PEN-221

PROTOCOL PEN-221-001

A Phase 1/2a, open-label multicenter study to assess the safety, tolerability, pharmacokinetics, and preliminary antitumor activity of PEN-221 in patients with somatostatin receptor 2 expressing advanced cancers, including gastroenteropancreatic or lung or thymus or other neuroendocrine tumors or small cell lung cancer or large cell neuroendocrine carcinoma of the lung

Protocol Version, Date:	Version 8.0, 12 July 2019 Includes Amendment 1, Amendment 2, Amendment 3, Amendment 4, Amendment 5, Amendment 6, and Amendment 7
EudraCT Number	2016-001468-12
NCT number	NCT02936323

Table of Contents Link

Sponsor:

Tarveda Therapeutics, Inc.
134 Coolidge Avenue
Watertown, MA 02472

USA
Telephone: +1 (617) 923 4100

INVESTIGATOR'S AGREEMENT

I have received and read the Investigator Brochure for PEN-221. I have read Protocol PEN-221-001 and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

SIGNATURE PAGE

Protocol Title: A Phase 1/2a, open-label multicenter study to assess the safety, tolerability, pharmacokinetics, and preliminary antitumor activity of PEN-221 in patients with somatostatin receptor 2 expressing advanced cancers, including gastroenteropancreatic or lung or thymus or other neuroendocrine tumors or small cell lung cancer or large cell neuroendocrine carcinoma of the lung

Protocol Approval: [redacted]

Date 7/12/2019

Tarveda Therapeutics

PROCEDURES IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

Role in Study	Name	Address and Telephone number
Medical Monitor	[redacted]	[redacted]
Serious Adverse Event Reporting (24-hour)	[redacted]	[redacted]

1. SYNOPSIS

Name of Sponsor/Company:
Tarveda Therapeutics, Inc.

Name of Investigational Product:
PEN-221

Name of Active Ingredient:
PEN-221

Title of Study:
A Phase 1/2a, open-label multicenter study to assess the safety, tolerability, pharmacokinetics, and preliminary antitumor activity of PEN-221 in patients with somatostatin receptor 2 expressing advanced cancers, including gastroenteropancreatic or lung or thymus or other neuroendocrine tumors or small cell lung cancer or large cell neuroendocrine carcinoma of the lung

Phase of development:
1/2a

Study Design:
PEN-221 is a peptide-drug conjugate combining a somatostatin analog and mertansine (DM1), a thiol-containing maytansinoid, using a cleavable disulfide linker. The molecule is designed as a potent and selective anti-cancer agent to treat patients whose tumors express the somatostatin receptor SSTR2, namely, neuroendocrine tumors (NETs), small cell lung cancer (SCLC) and large cell neuroendocrine carcinoma (LCNEC) of the lung. In preclinical studies, PEN-221 demonstrated potent anti-tumor activity in multiple cancer models that express SSTR2.

Protocol PEN-221-001 is an open-label, multi-center, first-in-human Phase 1/2a study evaluating PEN-221 in patients with SSTR2 expressing advanced gastroenteropancreatic (GEP) or lung or thymus or other NETs or SCLC or LCNEC of the lung.

Pre-screening phase

After provision of written informed consent for pre-screening, patients will have their cancers assessed for SSTR2 expression using an approved somatostatin analog radioisotope imaging (SARI) agent.

Patients who have undergone recent SARI, i.e., within the preceding approximately 6 months, by Octreoscan or ^{68}Ga-DOTATATE, ^{68}Ga-DOTATOC, or ^{68}Ga-DOTANOC, may have the results reviewed by the study Investigator for determination of tumor SSTR2 positivity in lieu of undergoing repeat imaging during the Pre-screening phase. Patients whose tumors are determined to be positive for SSTR2 expression by SARI are eligible to proceed to the Screening phase of the study.

Screening phase

After provision of written informed consent for the study, patients whose tumors were determined to be SSTR2 positive during the Pre-screening phase will proceed to the Screening phase of the study. Screening assessments include a careful review of the patient's medical history, assessment of Eastern Cooperative Oncology Group (ECOG) performance status (PS), physical examination, neurological examination, electrocardiogram (ECG) and laboratory assessments, and computed tomography (CT) or magnetic resonance imaging (MRI) of all sites of disease.

Screening assessments are to be performed within 14 days before the first study drug dose, with the exception of CT or MRI studies which may be performed within 28 days before the first study drug dose.

Patients who are determined to be eligible based on Screening assessments will be enrolled in the study on Cycle 1 Day 1 (C1D1; baseline).

Treatment phase (Phase 1 and Phase 2a)

Phase 1 will enroll patients with SSTR2 expressing advanced gastroenteropancreatic (GEP) or lung or thymus or other NETs or SCLC or LCNEC of the lung who have provided informed consent for the main study.

Phase 2a will enroll patients with advanced or metastatic, well differentiated, low or intermediate grade gastrointestinal mid-gut NET, or with advanced or metastatic, well differentiated, low-intermediate grade pancreatic NET or with advanced or metastatic SCLC.

The safety, pharmacokinetics (PK), pharmacodynamics (PDc) and anti-tumor activity of PEN-221 will be assessed. Safety will be assessed during the study by vital sign measurements, physical examinations, neurological examinations, ECOG PS, documentation of adverse events (AEs), clinical laboratory tests, and ECGs.

Serial blood samples for pharmacokinetic (PK) and pharmacodynamic (PDc) assessments will be collected from all patients.

Tumor response assessments will be performed using Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1 (Eisenhauer 2009). Patients with advanced NETs will undergo tumor assessments every third cycle, and patients with advanced SCLC or LCNEC of the lung will undergo tumor assessments every other cycle. For patients who have a tumor (complete or partial RECIST) response, a repeat evaluation to confirm response will be performed approximately 6 weeks (but not less than 4 weeks) after the initial response.

Patients may continue to receive PEN-221 as long as they are considered to show clinical benefit, as judged by the Investigator, and in the absence of discontinuation criteria.

Phase 1 (Dose escalation)

Phase 1 will employ an adaptive Bayesian logistic regression model (BLRM) with 2 parameters guided by the escalation with overdose control (EWOC) principle to make dose recommendations and estimate the maximum tolerated dose (MTD).

To minimize the number of patients treated at potentially subtherapeutic dose levels, the first dose cohort will enroll 2 patients, whereas subsequent cohorts will enroll a minimum of 3 and up to 6 patients. The initial patient in Cohort 1 will receive PEN-221 administered intravenously (IV) over 1 hour at the starting dose of 1.0 mg on an every 3 week cycle. This patient will be followed for 7 days, including assessments during the scheduled visit on C1D8, prior to allowing additional patients to begin treatment with PEN-221. If PEN-221 is tolerated by the initial patient for at least 7 days, then the first cohort will be opened to treatment of 1 additional patient. The first 2 patients will be assessed for safety and dose limiting toxicity (DLT) for at least 4 weeks (including C2D1 and C2D8 assessments) before enrollment in the second cohort may begin.

In each dose escalation cohort following the first cohort, a minimum of 3 patients within a cohort are required to have completed C1 and have been assessed for safety and DLT for at least 3 weeks (including C2D1 pre-dose assessments) before enrollment of the next cohort may begin.

The Safety Review Committee (SRC) will review the safety and tolerability of PEN-221 of each cohort to decide the next dose level to be tested. Statistical modeling will be performed using all safety data and will guide the SRC's selection of dose levels to be tested. In addition, PK and PDc data may be used to inform dose selection. Dose escalation increments will be the decision of the SRC. Dose escalation will continue until the MTD is determined.

During Phase 1, if a patient is tolerating PEN-221 without significant evidence of disease progression, the patient may, beginning with C3 or subsequent cycles, have the dose increased to a dose that has already been established as tolerable by the SRC, and with the agreement of the SRC.

Phase 2a

Phase 2a may begin, at the discretion of the Sponsor, once all patients treated in Phase 1 have been assessed for safety through and including C2D1, and the SRC has reviewed all safety data and recommends continuing with Phase 2a.

PEN-221 will be evaluated using the recommended Phase 2 dose (RP2D) defined by the SRC at the conclusion of Phase 1. The RP2D will be the decision of the SRC and will be based on the findings of the safety, tolerability, PK, and PDc profile of PEN-221 during Phase 1. The RP2D may be the same as the MTD, or may be below the MTD. In the event that the MTD is higher than the dose determined by the SRC to have an acceptable safety and tolerability profile after multiple cycles of administration, the SRC may select a RP2D that is below the MTD.

Approximately 75 patients will be treated in 3 expansion cohorts, each consisting of patients with distinct subsets of SSTR2-expressing solid tumors to assess the early efficacy, safety and PK of PEN-221 in these distinct populations.

Objectives:

Phase 1 (Dose escalation)

Primary

The primary objective of Phase 1 is to:

- Investigate the safety and tolerability, determine the MTD, and RP2D of PEN-221 when administered IV on an every 3 week schedule in patients with SSTR2-expressing advanced cancers, including GEP or lung or thymus or other NETs or SCLC or LCNEC of the lung.

Secondary

The secondary objectives of Phase 1 are to:

- Characterize the safety and tolerability of PEN-221, including both acute and chronic toxicities.
- Characterize the pharmacokinetics (PK) of PEN-221, DM1, and peptide from PEN-221, when administered IV in patients with SSTR2 expressing advanced cancers including GEP or lung or thymus or other NETs or SCLC or LCNEC of the lung.
- Assess the potential of PEN-221 to induce anti-PEN-221 antibodies in the serum when administered IV in patients with SSTR2 expressing advanced cancers including GEP or lung or thymus or other NETs or SCLC or LCNEC of the lung.
- Assess preliminary anti-tumor activity of PEN-221 in patients with SSTR2 expressing advanced cancers including GEP or lung or thymus or other NETs or SCLC or LCNEC of the lung, using tumor response criteria as defined by RECIST 1.1, and duration of response.

Exploratory

[redacted]

Phase 2a (Dose Expansion)

Primary

The primary objective of Phase 2a is to:

- Assess the efficacy of PEN-221 as a single-agent when administered IV using clinical benefit rate (CBR) as defined as the proportion of patients with the best overall response

of complete response (CR), partial response (PR), or stable disease (SD) using tumor response criteria as defined by RECIST 1.1 in the following tumor-specific cohorts:

- Patients with advanced or metastatic, well-differentiated, low or intermediate grade gastrointestinal mid-gut NETs.
- Patients with advanced or metastatic, well-differentiated, low or intermediate grade pancreatic NETs.

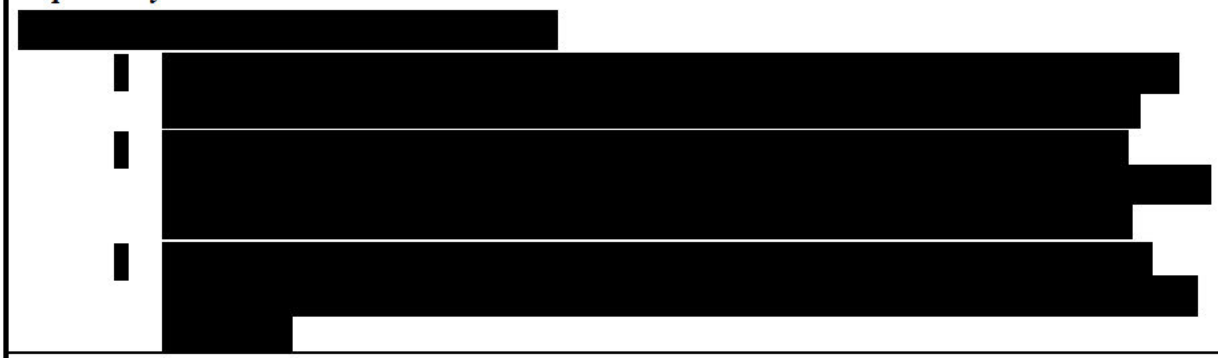
- Assess the efficacy of PEN-221 as a single-agent when administered IV using objective response rate (ORR) as defined as the proportion of patients with best overall response of CR or PR using tumor response criteria defined by RECIST 1.1, along with duration of response, in the following tumor-specific cohort:
  -
  - Patients with advanced or metastatic SCLC.

