-escalation method

In this clinical trial, a maximum of 6 patients per dose cohort are enrolled using the rolling six method. The SNU-KB-01 dose is set in two dose cohorts, 150 mCi and 200 mCi, and the patient is assigned to an appropriate dose level when the patient is secured.

Dose-escalation proceeds until the MTD is confirmed. If the MTD is not confirmed until the second dose level (200 mCi), which is the MPD, the study is terminated at that dose level.

Level	Dose (mCi)	%Increments	Ratio to SD
1	150	-	1.0
2	200	33.3	1.33

1. <u>Definition of dose-limiting toxicity (DLT)</u>

DLT is evaluated according to the National Cancer Institute (NCI)–Common Terminology Criteria for Adverse Events (CTCAE) ver. 5.0, and it is defined as an adverse drug reaction (ADR) that is any of the following toxicities. However, we exclude the case of temporary vasovagal syncope caused by intravenous insertion of a catheter for the administration of a drug, which is immediately recovered.

The DLT observation period is 8 weeks after the first administration of the SNU-KB-01 when it is performed as scheduled (In case of delay in the administration, the delayed schedule is included in the observation period). During the DLT observation period, it is not possible to change the dose (increase or decrease) of the SNU-KB-01. DLT observed after the first cycle is defined as delayed DLT, and is continuously collected and evaluated during the clinical trial period. Delayed DLT is not used in the determination of MTD, but is used in decisions such as discontinuation of SNU-KB-01, cessation of enrollment of new patient, or discontinuation of a clinical trial for the safety of patients.

1) Hematologic toxicity

	• Grade 4 anemia • Fever > 38.3 and absolute neutrophil count (ANC) < 500/μL • ANC < 500/μL lasting more than 8 days • Platelet < 25,000/μL (< 50,000/μL when patients have bleeding or need platelet transfusion) 2) Non-hematologic toxicity : Grade 3 or 4 ADRs (except in the following cases). • Grade 3 or 4 nausea, vomiting, diarrhea, and tumor pain are considered DLT only if they persist for more than 3 days despite the use of appropriate medications and treatments. • Grade 3 fatigue is considered DLT when it lasts more than 8 days. • Grade 3 or 4 aspartate transaminase/alanine transaminase elevation is considered DLT when it lasts more than 8 days. • Grade 3 hypertension is considered DLT when it is not controlled to systolic blood pressure (SBP) 140 mm Hg or diastolic blood pressure (DBP) 90 mm Hg or less within 8 days despite medication. • In addition, ADR that causes the inability to resume administration of the SNU-KB-01 in the next cycle within 16 weeks can also be evaluated as DLT. **2. <u>Determination of maximum tolerated dose (MTD)</u>** ✧ MTD is defined as the highest dose at which the incidence of DLT is lower than 33% (i.e., the highest dose at which DLT is observed in 0-1 of 6 patients). The DLT evaluation is performed only in cycle 1. (In case of delay in the administration, the delayed schedule is included in the DLT observation period.) ✧ For MTD determination, up to 6 patients are enrolled at each dose level and the DLT is evaluated for 8 weeks after administration of a single dose of SNU-KB-01. **3. <u>Rolling six design</u>** The rolling six design can enroll up to 6 patients consecutively at one dose cohort to prevent delay of patient enrollment. The dose level of the next patient to be enrolled is determined according to the number of patients enrolled at the time of enrollment of the next patient, the number of patients who have completed DLT evaluation, and the number of patients with DLT. The specific details are as follows. • Dose reduction criteria: In the case of DLT is observed 2 or more patients • Dose-escalation criteria: When [patients who have completed DLT