Secondary

The secondary objectives of Phase 2a are to:

- Confirm the maximum tolerated dose (MTD) identified during the dose-escalation phase, and further investigate the safety and tolerability of the recommended Phase 2 dose (RP2D) and schedule of PEN-221 when administered IV in patients with SSTR2-expressing advanced GEP NETs or SCLC.
- Evaluate progression-free survival and overall survival in all the above tumor-specific cohorts of patients whose tumors express SSTR2.
- Evaluate ORR and duration of response for gastrointestinal mid-gut NET and pancreatic NET.
- Evaluate the safety and tolerability of PEN-221 administration in the above tumor-specific cohorts of patients whose tumors express SSTR2.
- Characterize the pharmacokinetics (PK) of PEN-221, DM1, and peptide from PEN-221 in the above tumor-specific cohorts of patients whose tumors express SSTR2.

Exploratory



Number of patients (planned):

Phase 1

It is estimated that approximately 30 patients will be enrolled. Two patients will be treated at the first dose level. All subsequent cohorts will treat 3 to 6 patients at each dose level. An adaptive BLRM guided by the EWOC principle will be employed to make dose recommendations and estimate the MTD. Approximately 4 to 6 dose escalation cohorts are anticipated. The total number of patients to be enrolled is dependent upon the observed safety profile as well as the number of dose escalation cohorts required to achieve the MTD and establish the RP2D of PEN-221.

Each patient will participate in only 1 dose cohort with respect to assignment of starting dose.

Phase 2a

Approximately 75 patients will be enrolled as follows: gastrointestinal mid-gut NET (n=35, 25 PRRT-naïve, 10 PRRT recurrent), pancreatic NET (n=20), SCLC (n=20). These cohort sample sizes are considered sufficient to obtain an early assessment of efficacy of PEN-221 in patients with distinct tumor types.

Diagnosis and main criteria for inclusion:

All patients must meet all of the following criteria to be eligible to participate:

1. Provision and understanding of signed and dated, written informed consent prior to any mandatory study-specific procedures, sampling, analysis.
2. Male or female aged ≥ 18 years.
3. ECOG PS of 0 – 1.
4. Adequate organ function within 14 days before C1D1, defined as follows:
   - Bone marrow: Absolute neutrophil count (ANC) ≥ 1.5×10^9/L, platelet count ≥ 100×10^9/L, and hemoglobin ≥ 9 g/dl
   - Hepatic: total bilirubin ≤ 1.5× the upper limit of normal (ULN) and alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5× ULN
   - Renal: If serum creatinine concentration ≥ 1.5× ULN, then estimated creatinine clearance must be ≥ 50 mL/min (Cockroft-Gault formula).
5. Serum potassium, calcium, magnesium and phosphorus within normal limits. If values are low on the initial screening assessment, supplements may be given and values repeated to confirm within normal limits.
6. If a female of childbearing potential, negative serum pregnancy test within 3 days before C1D1, or in the event of a positive serum pregnancy test, exclusion of pregnancy as assessed by transvaginal ultrasound overseen by a health care professional with experience in investigating and diagnosing early pregnancy, as human chorionic gonadotropin (HCG) can be secreted by neuroendocrine tumor. A female of childbearing potential must agree to the use of highly reliable, physician-approved contraception from 14 days before C1D1 through 3 months after the last study drug dose. Highly reliable contraception means 2 of the following: (1) established use of oral, injected, or implanted hormonal methods of contraception, (2) placement of an intrauterine device, (3) condom or occlusive cap (diaphragm or cervical vault cap with spermicidal gel, foam, film, cream, or vaginal suppository), (4) male sterilization with verified absence of sperm in ejaculate post-vasectomy. Alternatively, true abstinence is acceptable when it is the preferred and usual lifestyle of the individual. Calendar, symptothermal, post-ovulation, coitus interruptus, spermicides only, and lactational amenorrhea are not acceptable methods of contraception.
7. If male, is surgically sterile or agrees to use a condom from C1D1 through 3 months after the last study drug dose. Alternatively, true abstinence is acceptable when it is the preferred and usual lifestyle of the individual.
8. SSTR2 positive tumor as assessed using a SARI agent and as defined as follows:
   - For SCLC patients, tumor uptake equal to or greater than liver uptake
   - For all other patients, tumor uptake greater than liver uptake.

   SARI performed during the Pre-screening phase must be an agent that is approved for use by the regional regulatory authority. Documented results of SARI performed as part of a patient's routine diagnostic assessments prior to the

Pre-screening phase and within 180 days of C1D1 may be used in place of a Pre-screening phase SARI assessment.

9. Patients in Phase 1 must have a histologically- or cytologically-confirmed solid tumor in 1 of the following categories:
    - Advanced SCLC or LCNEC of the lung having progressed after 1 or more prior lines of anticancer chemotherapy, or
    - Advanced low or intermediate grade GEP or lung or thymus NET, or NET of unknown primary, having progressed after 1 or more prior lines of anticancer therapy, unless no standard treatments are available or unless such treatments are deemed not appropriate, or
    - Advanced paraganglioma, pheochromocytoma, medullary thyroid carcinoma, Merkel cell carcinoma, or high grade extrapulmonary NEC, having progressed after 1 or more prior lines of anticancer therapy, unless no standard treatments are available or unless such treatments are deemed not appropriate.

    Anticancer therapies include liver-directed intra-arterial therapy, cytotoxic chemotherapy, everolimus, targeted inhibitors, metaiodobenzylguanidine (MIBG), and immunotherapies, but do not include somatostatin analogs.

For patients who provide written informed consent to undergo an optional tumor biopsy during the Screening phase, such patients must meet the following additional criterion before undergoing a biopsy procedure:

10. Patient must have at least 1 site of tumor that is accessible to biopsy and that is considered by the Investigator to be low risk and of sufficient size to undergo a biopsy procedure.

Patients in Phase 2a must meet the following additional criteria:

11. Measurable disease per RECIST 1.1 (i.e., at least 1 measurable lesion ≥ 20 mm by conventional techniques or ≥ 10 mm by spiral CT scan or MRI), with the last imaging performed within 28 days before C1D1 and documented radiographic disease progression.
12. Patients in Phase 2a must have a histologically- or cytologically-confirmed, advanced or metastatic solid tumor, in 1 of the following categories:
    - Well differentiated, low or intermediate grade, gastrointestinal mid-gut (arising from the lower jejunum, ileum, appendix, cecum, and proximal colon) NET with documented disease progression within 6 months prior to start of study treatment (i.e. maximum of 24 weeks from documentation of progression until study entry) and evidence of radiographic disease progression based on scans performed not more than 15 months apart. Patients may have received 1 or more prior lines of anticancer therapy, such as somatostatin analogues, targeted agents, or liver-directed intra-arterial therapy, but are NOT eligible if they have received prior systemic cytotoxic chemotherapy.
    - Well differentiated, low or intermediate, grade, pancreatic NET with documented disease progression within 6 months prior to start of study treatment (i.e. maximum of 24 weeks from documentation of progression until study entry), and evidence of radiographic disease progression based on scans performed not more than 15 months apart. Patients may have received 1 or more prior lines of anticancer therapy, such as somatostatin analogues, targeted agents, or liver-directed intra-arterial therapy, and up to 1 prior line of systemic cytotoxic chemotherapy, but are NOT eligible if they have received more than 1 prior line of systemic cytotoxic chemotherapy or if they have received prior peptide receptor radionuclide therapy (PRRT).
    - SCLC after having received up to three prior lines of anticancer therapy.

Patients meeting any of the following criteria are not eligible for study participation:

1. Treatment with anticancer therapy (as defined in inclusion criterion 9 and 12) or an investigational drug or device within 3 weeks (6 weeks for mitomycin C and nitrosoureas) or 5 half-lives of the agent (whichever is shorter) before C1D1. In addition, any drug-related toxicity, with the exception of alopecia, must have recovered to ≤ Grade 1.
2. Any other malignancy known to be active or treated within 3 years of the start of screening, with the exception of treated cervical intra-epithelial neoplasia, superficial (non-invasive) bladder cancer, and non-melanoma skin cancer.
3. One or more of the following cardiac criteria:
   - Unstable angina
   - Myocardial infarction within 6 months prior to screening
   - New York Heart Association Class II – IV heart failure
   - Corrected QT interval (QTc) > 470 msec obtained as the mean from 3 consecutive resting ECGs using the Fredericia formula
   - Clinically important abnormalities in rhythm, conduction, or morphology of resting ECG (e.g., complete left bundle branch block, third degree heart block)
   - Congenital long QT syndrome
   - Symptomatic orthostatic hypotension within 6 months prior to screening
   - Uncontrolled hypertension.
4. Stroke or transient ischemic attack within 6 month prior to screening.
5. Grade >1 peripheral neuropathy.
6. Patient requires medication with a strong CYP3A4 inhibitor, e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, and voriconazole.
7. History of leptomeningeal disease or spinal cord compression.
8. Brain metastases unless asymptomatic on a stable low dose of steroids.
   - Patients with SCLC or LCNEC of the lung only: CT or MRI of the brain required during screening. If positive for brain metastases, patients must have undergone radiotherapy prior to initiating treatment with PEN-221. If whole brain radiotherapy is performed, a 14-day washout is required prior to treatment with PEN-221. If stereotactic radiosurgery or stereotactic radiotherapy is performed, a 7-day washout prior to treatment with PEN-221 is required.
9. Major surgery within 28 days prior to C1D1.
10. Female who is pregnant or breast-feeding.
11. As judged by Investigator, evidence of severe or uncontrolled systemic disease, active bleeding diatheses, renal or liver transplant, or active infection including known hepatitis B, hepatitis C, or human immunodeficiency virus (HIV).
12. Hypersensitivity or history of anaphylactic reaction to octreotide or other somatostatin analogs.
13. Hypersensitivity or history of anaphylactic reaction to maytansinoids or their derivatives.
14. Any medical, psychological, or social condition that would interfere with the patient's participation in the study.

Investigational product, dosage and mode of administration:

PEN-221 Concentrate for Solution for Injection/Infusion is a [redacted] solution containing PEN-221, a DM1-peptide drug conjugate with affinity for the human SSTR2 receptor, [redacted]

[redacted]

Patients will receive PEN-221 administered IV over [redacted] on D1 every 3 weeks. Patients may be premedicated with an H1 antagonist and/or an IV corticosteroid per institutional policy if infusion-related reactions are experienced.

In Phase 1, the starting dose of PEN-221 is 1.0 mg. Dose escalation will employ an adaptive BLRM design following the EWOC principle.

If a patient is tolerating PEN-221 without significant evidence of disease progression, the patient may, beginning with C3 or subsequent cycles, have the dose increased to a dose that has already been established as tolerable by the SRC, at the discretion of the Investigator and with the agreement of the Medical Monitor.

In Phase 2a, PEN-221 will be administered at the RP2D, as established in Phase 1. If one or more DLTs are observed at any time up until 6 patients across any of the above three cohorts have been treated and evaluated for safety for at least 1 cycle, the BLRM will be run and the SRC will review all available safety data to determine whether the RP2D remains an appropriate dose to be continued for Phase 2a, or whether an alternative dose should be selected.

Duration of treatment:

Patients may receive PEN-221 as long as they continue to show clinical benefit, as judged by the Investigator, or until disease progression or other treatment discontinuation criteria are met.

Criteria for evaluation:

Safety: Safety will be assessed by periodic vital signs, physical examinations, neurological examinations, ECOG PS, 12-lead ECGs, clinical laboratory assessments, and monitoring of AEs. AEs will be graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4.03.

In Phase 1, an SRC, consisting of the Medical Monitor and participating Investigators, will hold teleconferences approximately every 3 weeks while PEN-221 dosing is in progress to review toxicities occurring in the current cohort and determine DLTs. The SRC will also review the safety and tolerability of ongoing patients treated in prior dosing cohorts. Based on its review, the SRC will determine whether the escalation to the next dose level may begin or the current cohort is to be expanded or an intermediate dose level explored.

Anti-tumor activity:

Disease response will be assessed by the Investigator, using RECIST 1.1 with CBR defined as the proportion of patients achieving the best overall response CR, PR, or SD, and ORR defined as the proportion of patients achieving the best overall response CR or PR. [redacted] All patients will be followed for progression-free survival and overall survival.

Pharmacokinetics:

The PK profile will be assessed by determining plasma levels of PEN-221, DM1, and peptide from PEN-221 at intervals throughout the study.

Statistical methods and data analysis:

Data will be summarized using descriptive statistics (continuous data) and/or contingency tables (categorical data) for demographic and baseline characteristics, efficacy measurements, safety measurements, and all relevant PK and PDc measurements.

Details of the statistical analysis and data reporting will be provided in the Statistical Analysis Plan (SAP) document finalized prior to database lock.

Analysis Populations

- The Full Analysis Set (Intention to Treat or ITT) set comprises all patients enrolled in the study who receive any amount of study drug.
- The Safety Analysis set comprises all patients who receive any amount of study drug and have at least 1 post-baseline safety evaluation.
- The efficacy analysis (EA) set comprises all patients who receive any amount of study drug and have at least 1 post-baseline efficacy assessment.
- The Dose Determining set comprises all patients who receive any amount of study drug and either experienced a DLT or have been followed for the full DLT evaluation period.
- The Pharmacokinetic Analysis set comprises all patients who receive any amount of study drug and provide adequate PK samples. Patients with major protocol violations will be assessed on a patient-by- patient basis for inclusion in the PK Analysis set.

Phase 1

It is estimated that 30 patients will be enrolled in Phase 1 Part A including at least 10 patients treated at MTD level. The actual number of patients will depend on the number of dose levels/cohorts that are tested.

An adaptive BLR model guided by the escalation with overdose control (EWOC) principle (Babb 1998; Neuenschwander 2008) will be employed to make dose recommendations and estimate the MTD. The MTD will be further evaluated for anti-tumor activity and overall tolerability during Phase 2a.

The MTD is defined as the highest dose for a given schedule that is not expected by the BLRM to cause DLTs in more than 33% of patients during the first cycle of treatment. The dose-toxicity (DLT) relationship will be described by a Bayesian 2-parameter logistic regression model. A vague bivariate normal prior for the model parameters will be used based on prior guesses (medians) from preclinical data and wide confidence intervals for the probabilities of a DLT at each dose.

Dose recommendation

After each cohort of patients has completed C1, the posterior distributions for the probabilities of DLT rates at different dose levels will be obtained and summarized in terms of the estimated probabilities that the true rate of DLT at each dose-level will have of lying in each of the following intervals:

- [0, 0.16) under-dosing
- [0.16, 0.33) targeted toxicity
- [0.33, 1.00] excessive toxicity.

Following the principle of EWOC, after each cohort of patients the recommended dose will be the one with the highest posterior probability of the DLT rate falling in the target interval [16%, 33%) among the doses fulfilling EWOC, i.e., it is unlikely (<25% posterior probability) that the DLT rate at the dose falls in the excessive toxicity interval.

The recommended dose for the next cohort via this algorithm will not represent more than a doubling of the current dose.

Phase 2a

During Phase 2a, approximately 75 patients will be enrolled in the following cohorts: gastrointestinal mid-gut NET (n=35), pancreatic NET (n=20), and SCLC (n=20). Each of these cohorts will be enrolled in 2 stages, with approximately 10 patients enrolled per cohort in Stage 1, and the remaining patients enrolled in Stage 2. Preliminary efficacy and safety will be assessed in approximately the first 10 patients per cohort before deciding whether to proceed to the second stage of each cohort.

If one or more DLTs are observed at any time up until 6 patients across any of the three cohorts have been treated for at least 1 cycle in Phase 2a, the BLRM will be run to re-evaluate the MTD. The SRC will convene to determine whether it is safe to proceed with dosing at the RP2D or whether an alternative lower dose is to be considered for subsequent patients. If an alternative lower dose is

selected, the SRC will reconvene after at least 6 patients have been treated at this new dose to review the data and confirm that subsequent patients be enrolled into the study at this new dose.

In addition, at any time during Phase 2a, the BLRM may be re-run to confirm the estimated MTD and verify that the dose under study still satisfies the overdose criterion. If the dose fails to satisfy the criterion a change to the dose under study may be decided by the SRC, according to the Bayesian model recommendation, and after review of the clinical data. The SRC decision to change dose may also be spurred by other safety and tolerability considerations (e.g. frequency of lower grade AEs or events in later treatment cycles). Subsequent patients may then be enrolled at this new dose until at least 6 patients are treated at this new dose level and upon SRC review of the data the SRC will decide whether the new dose level is appropriate for continued study.

After Phase 2a, the final recommended dose for future development will be based on considerations of the MTD estimated by the BLRM, and on an overall clinical assessment of all available safety, tolerability, PK, and PDc data from all cycles at all different dose levels tested, in both phases of the study.

In the gastrointestinal mid-gut NET or PNET group, a CBR of approximately 75% or greater would be considered promising. For a group of 20 patients, if the observed proportion is 0.75 (clinical benefit observed in 15 out of 20 patients), there is 90.4% probability that the true underlying proportion exceeds 0.6, and 63.7% probability that the true underlying proportion exceeds 0.7. If the true underlying proportion is 0.75, there is 1.4% probability to observe a CBR of 50% or less.For a group of 35 patients, if the observed proportion is 0.74 (clinical benefit observed in 26 out of 35 patients), there is 95.5% probability that the true underlying proportion exceeds 0.6, and 67.5% probability that the true underlying proportion exceeds 0.7. If the true underlying proportion is 0.75, there is 0.1% probability to observe a CBR of 50% or less.

For the SCLC cohort, a response rate of 30% or greater would be considered promising. For a group of 20 patients, if the observed proportion is 0.3, there is 99.7% probability that the true underlying proportion exceeds 0.1, and 55% probability that the true underlying proportion exceeds 0.3. If the true underlying proportion is 0.3, there is 0.1% probability to observe 0 responses.

Sample size calculations

Based on the performance characteristics computed and described in the previous section, the sample sizes are adequate to address the study's objectives. No formal statistical power calculations to determine sample size were performed.

General statistical considerations

As a general strategy, data will be analyzed by dose level for patients in Phase 1 and by cohort and dose group for patients in Phase 2a.

Demographic and baseline characteristics will be summarized using data from all patients in the Full Analysis (ITT) set by cohort and/or dose group. Treatment exposure, including duration on treatment and extent of exposure to study drug, will be summarized by cohort and/or dose group.

Safety analysis will include summaries by cohort and/or dose group of: AEs, laboratory measures, physical examinations, neurological examinations, ECG, and vital signs using data from patients in the Safety Analysis set.

The incidence of DLTs will be summarized using data from the Dose Determining set.

PK endpoints, including peak concentration, trough plasma concentration and area under the plasma concentration curve, will be tabulated for all patients in the PK Analysis set.

Objective response rate and CBR will be reported with category counts, percentage and 95% confidence interval. Duration of response (DOR), progression-free survival (PFS) and overall survival (OS) will be evaluated using Kaplan-Meier estimates and curves will be generated based on these estimates. Primary efficacy analyses will be based on data from all patients in the efficacy analysis (EA) population.

Table 2: Schedule of Events- Phase 1

Evaluation/Procedure	Treatment Period / Cycle / Day (Visit Window)											Protocol Section
	Pre-screening	Screening	C1 and C3			C2, C4, and subsequent cycles			EOT[26]	Safety Follow-Up (LDSD +28d)	Pro-gression Follow-Up[1]	
	D −180 to −1	D −14 to −1	D1	D8[2]	D15[2]	D1	D8[2]	D15[2]				
Window	–	–	–	±2d	±2d	–	±2d	±2d	±3d	±3d	±7d	
Baseline assessments												
Written informed consent	X	X										7.2
Approved SSTR tumor imaging	X[3]											9.2
Height		X										9.3.3
Medical history and demographics		X										9.1.1 9.1.2
Cancer diagnosis and history, including all prior systemic and radiation therapies and surgeries		X										9.1.2
Review of entrance criteria		X										7.3, 7.4
Safety Evaluations												
Physical examination:												9.3.1
Complete		X	X[4]			X			X	X		9.3.1
Neurological		X	X[4]			X			X	X		9.3.1
Targeted (i.e., symptom-directed)				X[2]	X[2]		X[2]	X[2]				9.3.1
Vital signs[5]		X	X			X			X	X		9.3.2
Weight		X	X			X			X	X		9.3.3
Electrocardiogram[6]		X	X			X			X			9.3.4
ECOG performance status		X	X[4]			X			X	X		9.3.6
Adverse events	Adverse events (AEs) are to be documented from first consent through safety follow-up.											9.3.7
Concomitant medications	All medications/procedures are to be documented from 30 days before first study drug dose on C1D1 through safety follow-up.											9.3.8
Safety Evaluations (Continued)												

Evaluation/Procedure	Treatment Period / Cycle / Day (Visit Window)											Protocol Section
	Pre-screening	Screening	C1 and C3			C2, C4, and subsequent cycles			EOT[26]	Safety Follow-Up (LDSD +28d)	Pro-gression Follow-Up[1]	
	D −180 to −1	D −14 to −1	D1	D8[2]	D15[2]	D1	D8[2]	D15[2]				
Window	–	–	–	±2d	±2d	–	±2d	±2d	±3d	±3d	±7d	
Clinical laboratory tests:												
Hematology[7]		X	X[4]	X[2]	X[2]	X	X[2]	X[2]	X	X		9.3.5.1
Clinical chemistries[8]		X	X[4,9]	X[2]	X[2]	X[9]	X[2]	X[2]	X	X		9.3.5.1
Estimated creatinine clearance		X	X			X				X		9.3.5.1
Coagulation studies[10]		X	X[4]			X				X		9.3.5.3
Urinalysis[11]		X	X[4]			X			X	X		9.3.5.2
Thyroid function[12]		X	X[4,13]			X[13]			X			9.3.5.1
Cholesterol and triglycerides (fasted)		X	X[4,13]			X[13]			X			9.3.5.1
Cortisol			X[14]			X[14]						9.3.5.1
Peripheral blood anti-drug antibodies		X	X[4,15]			X[15]			X			9.3.5.4
Pregnancy testing[16]	X	X	X[4]			X						9.3.5.5
Disease Activity Measurements												
Radiographic tumor assessments[17]		X[18]	X[19]			X[19]					X[1]	9.6
[redacted]												
Archival tumor sample		X										9.5.5
Optional tumor biopsy[23]		X[23]										9.5.6
[redacted]												
Study Drug Administration												
PEN-221 drug administration			X			X						8.6
Pharmacokinetics												
Blood sample collection for PK			X[25]									9.4
Survival											X[1]	5.1.4.3

LDSD = Last Dose of Study Drug

Note: PEN-221 dosing of each cycle should begin within 21±2 days of D1 of previous cycle unless PEN-221 is withheld for safety reasons. Visit windows may be lengthened for administrative reasons (e.g., holiday) after consultation with the Medical Monitor.