	evaluation/ patients enrolled] are 3/3, 4/4, 5/5, 5/6, or 6/6, and no DLT has occurred in all patients who have completed evaluation **4. <u>Discontinuation criteria for individual patients</u>** If one or more events corresponding to the discontinuation criteria occur during the clinical trial, the administration of SNU-KB-01 for the individual patient is discontinued. Reasons for discontinuation for the individual patient include but are not limited to the following. 1) When progressive disease is confirmed according to RECIST criteria or the investigator judges that the treatment effect is insufficient. (However, if the patient who showed a treatment response after administration of SNU-KB-01 had a disease progression, SNU-KB-01 can be administered with increased dose at the discretion of the investigator after the end of the study with the consent of the patient.) 2) When the administration of SNU-KB-01 is delayed more than 16 weeks from the previous cycle due to an adverse reaction (i.e., when the administration is delayed more than 8 weeks from the planned administration schedule). 3) Withdrawal of consent of the patient or the patient's representative. 4) When it is found during the clinical trial that the patient is enrolled but does not meet the inclusion and exclusion criteria at screening and baseline. 5) When it is difficult to continue the clinical trial due to an adverse reaction. 6) Patients who show ADRs equivalent to DLT again at a 50% reduced dose upon re-administration. 7) Significant protocol violation. 8) When it is impossible to follow up with the patient. 9) In case the patient is unable to continue treatment, or unable to perform tests and procedures on regular visits (e.g., pregnancy of female patient, etc.). **5. <u>Criteria for dose modification</u>** ✧ After the DLT observation period, if the DLT is recovered within 16 weeks in a patient who has experienced an adverse drug reaction equivalent to the DLT, re-administration of the SNU-KB-01 is possible in the next cycle. In case of re-administration, it is administered with a 50% reduced dose. SNU-KB-01 should be discontinued if the DLT reappears at the 50% reduced dose. If DLT does not develop at the 50% reduced

dose, the next cycle is administered at the planned 100% dose.

✧ Recommended dose modification for adverse drug reactions equivalent to DLT is as follows.

<table>
<tr><th>Toxicity</th><th>Recovery</th><th>Action</th><th>Next result</th><th>Next action</th></tr>
<tr><td rowspan="3">DLT</td><td rowspan="2">Recovery within 16 weeks</td><td rowspan="2">50% dose reduction for the next cycle</td><td>No DLT</td><td>Full Dose
(planned 100% dose)</td></tr>
<tr><td>DLT</td><td>Discontinue SNU-KB-01
+ Best supportive care (BSC) including long-acting octreotide</td></tr>
<tr><td>Lasts more than 16 weeks</td><td colspan="3">Discontinue SNU-KB-01
+ BSC including long-acting octreotide</td></tr>
</table>

✧ Dose-modifying toxicity (DMT) is defined as an adverse drug reaction that does not fulfill the criteria for a DLT but requires dose modification in the next cycle, and the dose must be adjusted as follows. However, in the case of a DMT after the DLT observation period (after the first cycle of SNU-KB-01), the patient is allowed to continue the next cycle at the discretion of the investigator, and the dose adjustment may be clinically determined by the investigator.

<table>
<tr><th colspan="2">Dose-modifying toxicities (DMT)</th><th rowspan="2">Dose modification</th></tr>
<tr><td>Adverse reaction</td><td>Severity</td></tr>
<tr><td>Thrombocytopenia</td><td>Grade ≥ 2</td><td>• Permanently discontinue SNU-KB-01, if the patient does not recover to grade 0 to 1 within 16 weeks after administration.
• 50% dose reduction for the next cycle, if the patient recovers to grade 0 to 1 within 16 weeks.
• If grade ≥ 2 thrombocytopenia is not observed after 50% dose reduction, administer the dose before the reduction.</td></tr>
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			• If grade ≥ 2 thrombocytopenia is observed after 50% dose reduction, permanently discontinue SNU-KB-01.
	Anemia neutropenia	Grade ≥ 3	• Permanently discontinue SNU-KB-01, if the patient does not recover to grade 0 to 2 within 16 weeks after administration. • 50% dose reduction for the next cycle, if the patient recovers to grade 0 to 2 within 16 weeks. • If grade ≥ 3 anemia or neutropenia is not observed after 50% dose reduction, administer the dose before the reduction. • If grade ≥ 3 anemia or neutropenia is observed after 50% dose reduction, permanently discontinue SNU-KB-01.
	Renal toxicity	CrCl < 40 mL/min, or 40% increase in baseline serum creatinine, or 40% decrease in baseline serum creatinine	• Permanently discontinue SNU-KB-01, if the patient does not recover from renal toxicity. • 50% dose reduction for the next cycle, if the patient recovers renal toxicity within 16 weeks. • If renal toxicity is not observed after 50% dose reduction, administer the dose before the reduction. • If renal toxicity is observed after 50% dose reduction, permanently discontinue SNU-KB-01. ※ CrCl is calculated using Cockcroft Gault Formula (with actual body weight).
	Hepatotoxicity	Bilirubinemia	• Permanently discontinue SNU-