1. If a patient discontinues treatment prior to objective disease progression, then the patient should continue to be followed until objective disease progression as defined by RECIST 1.1. For SCLC or LCNEC of the lung patients, approximately every 6 weeks from prior scan, or as clinically indicated. For all other patients, approximately every 9 weeks from prior scan, or as clinically indicated. After disease progression, patients should be followed approximately every 3 months for survival.
2. D8 and D15 evaluations are required for C1, C2, and for the first two cycles starting with a dose escalation . If no Grade 2 or higher abnormalities in clinical chemistries or hematology parameters during Cycles 1 and 2, or in the two cycles starting with a dose escalation (Section 8.11.1), then the D8 and D15 evaluations may be eliminated in subsequent cycles, subject to Investigator discretion. If Grade 2 or higher abnormalities in clinical chemistries or hematology parameters are observed, the D8 and D15 evaluations are required for 2 additional cycles. If Grade 2 or higher abnormalities do not recur during the subsequent 2 cycles, the D8 and D15 evaluations may be eliminated in cycles thereafter, subject to Investigator discretion.
3. Historical scans up to 180 d prior to C1D1 are permitted.
4. If screening evaluation is done within 3 d before C1D1, it need not be repeated on C1D1.
5. For any patients on concomitant beta blockers, blood pressure should be monitored carefully and doses of these medications should be adjusted if needed, as somatostatin analogs have been associated with bradycardia.
6. Triplicate ECGs are to be collected approximately 5 minutes apart. On C1D1 and C3D1, ECGs are to be performed immediately prior to the start of study drug infusion, at 30 minutes after the start of the infusion, precisely at the end of infusion, and at all scheduled PK timepoints thereafter; the date and time of each ECG start and stop are to be documented. On all other dosing days, ECGs should be performed prior to infusion and at end of infusion.
7. Hematology parameters include hemoglobin, red blood cell (RBC) count, platelet count, and white blood cell (WBC) count with differential. Samples may be collected up to 48 hours prior to scheduled clinic visits. On study drug administration days, results must be available and reviewed before study drug administration and must continue to qualify patients as defined in the study eligibility (inclusion/exclusion) criteria.
8. Clinical chemistries include chloride, bicarbonate, sodium, potassium, calcium, magnesium, phosphorus, blood urea nitrogen, creatinine, glucose, total protein, albumin, alkaline phosphatase (ALP), AST, ALT, total and direct bilirubin, amylase, and lipase. Samples may be collected up to 48 hours prior to scheduled clinic visits. On study drug administration days, results must be reviewed by the Investigator prior to study drug administration and must continue to qualify patients as defined in the study eligibility (inclusion/exclusion) criteria.
9. On C1D1, glucose will be monitored along with PK samples: pre-dose, at 0.5 hours (±5 minutes) after the start of study drug infusion; precisely at the end of infusion (±1 minute); and 1.5 hours (±10 minutes), 2 hours (±10 minutes), 4 hours (±10 minutes), 6 hours (±10 minutes), 8 hours (±30 minutes), and 10 hours (±60 minutes) after the start of study drug infusion. If the 10 hour time point requires an inpatient admission at the center, the 10 hour time point will not be collected. If the patient experiences symptomatic hypoglycemia or hyperglycemia, or if any glucose level falls below 55 mg/dL (or below 3.0 mmol/L) or above 250 mg/dL (or above 13.9 mmol/L) at any timepoint on C1D1, this intense sampling will be repeated (regardless of whether PK samples are collected) on D1 of each subsequent cycle until the above criteria are no longer met throughout an entire treatment day.
   For any patients on concomitant anti-hyperglycemic medications, glucose should be monitored carefully and doses of these medications should be adjusted if needed, as somatostatin analogs have been associated with changes in blood glucose levels and regulation.
10. Coagulation studies include prothrombin time (PT) and activated partial thromboplastin time (aPTT). For patients on Coumadin or warfarin only, international normalized ratio should also be included.
11. Urinalysis includes specific gravity, pH, blood, glucose, protein, ketones, and microscopic examination of sediment.
12. Thyroid function to be monitored as free T4 and thyroid-stimulating hormone (TSH).

13. Every third cycle beginning with C3 (C3, C6, C9, etc.).
14. C1D1 and C2D1 only, to be collected in the morning pre-dose.
15. Every odd cycle only beginning on C3.
16. Pregnancy testing, either urine or serum, is required only for females of childbearing potential. Pregnancy testing is to be repeated on-study any time pregnancy is suspected. If pregnancy test is positive, pregnancy should be assessed by transvaginal ultrasound overseen by a health care professional with experience in investigating and diagnosing early pregnancy.
17. Disease response is to be assessed by the Investigator at the indicated times using RECIST 1.1. For baseline tumor assessment, all sites of disease should be imaged by CT or MRI. Repeat assessments should use the same radiographic methods as used at baseline.
18. Baseline imaging studies may be performed within 28 days before C1D1.
19. For SCLC or LCNEC of the lung, tumor measurements are to be performed within 7 days prior to C3, and within 7 days prior to every odd cycle thereafter. For other patients, tumor measurements are to be performed within 7 days prior to C4, and within 7 days prior to every third cycle thereafter.

[redacted]

23. Only for patients who provide written informed consent to undergo an optional tumor biopsy procedure during the Screening phase and who meet the additional eligibility criterion in Section 7.3. Biopsy procedure will be performed within 14 days prior to C1D1.

[redacted]

25. Serial blood samples are to be collected pre-dose (time zero) and at 0.5 hours (±5 minutes) after the start of study drug infusion, precisely at the end of infusion (±1 minute); and 1.5 hours (±10 minutes), 2 hours (±10 minutes), 4 hours (±10 minutes), 6 hours (±10 minutes), 8 hours (±30 minutes), and 10 hours (±60 minutes) after the start of study drug infusion. If collection of the 10 hour time point would require an inpatient admission, the 10 hour time point is NOT to be collected. If the study drug infusion is interrupted and re-started for any reason, then the time of interruption and re-start of infusion should be recorded, a second pre-dose (time zero) time point should be collected just prior to re-start of the infusion, and subsequent sampling time points should then be adjusted to follow the above schedule in relation to the time of the re-start of the infusion. PK should be done prior to glucose monitoring and ECGs.
26. Patients who discontinue treatment for any reason (see Section 7.8) should have an EOT visit. The EOT visit should occur within 3 days from the event resulting in treatment discontinuation (i.e. disease progression, AE, withdraw consent).

Table 3: Schedule of Events Phase 2a

Evaluation/Procedure	Treatment Period / Cycle / Day (Visit Window)												Protocol Section
	Pre-screening	Screening	C1				C2 and subsequent cycles			EOT[26]	Safety Follow-Up LDSD+28d	Pro-gression Follow-Up[1]	
	D −180 to −1	D −14 to −1	D1	D2	D8[2]	D15[2]	D1	D8[2]	D15[2]				
Window	–	–	–	–	±2d	±2d	–	±2d	±2d	±3d	±3d	±7d	
Baseline assessments													
Written informed consent	X	X											7.2
Approved SSTR tumor imaging	X[3]												9.2
Height		X											9.3.3
Medical history and demographics		X											9.1.1 9.1.2
Cancer diagnosis and history, including all prior systemic and radiation therapies and surgeries		X											9.1.2
Review of entrance criteria		X											7.3, 7.4
Safety Evaluations													
Physical examination:													9.3.1
Complete		X	X[4]				X[27]			X	X		9.3.1
Neurological		X	X[4]				X[27]			X	X		9.3.1
Targeted (i.e., symptom-directed)					X[2]	X[2]		X[2]	X[2]				9.3.1
Vital signs[5]		X	X				X			X	X		9.3.2
Weight		X	X				X[27]			X	X		9.3.3
Electrocardiogram[6]		X	X				X			X			9.3.4
ECOG performance status		X	X[4]				X[27]			X	X		9.3.6
Adverse events		Adverse events (AEs) are to be documented from first consent through safety follow-up.											9.3.7
Concomitant medications		All medications/procedures are to be documented from 30 days before first study drug dose on C1D1 through safety follow-up.											9.3.8
Clinical laboratory tests:													
Hematology[7]		X	X[4]		X[2]	X[2]	X	X[2]	X[2]	X	X		9.3.5.1
Clinical chemistries[8]		X	X[4,9]		X[2]	X[2]	X[9]	X[2]	X[2]	X	X		9.3.5.1
Estimated creatinine clearance		X	X				X[27]				X		9.3.5.1

Evaluation/Procedure	Treatment Period / Cycle / Day (Visit Window)												Protocol Section
	Pre-screening	Screening	C1				C2 and subsequent cycles			EOT[26]	Safety Follow-Up LDSD+28d	Pro-gression Follow-Up[1]	
	D −180 to −1	D −14 to −1	D1	D2	D8[2]	D15[2]	D1	D8[2]	D15[2]				
Window	–	–	–	–	±2d	±2d	–	±2d	±2d	±3d	±3d	±7d	
Clinical laboratory tests continued:													
Coagulation studies[10]		X	X[4]				X[27]				X		9.3.5.3
Urinalysis[11]		X	X[4]				X[27]			X	X		9.3.5.2
Thyroid function[12]		X	X[4,13]				X[13, 27]			X			9.3.5.1
Cholesterol and triglycerides (fasted)		X	X[4,13]				X[13, 27]			X			9.3.5.1
Cortisol			X[14]				X[14]						9.3.5.1
Peripheral blood anti-drug antibodies			X				X[15,27]			X			9.3.5.4
Pregnancy testing[16]	X	X	X[4]				X[27]						9.3.5.5
Disease Activity Measurements													
Radiographic tumor assessments[17]		X[18]					X[19]					X[1]	9.6
[redacted]													
Archival tumor sample		X											9.5.5
Optional tumor biopsy[23]		X[23]											9.5.6
[redacted]													
Study Drug Administration													
PEN-221 drug administration			X	-			X						8.6
Pharmacokinetics													
Blood sample collection for PK			X[25]	X[25]	X[25]								9.4
Survival Status												X[1]	5.1.4.3

LDSD = Last Dose of Study Drug

Note: PEN-221 dosing of each cycle should begin within 21±2 days of D1 of previous cycle unless PEN-221 is withheld for safety reasons. Visit windows may be lengthened for administrative reasons (e.g., holiday) after consultation with the Medical Monitor.