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<tr><td></td><td>Grade ≥ 3, or

Hypoalbuminemia < 3.0 g/dL (Grade 2) with prothrombin time (INR) > 1.5 (Grade 2)</td><td>KB-01, if the patient does not recover from hepatotoxicity.
• 50% dose reduction for the next cycle, if the patient recovers hepatotoxicity within 16 weeks.
• If hepatotoxicity is not observed after 50% dose reduction, administer the dose before the reduction.
• If hepatotoxicity is observed after 50% dose reduction, permanently discontinue SNU-KB-01.</td></tr>
<tr><td>Other non-hematologic toxicity</td><td>Grade ≥ 3</td><td>• Permanently discontinue SNU-KB-01, if the patient does not recover to grade 0 to 2 within 16 weeks after administration.
• 50% dose reduction for the next cycle, if the patient recovers to grade 0 to 2 within 16 weeks.
• If grade ≥ 3 toxicity is not observed after 50% dose reduction, administer the dose before the reduction.
• If grade ≥ 3 toxicity is observed after 50% dose reduction, permanently discontinue SNU-KB-01.</td></tr>
</table>

6. <u>Replacement of patients</u>
If there is a dropout during the DLT observation period even though no DLT occurred, a patient can be replaced.</td></tr>
<tr><td>Inclusion criteria</td><td>Patients must meet all of the following criteria.
1) Patients ≥ 19 and ≤ 79 years of age.
2) Patients with inoperable (curative intent), progressive under previous therapy*, histologically confirmed metastatic or locally advanced neuroendocrine tumor.</td></tr>
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	- Previous therapy* includes the following treatments, either alone or in combination. • Patients on somatostatin analog (long-acting octreotide 20-30 mg, monthly or lanreotide 120 mg, monthly) for at least 12 weeks prior to enrollment in this study • Everolimus • Interferon-alpha • Sunitinib • Cytotoxic chemotherapy • Hepatic-directed therapy in case of hepatic-predominant disease (transarterial chemo-/radio-embolization, cytoreductive surgery) 3) Positive on somatostatin receptor whole-body scan (Krenning score of 2 and above on ^{111}In-Pentetreotide scan, ^{68}Ga-DOTA-TATE or ^{68}Ga-DOTA-TOC PET/CT) - Tumor uptake score defined as Krenning scale Grade 1: Uptake very lower than that in the liver Grade 2: Uptake equal to that in the liver Grade 3: Uptake greater than that in the liver Grade 4: Uptake greater than that in kidneys, spleen 4) Ki67 index ≤ 20% 5) Patients who are confirmed to have disease progression under previous therapy based on RECIST criteria, ver. 1.1 evidenced with CT/MRI. 6) Life expectancy > 12 weeks 7) Karnofsky Performance Score ≥ 50. 8) Patients who have a willingness to actively participate, and can comply with the clinical trial schedule and procedures, and have signed the informed consent after being fully explained and understood about the purpose and procedure of the clinical trial.
Exclusion criteria	Patients who meet any of the following criteria cannot participate in this study. 1) Exclude patients with the following organ dysfunctions: [Renal function] • Serum creatinine > 1.7 mg/dL or creatinine clearance < 50 mL/min (Cockcroft Gault method with actual body weight). [Hematologic function] • Hgb < 8.0 g/dL • White blood cell < 2,000/μL