1. If a patient discontinues treatment prior to objective disease progression, then the patient should continue to be followed until objective disease progression as defined by RECIST 1.1. For SCLC, approximately every 6 weeks from prior scan, or as clinically indicated. For all other patients, approximately every 9 weeks from prior scan, or as clinically indicated. After disease progression, patients should be followed approximately every 3 months for survival.

2. D8 and D15 evaluations are required for C1. If no Grade 2 or higher abnormalities in clinical chemistries or hematology parameters are observed during C1, then D8 and D15 evaluations are not required for C2 and subsequent cycles. If Grade 2 or higher abnormalities in clinical chemistries or hematology parameters (excluding hyperglycemia in diabetic patients) are observed during C1, the D8 and D15 evaluations are required for C2 and C3. If Grade 2 or higher abnormalities do not recur during C2 and C3, the D8 and D15 evaluations may be eliminated in cycles thereafter, subject to Investigator discretion. If Grade 2 or higher abnormalities occur after C3, evaluations may be performed at a schedule determined by the Investigator, based on the patient's clinical status.
3. Historical scans up to 180 d prior to C1D1 are permitted.
4. If screening evaluation is done within 3 d before C1D1, it need not be repeated on C1D1.
5. For any patients on concomitant beta blockers, blood pressure should be monitored carefully and doses of these medications should be adjusted if needed, as somatostatin analogs have been associated with bradycardia.
6. Triplicate ECGs are to be collected approximately 5 minutes apart. On C1D1 ECGs are to be performed immediately prior to the start of study drug infusion, at 30 minutes after the start of the infusion (±5 minutes), at the end of infusion (±5 minutes), and at all scheduled PK timepoints thereafter on C1D1; the date and time of each ECG start and stop are to be documented. On all other dosing days, ECGs should be performed prior to infusion and at end of infusion (±5 minutes). When multiple study assessments are scheduled at the same time, ECGs should be performed after the PK blood draw and glucose monitoring.
7. Hematology parameters include hemoglobin, red blood cell (RBC) count, platelet count, and white blood cell (WBC) count with differential. Samples may be collected up to 48 hours prior to scheduled clinic visits. On study drug administration days, results must be available and reviewed before study drug administration and must continue to qualify patients as defined in the study eligibility (inclusion/exclusion) criteria.
8. Clinical chemistries include chloride, bicarbonate, sodium, potassium, calcium, magnesium, phosphorus, blood urea nitrogen, creatinine, glucose, total protein, albumin, alkaline phosphatase (ALP), AST, ALT, total and direct bilirubin, amylase, and lipase. Samples may be collected up to 48 hours prior to scheduled clinic visits. On study drug administration days, results must be reviewed by the Investigator prior to study drug administration and must continue to qualify patients as defined in the study eligibility (inclusion/exclusion) criteria.
9. On C1D1, glucose will be monitored pre-dose and at the end of infusion (±3 minute); and 2 hours (±10 minutes), 4 hours (±10 minutes), 6 hours (±10 minutes), and 8 hours (±30 minutes) after the start of study drug infusion. When multiple study assessments are scheduled at the same time, glucose monitoring should be done after PK blood draws and prior to ECGs. If the patient experiences symptomatic hypoglycemia or hyperglycemia, or if any glucose level falls below 55 mg/dL (or below 3.0 mmol/L) or above 250 mg/dL (or above 13.9 mmol/L) at any timepoint on C1D1 additional monitoring may be required per Investigator discretion. For any patients on concomitant anti-hyperglycemic medications, glucose should be monitored carefully and doses of these medications should be adjusted if needed, as somatostatin analogs have been associated with changes in blood glucose levels and regulation.
10. Coagulation studies include prothrombin time (PT) and activated partial thromboplastin time (aPTT). For patients on Coumadin or warfarin only international normalized ratio should also be included.
11. Urinalysis includes specific gravity, pH, blood, glucose, protein, ketones, and microscopic examination of sediment.
12. Thyroid function to be monitored as free T4 and thyroid-stimulating hormone (TSH).
13. Every third cycle beginning with C3 (C3, C6, C9, etc.).
14. C1D1 and C2D1 only, to be collected in the morning pre-dose.
15. Every odd cycle only beginning on C3.
16. Pregnancy testing, either urine or serum, is required only for females of childbearing potential. Pregnancy testing is to be repeated on-study any time pregnancy is suspected. If pregnancy test is positive, pregnancy should be assessed by transvaginal ultrasound overseen by a health care professional with experience in investigating and diagnosing early pregnancy.

17. Disease response is to be assessed by the Investigator at the indicated times using RECIST 1.1. For baseline tumor assessment, all sites of disease should be imaged by CT or MRI. Repeat assessments should use the same radiographic methods as used at baseline.
18. Baseline imaging studies may be performed within 28 days before C1D1.
19. For SCLC, tumor measurements are to be performed within 7 days prior to C3, and within 7 days prior to every odd cycle thereafter. For other patients, tumor measurements are to be performed within 7 days prior to C4, and within 7 days prior to every third cycle thereafter.

[redacted]

23. Only for patients who provide written informed consent to undergo an optional tumor biopsy procedure during the Screening phase and who meet the additional eligibility criterion in Section 7.3. Biopsy procedure will be performed within 14 days prior to C1D1.

[redacted]

25. Serial blood samples are to be collected pre-dose (time zero) and at 0.5 hours (±5 minutes) after the start of study drug infusion, precisely at the end of infusion (±1 minute); and 1.5 hours (±10 minutes), 2 hours (±10 minutes), 4 hours (±10 minutes), 6 hours (±10 minutes), 8 hours (±30 minutes), after the start of study drug infusion. On Day 2 of C1 a single 24 hours (±120 minutes) sample will be collected. On C1D8 a single sample should be collected. If the study drug infusion is interrupted and re-started for any reason, then the time of interruption and re-start of infusion should be recorded, a second pre-dose (time zero) time point should be collected just prior to re-start of the infusion, and subsequent sampling time points should then be adjusted to follow the above schedule in relation to the time of the re-start of the infusion. When multiple study assessments are schedule at the same time, PK blood draws should be done prior to glucose monitoring and ECGs.
26. Patients who discontinue treatment for any reason (see Section 7.8) should have an EOT visit. The EOT visit should occur within 3 days from the event resulting in treatment discontinuation (i.e. disease progression, AE, withdraw consent).
27. Evaluation/procedure may be conducted up to 48 hours prior to scheduled clinic visits.

2. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

3. LIST OF ABBREVIATIONS

Abbreviation	Explanation
[redacted]	[redacted]
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AJCC	American Joint Committee on Cancer
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC_{0-t}	Area under the plasma concentration time curve from time zero to time of the last measurable concentration
AUC_{0-36h}	Area under the concentration time curve from time zero to 36h
AUC_{∞}	Area under the concentration time curve from time zero to infinity
BLRM	Bayesian logistic regression model
BMI	Body mass index
BSA	Body surface area
BUN	Blood urea nitrogen
C	Cycle (as in C1D1 for Cycle 1 Day 1)
CBC	Complete blood count
CFR	Code of Federal Regulations
[redacted]	[redacted]
CI	Confidence intervals
CL	Clearance
C_{max}	Maximum plasma concentration
CR	Complete response
CRA	Clinical research associate
CSR	Clinical study report
CT	Computed tomography
[redacted]	[redacted]
CTCAE	Common Terminology Criteria for Adverse Events
D	Day (as in C1D1 for Cycle 1 Day 1)
DD	Dose-determining

Abbreviation	Explanation
DDS	Dose-determining set
DLL3	Delta-like 3
DLT	Dose-limiting toxicity
DM1	Mertansine
DOR	Duration of Response
EA	Efficacy analysis
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
ED	Extensive disease
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EOT	End of treatment
EWOC	Escalation with overdose control
FDA	Food and Drug Administration
FFPE	Formalin-fixed paraffin-embedded
FOB	Functional observational battery
FOCBP	Females of childbearing potential
GCP	Good Clinical Practice
GEP	Gastroenteropancreatic
GI	Gastrointestinal
HCG	Human chorionic gonadotropin
HIV	Human immunodeficiency virus
HNSTD	Highest non-severely toxic dose
ICF	Informed consent form
ICH	International Conference on Harmonisation
IHC	Immunohistochemistry
IP	Investigational product
IRB	Institutional Review Board
ITT	Intent-to-treat
IV	Intravenous or intravenously
LCNEC	Large cell neuroendocrine carcinoma

Abbreviation	Explanation
LD	Longest diameter (when used with RECIST and tumor measurements) or limited disease (when used with SCLC cancer staging)
MCC	Merkel cell carcinoma
MedDRA	Medical Dictionary for Regulatory Activities
MEN	Multiple endocrine neoplasia
MIBG	Metaiodobenzylguanidine
MRI	Magnetic resonance imaging
MTC	Medullary thyroid carcinoma
mTOR	Mammalian target of rapamycin
NCCN	National Cooperative Cancer Network
NCI	National Cancer Institute
NET	Neuroendocrine tumor
[redacted]	[redacted]
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PDc	Pharmacodynamic
PFS	Progression-free survival
PK	Pharmacokinetic or pharmacokinetics
PNET	Pancreatic neuroendocrine tumor
PP	Per-protocol
PR	Partial response
PRRT	Peptide receptor radionuclide therapy
PS	Performance status
PT	Prothrombin time
RBC	Red blood cells
RECIST	Response Evaluation Criteria in Solid Tumors v1.1 (Eisenhauer 2009)
RET	Ret proto-oncogene
RP2D	Recommended phase 2 dose
SA	Safety analysis
SAE	Serious adverse event
SAP	Statistical Analysis Plan

Abbreviation	Explanation
SARI	Somatostatin analog radioisotope imaging
SCLC	Small cell lung cancer
SD	Stable disease
SRC	Safety Review Committee
SSTR	Somatostatin receptor
$t_{½}$	Elimination half-life
TEAE	Treatment-emergent adverse event
TGI	Tumor growth inhibition
T_{max}	Time to maximum plasma concentration
TKI	Tyrosine kinase inhibitor
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
V	Volume of distribution
V_{ss}	Volume of distribution at steady state
VEGFR	Vascular endothelial growth factor receptor
WBC	White blood cells

4. INTRODUCTION

4.1. Investigational Agent

PEN-221 is a novel peptide-drug conjugate that is being developed as a targeted anticancer agent for the treatment of patients with neuroendocrine tumors or other tumors of neuroendocrine origin or small cell lung cancer (SCLC) whose tumors overexpress the somatostatin receptor 2 (SSTR2). PEN-221 contains a somatostatin analog with high potency and selectivity for SSTR2 conjugated to DM1 (mertansine), a thiol-containing maytansinoid, using a cleavable disulfide linker. The linker is designed to be preferentially cleaved in the reducing environment of the tumor, thereby selectively releasing DM1 in tumor cells where it acts by disrupting microtubule networks and intracellular trafficking, resulting in apoptosis and mitotic catastrophe (Barok 2014). Significant antitumor activity has been seen in multiple SSTR2 positive xenograft models. Higher levels of anti-tumor activity, including complete regressions, were observed with either repeat dosing at a relatively low dose or with a single relatively high dose. These observations suggest potential for activity in patients with SSTR2-expressing tumors.