	• Platelets < 75,000/μL [Liver function] • Total bilirubin > 3×upper limit of normal (ULN) • Serum albumin < 3.0 g/dL and prothrombin time (INR) > 1.5 2) Pregnancy and lactation. 3) Patients who were administered long-acting octreotide (> 30 mg, monthly) within 12 weeks prior to enrollment in this study. 4) Patients with other co-existing malignancies (solid tumor and hematologic malignancy including lymphoma). However, there are exceptions in the following cases. • If the patient has not received treatment of the tumor or is in a disease-free state for at least 5 years. (However, the patient with papillary thyroid cancer can participate in the clinical trial even if it has not been 5 years if the patient underwent radical resection.) • At least 1 year after complete resection of basal cell carcinoma/squamous cell carcinoma of the skin or successful treatment of carcinoma in situ of the uterine cervix 5) Any previous therapy for neuroendocrine tumors with described conditions. • Surgery, radioembolization, chemoembolization, chemotherapy, and radiofrequency ablation within 12 weeks prior to SNU-KB-01 administration • Interferons, Everolimus, and Sunitinib within 6 weeks prior to SNU-KB-01 administration 6) Prior external beam radiation therapy to more than 25% of the bone marrow. 7) Patients who received high-dose chemotherapy requiring hematopoietic stem cell transplantation within 2 years prior to SNU-KB-01 administration. 8) Patients with symptomatic central nervous system metastasis (except in cases where systemic corticosteroids were discontinued at least 4 weeks prior to baseline and were radiologically and neurologically stable for 4 weeks or longer). 9) Patients who have the following medical history or history of following surgery/procedure: • Deep vein thrombosis or pulmonary embolism within 1 year prior to baseline • Acute coronary syndrome (unstable angina or myocardial infarction) within 6 months prior to baseline

	• Serious cerebrovascular disease, such as stroke, within 6 months prior to baseline • Major surgery requiring general anesthesia or respiratory support within 4 weeks prior to baseline (however, 2 weeks for video-assisted thoracoscopic surgery or open-and-close [ONC] surgery) 10) Patient with the following diseases: • Congestive heart failure (NYHA class II, III, IV) • Uncontrolled hypertension (SBP > 160 mmHg or DBP > 90 mmHg) • Clinically significant cardiovascular abnormality (e.g., left ventricular ejection fraction < 50%, clinically significant cardiac wall abnormality or myocardial damage, etc.) which is decided by the investigator • Uncontrolled diabetes mellitus (fasting blood glucose > 2 ULN) • Uncontrolled arrhythmia • Spontaneous urinary incontinence • Known human immunodeficiency virus–positive patient or patient with other uncontrolled active infectious disease 11) Patients who are taking antithrombotic drugs (however, patients who are taking low-dose aspirin less than 325 mg to inhibit platelet aggregation can participate in the study) or patients with a bleeding predisposition, massive hemoptysis, gastrointestinal bleeding, and peptic ulcer 12) Patients with severe drug hypersensitivity, or hypersensitivity to investigational drugs (and their components) and similar drugs 13) Patients taking nephrotoxic drugs (e.g., aminoglycosides) 14) Patients with severe claustrophobia that is not controlled with antianxiety medications 15) If there is no intention to use an appropriate method of contraception during and after the period of a clinical trial (at least 7 months for female patients of childbearing potential; at least 4 months for male patients who are not surgically sterile or with female partners of childbearing potential). 16) Patients who have administered other clinical trial drugs or have received procedures using medical devices under clinical trial within 12 weeks prior to the baseline 17) Patients who cannot participate in clinical trials when judged by investigator
Dose level and administration	**Dose level and interval between cycles** • Dose level: 150, 200 mCi.

method

- Interval between cycles: Every 8 weeks (total 4 cycles, maximum 800 mCi). However, if the delay of SNU-KB-01 supply occurs due to problems in manufacturing and/or material supply, the administration schedule may be delayed at the discretion of the investigator.