4.2. Neuroendocrine Tumors

Neuroendocrine tumors (NETs) are a relatively rare, biologically and clinically heterogeneous group of malignant neoplasms that arise from neuroendocrine cells throughout the body and are most commonly formed in the gastrointestinal (GI) tract, pancreas, or lung. Other less common neuroendocrine tumors include those arising in the parathyroid, thyroid, adrenal and pituitary glands. These tumors are characterized by their ability to produce peptides that may or may not produce symptoms related to oversecretion. They are often associated with characteristic symptoms such as flushing and diarrhea. Epidemiological studies indicate that the incidence of NET is rising in the US and Europe (NCCN 2016).

NETs are generally classified by site of origin, histological characteristics, stage, and grade. Histological classification is based on tumor differentiation (well or poorly differentiated). NETs are staged according to the American Joint Committee on Cancer (AJCC) TNM staging system. Tumor grade (Grades 1 – 3) is generally defined by mitotic count and/or Ki-67 index. Functioning vs. non-functioning tumors are part of the clinical diagnosis based on whether or not tumors are associated with symptoms of hormone hypersecretion. The National Cancer Institute (NCI at http://cancer.gov/) separates its detailed information on background, staging, and treatment of NETs into 4 main groups: gastrointestinal carcinoids (well-differentiated NETs or carcinomas of the gastrointestinal tract); pancreatic NETs; small cell lung cancer (SCLC); and typical and atypical lung carcinoid tumors and large cell neuroendocrine carcinoma of the lung as types of non-small cell lung cancer. The National Comprehensive Cancer Network (NCCN at http://nccn.org) practice guidelines group NETs into 9 distinct tumors: neuroendocrine tumors of the GI tract, lung and thymus (carcinoids), pancreatic NETs (PNETs), NETs with an unknown primary, adrenal gland tumors, pheochromocytomas and paragangliomas, poorly differentiated neuroendocrine carcinoma or large or small cell carcinoma other than lung, multiple endocrine neoplasia type 1 (MEN1), MEN type 2 (MEN2), and Merkel cell carcinoma.

Surgical resection is the only curative treatment and is generally recommended for patients with localized disease or those whose primary and metastatic sites that are amenable to a complete resection. If the tumor is not resectable, standard of care varies depending on the anatomical site

of the primary tumor as well as tumor grade. Somatostatin analogs are prescribed to palliate symptoms of functional tumors and to slow tumor growth. Liver-directed therapies such as radiofrequency ablation or hepatic regional therapy may be considered for patients with unresectable, liver-predominant metastatic disease. In addition, everolimus, interferon alfa-2b, or cytotoxic chemotherapy may be indicated for clinically significant progressive disease; sunitinib may be an option for PNETs (NCCN 2016).

Somatostatin analogs are used routinely to control symptoms related to hormone hypersecretion in patients with neuroendocrine tumors (Chan 2016). In addition, randomized controlled trials have established that somatostatin analogs delay tumor growth in patients with advanced, well-differentiated or moderately-differentiated enteropancreatic tumors. In the randomized, double-blind PROMID trial (Rinke 2009), eighty-five patients with locally inoperable or metastatic well-differentiated, functioning or nonfunctioning intestinal NETs were randomized to receive treatment with either long-acting octreotide (Octreotide LAR) or placebo. There was a statistically significant prolongation in time to progression, compared to placebo (median 14.3 versus 6.0 months). In the randomized, double-blind CLARINET trial (Caplin 2014), 204 patients with advanced well- or moderately-differentiated, non-functioning, enteropancreatic NETs, patients were randomized to receive treatment with either an extended release aqueous-gel formulation of lanreotide (n=101) or placebo (n=103). Lanreotide, as compared to placebo, was associated with significantly prolonged progression-free survival (median not reached vs. median 18.0 months).

Molecularly targeted therapies have been proven to be effective for patients with advanced, low or intermediate grade NETs. The mTOR inhibitor everolimus showed a significant improvement in progression-free survival in advanced pancreatic (Yao 2011) and advanced gastrointestinal or lung NETs (Yao 2016), but was associated with RECIST tumor response rates of only 2 to 5%. For patients with advanced pancreatic NET, sunitinib is approved based on the results of a randomized Phase 3 study that demonstrated improved progression-free survival compared to placebo (Raymond 2011).

Cytotoxic chemotherapy can lead to objective tumor responses in patients with pancreatic NETs, and is recommended for patients with well differentiated NETs who have bulky, rapidly progressive disease; however, no prospective clinical trials have observed benefits in progression free or overall survival (Kunz 2015).

The concept of targeting somatostatin receptor with somatostatin analogs linked to an anti-cancer payload has been demonstrated in the clinic. Peptide receptor radionuclide therapy (PRRT) delivers yttrium-90 or lutetium-177 coupled to DOTATATE, an amide of the acid DOTA, which acts as a chelator for a radionuclide, and (Tyr^3)-octreotate, a derivative of the somatostatin analog octreotide. The latter binds to somatostatin receptors, which are found on the cell surfaces of a number of NETs and direct the radioactivity into the tumor. PRRT has resulted in tumor response rates of approximately 15 to 35% in patients with advanced GEP NETs in nonrandomized studies (van der Zwan 2015). A recent Phase 3 study randomized 230 patients with advanced mid-gut NETs to receive 4 doses of ^{177}Lu-DOTATATE (4 × 7.4 GBq every 8 weeks) plus symptom control treatment with 30 mg long-acting octreotide (Octreotide LAR) compared to high dose (60 mg) Octreotide LAR every 4 weeks (Strosberg 2015). There was a statistically significant improvement in progression-free survival in the ^{177}Lu-DOTATATE plus 30 mg Octreotide LAR group; the median PFS was not reached for ^{177}Lu-DOTATATE plus 30

mg Octreotide LAR and was 8.4 months with 60 mg Octreotide LAR (hazard ratio 0.21 [95% CI: 0.13-0.34], p<0.0001) Objective response rates were 19% in the patients randomized to ^{177}Lu-DOTATATE plus 30 mg Octreotide LAR vs. 3% in patients randomized to 60 mg octreotide LAR.

Pheochromocytomas and paragangliomas are catecholamine-secreting neuroendocrine tumors that arise from chromaffin cells of the adrenal medulla (pheochromocytomas) and the extra-adrenal autonomic paraganglia (paragangliomas). Approximately 10 percent of pheochromocytomas, 20 to 25% of extra-adrenal abdominal and mediastinal paragangliomas, and 2 to 19% of skull base and neck paragangliomas are metastatic; 5-year survival rates are generally less than 50% (Chan 2016; McGranahan 2016). For patients with meta-iodobenzylguanidine (MIBG)-positive tumors with unresectable, symptomatic progressive disease, ^{131}I-MIBG is a first-line treatment approach. For patients with rapidly progressive, MIBG-negative disease or disease that is predominantly localized to the skeleton, chemotherapy such as combination therapy with cyclophosphamide, vincristine, and dacarbazine is an option. Clinical trials of sunitinib in patients with advanced/malignant pheochromocytoma/paraganglioma are ongoing (Chan 2016; McGranahan 2016).

As reviewed by Duprat (2011), Merkel cell carcinomas (MCCs) are very rare but very aggressive skin cancers likely arising from cutaneous mechanoreceptor cells (Merkel cells) in the epidermis basal layer. They mostly occur as red or bluish nodules, growing on the head, neck, extremities, or trunk, and are associated with sun exposure, immunocompromise, and a polyomavirus. Disease that is not treatable by resection or local radiotherapy is treated with cisplatin or carboplatin, combined with either etoposide or doxorubicin. Response rates as high as 40% have been observed, but are rarely sustained. Recurrent disease has been treated with radiation or chemotherapy but results have been poor. Nghiem (2016) describe a phase 2 study of pembrolizumab (an anti-PD-1 agent) where 56% overall response and 16% complete response was observed in 25 evaluable MCC patients.

Medulary thyroid carcinomas (MTCs) arise from calcitonin-producing C-cells (Hadoux 2016). Distant metastases are the main cause of death. Vandetanib, an inhibitor of kinases of the vascular endothelial growth factor rectptors (VEGFRs) 2 and 3, Ret proto-oncogene (RET), and epidermal growth factor, is approved in both the US and EU for treatment of MTC. A placebo-controlled phase 3 trial with 331 patients showed significant prolongation of PFS with a 65% relative reduction of risk of disease progression, and 44% partial response rate (Wells 2012). (No complete responses were observed.) Cabozantinib, an inhibitor of RET, VEGFR2, and hepatocyte growth factor receptor, produced partial response in 28% of patients (Elisei 2013). In contrast, chemotherapy with single or multiple agents has only yielded response rates of less than 20% (Hadoux 2016).

4.3. Small Cell Lung Cancer and Large Cell Neuroendocrine Carcinoma of the Lung

SCLC represents 15 – 20% of all lung cancers. Little progress has been made over the last 30 years in identifying effective new treatments and median overall survival is only about 12 months (Morabito 2014). The traditional staging system classifies SCLC into 2 stages, according to the extent of disease (Mountain 2000). Limited disease (LD), diagnosed in about 1/3 of patients, is confined to the hemithorax with regional lymph node metastasis and can be treated

within a single field of radiation. Extensive disease (ED), diagnosed in approximately 2/3 of patients, extends beyond a single radiation field (National Cancer Institute 2016).

Patients with LD can be treated with surgery, radiotherapy, or both, and also may be candidates for chemotherapy, especially if Ki-67 score is greater than 50% (National Cancer Institute 2016). Patients with ED do not typically benefit from resection or radiotherapy; chemotherapy with platinum and etoposide is first-line standard of care. Upon relapse, topotecan is approved for second-line therapy, and paclitaxel, docetaxel, irinotecan, temozolomide, gemcitabine, or ifosfamide may be used for subsequent therapy (National Cancer Institute 2016). A variety of agents, including tyrosine kinase inhibitors (TKIs), mammalian target of rapamycin (mTOR) inhbitors, and other targeted agents have been tested unsuccessfully as SCLC treatments. DNA repair and cellular developmental pathway inhibitors, antibody-drug conjugates, immunomodulators, immune checkpoint inhibitors, and anti-SCLC vaccines are in studies (Mamdani 2015). Recent testing of an antibody-drug conjugate targeting delta-like 3 (DLL3) has shown promise, with a cohort of 29 $DLL3^+$ patients demonstrating 34% partial response and 31% disease stabilization, and durable response of more than 178 days.

Large cell neuroendocrine carcinoma (LCNEC) of the lung is a biologically aggressive, high grade cancer that accounts for approximately 3% of all lung cancers. Due to the lack of controlled clinical trials, there are no standard treatment regimens. Retrospective analyses of clinical outcomes in small series of patients with advanced or metastatic disease suggest that response rates to platinum based doublet chemotherapy in the first-line, advanced disease setting are similar to those achieved in patients with SCLC; overall survival is poor, with median OS ranging from 8 to 16 months depending on the study (Fasano 2015). In the second-line or later setting, data are sparse; a retrospective analysis of 18 LCNEC of the lung treated with amrubicin as a single agent, all of whom were previously treated with platinum based doublet chemotherapy, resulted in an objective response rate of 27.7% (Yoshida 2011).

4.4. Somatostatin Receptor Expression in Cancers of Neuroendocrine Origin

Somatostatin is a small cyclic peptide. As described by Hofland (2001), it is widely expressed in the body, predominantly in the central nervous system and peripheral tissues. In brain, it can be both stimulatory and inhibitory, but in peripheral tissue it mostly inhibits secretion processes. Somatostatin acts through binding to five different high-affinity G-protein coupled membrane SSTRs. All five receptors are expressed in brain and islets; all but SSTR4 are expressed in the pituitary gland. Tumors originating from somatostatin target tissues often express a high density of various receptors.

Overexpression of these receptors on tumors provides a potential target for direct delivery of anti-cancer agents. Cancers of neuroendocrine origin including NETs of pancreatic, gastrointestinal, lung or other tissue origin, SCLC (Barbieri 2013; O'Byrne 1994; Reubi 2001), medullary thyroid cancers, and others (Barbieri 2013; de Herder 2003; Hofland 2001) have often been found to overexpress SSTR and are drug development targets for SSTR-drug treatment. Reubi (2001) describe expression of SSTRs in both normal and various neoplastic tissues using autoradiography.

4.5. Rationale for the Study

As described in Section 4.2 and Section 4.3, treatment options for patients with tumors of neuroendocrine origin are limited. New, effective therapies are urgently needed to improve the clinical outcome for patients with these cancers. PEN-221 is designed specifically to target tumor cells that express SSTR2 such that the delivery of the DM1 payload is directed to the SSTR2 expressing tumors to drive efficacy, while minimizing the uptake of the conjugate in other tissues. A series of nonclinical studies have been performed to evaluate the pharmacology of PEN-221 to support and guide its clinical evaluation.

4.6. Nonclinical Pharmacology Studies

PEN-221 is designed to bind to the somatostatin receptor SSTR2 and be internalized into cancer cells overexpressing this receptor to deliver a cytotoxic payload. *In vitro* radioligand competitive binding assays comparing PEN-221 affinity to the 5 somatostatin receptor family members (SSTR1-5) demonstrated PEN-221 selectively binds SSTR2. *In vitro*, PEN-221, like the SSTR2 natural ligand, was shown to stimulate SSTR2 internalization. PEN-221 receptor dependent, functional and mechanistic cellular activity was also demonstrated *in vitro*. Incubation of PEN-221 with the NCI-H524, an SSTR2 positive cell line, induced dose-dependent increases in mitotic arrest (as measured by phosphohistone H3, or PHH3) and decreases in cellular proliferation. These effects were shown to be dependent upon PEN-221 specific binding to SSTR2. These *in vitro* data demonstrate that PEN-221 affects cancer viability via selective SSTR2 binding, stimulation of receptor internalization, induction of cell cycle (mitotic) arrest and apoptosis.

The mechanism of action of PEN-221 was explored *in vivo* in a study that examined the PDc effects in tumors after PEN-221 dosing of mice. Rapid SSTR2 internalization by NCI-H524 SCLC tumor cells was demonstrated, with measurement of high levels of internalized SSTR2 following a single dose of PEN-221 to tumor xenograft-bearing mice. Additional *in vivo* PDc studies were carried out to measure the biological effects of a single dose of PEN-221 treatment on a second SSTR2 expressing SCLC xenograft model, NCI-H69. Using either an immunohistochemistry (IHC) or an enzyme-linked immunosorbent assay (ELISA) based approach, significant increases in the apoptotic marker, cleaved caspase 3 and the mitosis marker, PHH3, were observed in tumors in response to administration of PEN-221at doses as low as 0.5 mg/kg to mice. The PEN-221 effects on the tumor cells were time- and dose-dependent. These results demonstrate active targeting of the receptor *in vivo* leading to mitotic arrest and apoptosis of tumor cells and support the mechanism of antitumor efficacy with tumor regressions seen in the xenograft models described below.

Significant anti-tumor activity, including complete regressions with some treatment regimens, was demonstrated in 3 SSTR2-positive SCLC models (NCI-H69, MCI-H524 MD, HCC-33 NCI-H82) and 1 neuroblastoma model (IMR-32). Doses tested ranged from 0.25 to 2.5 mg/kg with complete regressions seen following a single dose as low as 1.0 mg/kg in the NCI-H69 model. In the HCC-33 model, with a dose as low as 0.33 mg/kg administered once a week for 4 weeks. Tumor growth inhibition (TGI) of 83% was observed. Additionally, superior efficacy was observed with a single dose of PEN-221 compared to a single cycle of standard of care treatment, cisplatin plus etoposide, in the NCI-H69 model.

In summary, these data collectively support the hypothesis that active targeting of tumors through PEN-221 specific binding to SSTR2 drives the antitumor efficacy observed in multiple SSTR2 expressing xenograft models. Higher levels of antitumor activity, including complete tumor control with regressions, were observed with either repeat dosing at a relatively low dose or with a single relatively high dose. These observations suggest potential for activity in patients with SSTR2-expressing tumors.

4.7. Nonclinical Pharmacokinetics and Drug Metabolism

PEN-221 is a peptide-drug conjugate consisting of a somatostatin analog attached to the cytotoxin DM1, a thiol-containing maytansinoid, using a disulfide linker. The somatostatin analog provides tumor targeting, while DM1 provides antitumor activity. A series of nonclinical studies were conducted to characterize the pharmacokinetic properties of PEN-221.

A single bolus IV administration of PEN-221 resulted in the similar plasma pharmacokinetics for NCr nude mice, Sprague-Dawley rats, and beagle dogs. The pharmacokinetic curves showed bi-phasic profiles, with low clearances (CL) and low to moderate steady state volumes of distribution (V_{ss}) resulting in the average PEN-221 plasma half-lives ($t_{1/2}$) of 12.2 h, 8.07 h and 4.88 h for mice, rats and dogs respectively. Allometric scaling showed a strong relationship among the 3 nonclinical species and was used to predict human pharmacokinetics. The low plasma PEN-221 clearance rate with the low volume of distribution were projected for humans resulting in a predicted half-life for PEN-221 of 2.4 hours.

The membrane permeability of PEN-221 was shown to be very low in a Caco-2 cell monolayer assay indicating low passive permeability across cell membranes. The reversible binding in plasma of PEN-221 was studied in mouse, rat, dog, and human plasma. The unbound fraction of PEN-221 was similar across species (3.3% –10.6%) and was not dependent on the concentration.

Since PEN-221 is designed to deliver the toxin DM1 into the cells, measurement of total DM1 in the tumors and tissues was used to evaluate PEN-221 distribution. Following administration of a single dose of PEN-221 to mice bearing NCI-H69 xenograft tumors expressing high levels of SSTR2, the maximum DM1 levels in tumors were seen between 2 and 8 hours after the dosing. The total DM1 levels in tumors showed a significantly longer half-life than PEN-221 in plasma. Decreases in DM1 tumor levels of less than 50% were seen between day 1 and day 5. In a tissue distribution study in Sprague-Dawley rats, the highest total DM1 levels were seen in the kidneys followed by other highly perfused organs in the order kidneys > lungs > spleen > liver > rough pituitary > pancreas. Very low levels of total DM1 were detected in the skeletal muscle and the bone marrow.

PEN-221 excretion after a single IV dose was evaluated in Sprague-Dawley rats. Over a 24 hour period, 8.48% of the PEN-221 dose was excreted in an unchanged form, with a majority of the intact PEN-221 excreted in urine.

4.8. Nonclinical Toxicology Studies

PEN-221 toxicity was evaluated in 6 exploratory/dose range finding studies and 2 repeat dose IV GLP toxicology studies. Both rat and dog are relevant species for assessment of toxicity, based on sequence conservation of the PEN-221 targeting moiety (somatostatin) and the somatostatin receptor (SSTR2) across species (Creutzfeldt 1987; Flyvbjerg 1992; Hatzoglou 1995; Kaupmann

1995; Liapakis 1996; Misumi 1988; Robben 1997; Waser 2009; Zhang 1995) and the known toxicities of maytansinoid compounds in humans, dogs and rats (Leighton 2013; Poon 2013; Thake 1975). Dose-range finding studies in rat and dog, established the dose levels and timing of measurements and endpoints for GLP repeat-dose studies in both species. Findings showed rat to be the more PEN-221 sensitive species and therefore the STD_{10} in rat has been used to justify the Phase 1 starting dose as noted in Section 5.1.3.1.

The non-GLP studies were designed as exploratory or dose-range finding studies to assist in the dose selection for the GLP repeat dose toxicity studies in rats and dogs and for the GLP cardiovascular safety pharmacology study in dogs. The highest dose in the rat GLP study was set at 1.0 mg/kg while the highest dose in the dog GLP study was set at 0.24 mg/kg.

Repeat-dose GLP toxicology studies in rat and dog were designed to evaluate PEN-221 safety and to characterize the toxic effects with respect to target organs, dose-dependence, relationship to exposure progression, or delayed appearance of any changes and reversibility. In the repeat-dose GLP studies, PEN-221 was administered on Days 1 and 21 to mimic the intended clinical regimen. Studies were designed to examine early effects after the first dose through blood sampling at multiple time points and histopathology and to evaluate the consequences and recovery from repeat dosing. Dose levels tested in the rat repeat dose GLP study were 0.55 mg/kg, 0.76 mg/kg, and 1.0 mg/kg. In dogs, the dose levels for the GLP study were 0.16 mg/kg, 0.20 mg/kg, and 0.24 mg/kg. Terminal groups of animals were euthanized on Day 8 while recovery groups were euthanized on Day 42. Assessment of toxicity was based on mortality, clinical observations, body weight, food consumption, ophthalmoscopic examinations, and clinical and anatomic pathology. Safety pharmacology endpoints including a functional operational battery (FOB) of tests were conducted and clinical observations were monitored that included assessment of CNS (e.g. tremors, convulsion, unusual/abnormal behaviors or motor movements, sensorimotor responses), respiratory (rate and ease), and cardiovascular safety pharmacology parameters.

Toxicokinetic assessments and collections for immunogenicity assessments were included in both rat and dog GLP studies. Blood sampling for determination of plasma concentrations of PEN-221, total DM1, and peptide ligand (BT-979) was conducted for 36 hours starting on Days 1 and 21. In rats the mean plasma C_0 and mean area under the plasma concentration time curve from zero to 36 hours ($AUC_{0\text{-}36h}$) values of PEN-221, total DM1, and BT-979 increase in an approximately dose proportional manner on Days 1 and 21. $AUC_{0\text{-}36h}$ did not change significantly following repeat administration. A moderate sex difference was observed in rats with a 1.5 – 1.9-fold higher PEN-221 $AUC_{0\text{-}36h}$ in males and a 1.5 – 2.2-fold higher total DM1 $AUC_{0\text{-}36h}$ in females. These differences in $AUC_{0\text{-}36h}$ values resulted in differences in the ratio of DM1 to PEN-221. In females, ratios > 8 were observed and in males the ratio remained ≤ 2.4. The net result was a higher $AUC_{0\text{-}36h}$ for DM1 in female rats. In dogs the mean C_0 and mean $AUC_{0\text{-}36h}$ values of PEN-221, total DM1, and BT-979 increased in an approximately dose proportional manner on Days 1 and 21. $AUC_{0\text{-}36h}$ to PEN-221, total DM1, and BT-979 did not change following repeat administration. There was no difference in the toxicokinetics of PEN-221, DM1, or BT-979 in male and female dogs. The DM1 $AUC_{0\text{-}36h}$ was on average 1.37-fold higher than the PEN-221 $AUC_{0\text{-}36h}$.