Administration method

- SNU-KB-01 (investigational drug) is administered slowly intravenously (IV infusion) using a syringe pump. However, if there is a problem with syringe pump infusion, a manual injection can be performed. The infusion rate is as shown in the table below and can be adjusted by the investigator if necessary in consideration of clinical findings.
- About 2,000 mL of amino acid is administered intravenously 30 minutes before administration of SNU-KB-01 and continued for 4 to 6 hours. An antiemetic is administered prophylactically.

Administration procedure

Administered agents	Start time	Infusion rate	Duration	Purpose
Antiemetics[a)]	0-15 min	200 mL/hr	15 min (±10 min)	Prevention of vomiting
Amino acid solution: 2L[b)]	30 min	500 mL/hr	4 hr (+2 hr)	Renal protection
0.9% NaCl: 1L[c)]	30 min	250 mL/hr	4 hr (+2 hr)	Improvement of side effects of amino acid solution
SNU-KB-01[d)]	60 min	10 mL/hr	30 min (±10 min)	Investigational drug
0.9% NaCl[e)]	90 min	50 mL/hr	15 min (±10 min)	Saline flush

[a)] Granisetron (3 mg), or Ondansetron (8 mg) diluted in 50 ml of 0.9% NaCl is administered 45-60 minutes before administration of the SNU-KB-01. Additional administration may be performed if necessary.

[b)] Amino acid solution is administered 30 minutes before the administration of SNU-KB-01 and is continued for about 4 hours through an IV line different from SNU-KB-01. If symptoms such as nausea/vomiting appear during infusion, the infusion rate can be adjusted slowly, but it is recommended not

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to exceed 6 hours. If the infusion time is delayed for more than 6 hours due to the side effects of amino acid infusion, the administration may be discontinued. The recommended composition of the amino acid solution is as follows, but it can be adjusted at the discretion of the investigator (e.g. prepared total parenteral nutrition solution or a commercialized solution with the same or similar composition).
<table>
<tr><th>Component</th><th>Specification</th><th>Function</th></tr>
<tr><td>Lysine</td><td>≥ 18 g, ≤ 24 g</td><td>Renal protection</td></tr>
<tr><td>Arginine</td><td>≥ 18 g, ≤ 24g</td><td>Renal protection</td></tr>
<tr><td>Saline or other suitable diluent</td><td>< 2L ± 25%</td><td>Osmolarity (< 1,050 mOsmol), solvent</td></tr>
<tr><td>All other amino acids</td><td>No Specification</td><td>Inert nutrients</td></tr>
</table>
c) The administration starts at the same time as the amino acid infusion, and the infusion rate can be adjusted according to the amino acid infusion rate. When amino acid administration is completed or discontinued, the administration should be discontinued together.
d) SNU-KB-01 is administered slowly intravenously using a syringe pump without mixing with other solutions. However, if there is a problem with syringe pump infusion, a manual injection can be performed.
e) After injecting SNU-KB-01, flush IV line with at least 10 ml of normal saline.
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<td>Endpoints</td>
<td>
1. Safety and tolerability
1) Tolerability
• Frequency and characteristics of DLT; Determination of MTD and RP2D
• Discontinuation or dose reduction due to adverse reactions
2) Safety
• Adverse events
• Multiple test results such as laboratory tests, vital signs, and electrocardiograms
2. Dosimetry
1) Time-activity curve
2) Cumulative activity
3) Residence time
4) Effective dose
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	3. Efficacy Tumor response (based on RECIST ver. 1.1) and tumor-related symptoms/tests. 1) Overall response rate (ORR) • ORR=complete response+partial response 2) PFS: time from C1D1 to disease progression or death 3) OS: time from C1D1 to death 4) Changes in CgA, 5-HIAA levels 5) Frequency of carcinoid syndrome 6) Quality of life: EORTC QLQ-G.I.NET21 questionnaire assessment. 7) Somatostatin receptor imaging (^{111}In-Pentetreotide scan, ^{68}Ga-DOTA-TATE or ^{68}Ga-DOTA-TOC PET/CT)-based treatment response evaluation