In the rat study, a single female administered 1 mg/kg PEN-221 was found dead on Day 29. This animal was noted with decreased body weight and clinical observations of thin appearance, red

material around the nose, and forefeet discolored red. Histopathology findings were lymphoid depletion in thymus, decreased hematopoietic cells in the bone marrow of the femur and sternum, bilateral severe hemorrhage in the adrenal glands, Kupffer cell hypertrophy, and cytoplasmic alteration of hepatocytes including increased mitotic figures. The cause of death was considered treatment related. In the repeat dose GLP study in dogs, there were no mortalities.

Weight loss and decreases in food consumption were observed in rats after dosing with reversal and weight gains seen during the study. Overall, by the end of the recovery period, the mean body weight for high-dose males and females were reduced by 4.9% and 12.4%, respectively, when compared to control values. Notable clinical observations in the GLP rat study were decreased activity, thin, unkempt appearance in a few animals at the higher doses. In dogs, minimal, transient decreases in body weight were noted in all PEN-221 treated groups following the first dose which correlated with transiently decreased food consumption in the high PEN-221 dose group. Similarly, a minimal, transient decrease in body weight was noted in high dose group male and female dogs following the second administration of PEN-221. These changes in the dogs exhibited complete resolution.

There were no treatment-related effects noted in ophthalmic exams in the rat or dog GLP studies.

In rats, hematology and coagulation changes at the terminal necropsy were decreased red cell mass in both sexes at all PEN-221 dose levels with decreased reticulocyte counts (females, mid- and high dose groups) and decreased total leukocyte, neutrophil, and lymphocyte counts (males, mid- and high-dose groups and all female groups). Due to the severity of the changes, decreases in red cell mass, reticulocyte and neutrophil counts were considered adverse in high dose group males and mid-and high-dose female animals. The noted differences may be due to the higher DM1 exposure in the female rats. Also noted was an increase in platelet counts in PEN-221 treated males. Following the second dose, at the recovery necropsy, increased reticulocyte counts in mid-dose males and high-dose females were noted that correlated with resolution of red cell mass changes (noted following the first PEN 221 dose). The clinical pathology changes observed in dogs were decreases in reticulocyte counts and platelet counts in both sexes in mid- and high-dose PEN-221 dose groups. Transient decreases in lymphocyte counts in both sexes at the high dose were noted on Days 4 and 24 that resolved 7 days following administration.

Decreased activated partial thromboplastin time (aPTT) and prolonged prothrombin time (PT) were observed in high dose group female rats and increased fibrinogen was noted in females at the mid and high PEN-221 dose levels. In the GLP study in dogs, there were no PEN-221 related effects noted for coagulation.

Urinalysis evaluation on Day 42 revealed absence of sperm in the urine of male rats in the high dose PEN-221 group. There were no notable urinalysis findings in dogs.

In rats, clinical chemistry findings on Day 4 indicated hepatocellular and hepatobiliary effects in both sexes at all dose levels with observations of increased aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP) activities, and increased total bilirubin concentration that was primarily attributable to direct bilirubin. Despite the changes in AST, ALT, ALP, and total bilirubin levels, these changes were transient and were not associated with correlative microscopic liver changes at either terminal or recovery necropsies. Erythrocyte hemolysis may have contributed to the elevations in AST and ALT activities and total bilirubin concentration, as well. However, no significant hemolysis was observed ex vivo with PEN-221

in whole blood from rat at 10 μM, compared to the 5.6 μM maximum concentration achieved in the toxicokinetic analysis. In addition, no significant hemolysis was observed ex vivo in human or dog whole blood at 5 μM. The maximum concentration of PEN-221 achieved in the dog toxicokinetic analysis was 1.6 μM. Using PEN-221 pharmacokinetic parameters and allometric scaling, the proposed starting dose for humans predicts a maximum PEN-221 concentration in humans of 0.08 μM, 62-fold less than the concentration tested in the human whole blood hemolysis assay. Albumin was decreased in PEN-221 treated rats and cholesterol concentration was increased in high dose group males and in all PEN-221 treated females. ALT and AST increases were resolved by Day 8 and cholesterol and albumin changes were partially or fully resolved on Day 8. Bilirubin and ALP changes were resolved by Day 15. Following the second dose on Day 21, similar effects were noted 3 days post dose albeit to a lesser degree which resolved by the end of the recovery period. The magnitude of these clinical chemistry changes was generally higher after both dosing days in the female compared to male rats which may be due to the higher DM1 exposure in the female rats. In dogs, no PEN-221-related effects were noted in clinical chemistry parameters.

Postmortem findings in the rat GLP study were macroscopic findings of small thymus in males and females in the mid- and high-dose PEN-221 groups at the terminal necropsy. Small testes were noted in males in the mid- and high-dose PEN-221 groups at the recovery necropsy. In the dog GLP study, decreased thymus weights were observed in high dose PEN-221-treated animals.

Microscopically, in rats at the terminal necropsy, dose-dependent lymphoid depletion was present in the thymus in males and females at all PEN-221 dose levels. This depletion was characterized by varying degrees of cortical and medullary lymphocyte loss. In severe cases, only the remaining thymus stroma was present. At the recovery necropsy, lymphoid depletion was noted in the thymus in some animals in all dose groups in both sexes and severe lymphoid depletion was present in the 1 female at the high dose, which was found dead on Day 29. In the testes, there was seminiferous tubule degeneration/atrophy at the high dose and minimal germ cell degeneration at the mid- and high-PEN-221 doses, at the terminal necropsy. Testes findings had progressed at the recovery necropsy compared to the terminal necropsy in males at mid and high doses. In the kidney, single cell necrosis and/or tubular regeneration was observed in male rats at all dose levels and female rats at the mid and high doses at the terminal necropsy, but not the recovery necropsy. The rat kidney findings were minimal and reversible and, therefore, considered non-adverse. Bone findings (femur and sternum) were predominantly noted in females at the terminal necropsy and were characterized as increased endosteal osteoid deposition at the mid and high doses. Bone findings had progressed at the recovery necropsy compared to the terminal necropsy in female rats at mid and high doses. At the recovery necropsy, decreased cellularity of the bone marrow was present in the femur and/or sternum of male and female rats at all PEN-221 dose levels, and increased cellularity was present in the bone marrow of the sternum in 1 male at the mid-dose. Also noted was extramedullary hematopoiesis in the liver of females at the mid and high doses and 1 male at the high dose, and in the spleen extramedullary hematopoiesis was observed in males and females at the high dose at the recovery necropsy. The noted microscopic differences that are more marked in the female rats may be due to the higher DM1 exposure. In dogs, microscopic findings were observed in the kidneys (single cell necrosis, tubular degeneration/necrosis, increased mitotic figures, and/or tubular regeneration) in males and females at all PEN-221 dose levels. Most of the findings were graded minimal and were completely reversible and were, therefore, considered non adverse.

Lymphoid depletion was seen in the thymus of mid and high dose PEN-221 treated male animals and in high dose PEN-221 treated females that resolved by the end of the recovery period.

Local tolerance of PEN-221 following IV administration was assessed in the repeat dose GLP studies. There were no macroscopic findings. Microscopic findings were generally minimal.

A dedicated dog telemetry study was conducted to evaluate the potential cardiovascular and respiratory effects of the test article, PEN-221, in conscious freely moving beagle dogs. Dose levels tested were identical to those used in the dog GLP study. PEN-221, administered as a single IV infusion over 6 minutes to male beagle dogs at dose levels of 0.16, 0.20, and 0.24 mg/kg, was generally well tolerated and did not produce any clinical observations or mortality. There were no test article-related effects on the QRS duration, electrocardiogram (ECG) morphology, or tidal volume at any dose level tested. At a dose level of 0.24 mg/kg, from the time of dosing through 1.5 to 2 hours following dosing, PEN-221 induced statistically significant increases in blood pressure, heart rate, and respiratory rate with (Leighton 2013; Poon 2013) decreases (reflective of the heart rate changes) in the RR, PR, and QT intervals, as well as increases in body temperature that did not reach statistical significance. From 7 to 24 hours post dose, slight increases in respiratory rate and minute volume were observed at 0.24 mg/kg. From 2 to 17 hours post dose, non-dose-dependent increases in blood pressure were observed for all test article treatments. Decreases in the PR and QT intervals were observed beginning at 5 or 12 hours, respectively, following the 0.24 mg/kg treatment, lasting through the 24 hour monitoring period. Given the transient nature of the immediate effects observed at 0.24 mg/kg and the relatively small magnitude of the sustained effects observed at all dose levels, these changes are not considered to be adverse; intravenous (IV) administration of PEN-221 produced no adverse effects on cardiovascular or respiratory function in male beagle dogs at doses up to and including 0.24 mg/kg.

The findings in the PEN-221 studies identified target organ toxicities consistent with those identified in toxicology studies with DM1 or the DM1-containing antibody drug conjugate ado-trastuzumab emtansine in rats, with maytansine in dogs (Thake 1975), and with ado-trastuzumab emtansine in cynomolgus monkeys (Leighton 2013; Poon 2013). Notable microscopic findings in Sprague-Dawley rats dosed with ado-trastuzumab emtansine were seen in the liver, thymus, kidney, testis, spleen, mesenteric lymph node, femur marrow and sternum marrow (Poon 2013). In rats dosed with DM1, hematologic changes included decreased platelet, reticulocyte and lymphocyte counts. DM1 and ado-trastuzumab emtansine related decreases in platelets have been observed in preclinical safety studies in rats and monkeys and thrombocytopenia is an adverse reaction to ado-trastuzumab emtansine in humans (KADCYLA® (ado-trastuzumab emtansine) [Package Insert]). Changes in serum chemistry with DM1 dosing in rats reflected adverse effects on the liver: increases in ALT, AST, and total bilirubin (ado-trastuzumab emtansine). In monkeys, ado-trastuzumab emtansine induced changes observed in blood and target organs were as noted in rats (Poon 2013). Increases in aPTT, fibrinogen, and cholesterol were observed in monkeys following dosing with ado-trastuzumab emtansine (Leighton 2013). Observations were noted in the testes of rats dosed with ado-trastuzumab emtansine.

Bone marrow to induce ectopic calcification has been observed with potent tubulin-binding drugs in rats (Tamura 1986). Large doses of vinblastine or colchicine (potent microtubule poisons) produced ectopic calcified tissue in the rat bone marrow cavity. Vinblastine sulfate is an effective single agent treatment for patients with Hodgkin's disease and is indicated for the

palliative treatment of several malignancies. No data included in the product label suggest potential for adverse effects on bone in humans (VinBLAStine Sulfate for Injection USP [package insert]).

In the PEN-221 toxicology studies, effects were demonstrated to be dose-dependent and generally reversible and readily monitored, with rats being the more sensitive species. The microscopic changes were reflected in hematology or clinical chemistry changes in animals, providing guidance for clinical safety monitoring in humans.

5. INVESTIGATIONAL PLAN

5.1. Overall Study Design

Protocol PEN-221-001 is a first-in-human, open-label, Phase 1/2a study evaluating the safety, PK, pharmacodynamics, and anti-tumor activity of PEN-221 in patients with SSTR2 expressing advanced GEP or lung or thymus or other NETs or SCLC or LCNEC of the lung. The study will be carried out in 2 stages: Phase 1 (dose escalation), and Phase 2a (disease-specific cohort expansion).

The overall study design is presented in Figure 1.

Figure 1: Protocol PEN-221-001 Study Design

<table>
<tr><th>Phase 1
Dose Escalation</th><th>Phase 2a
Expansion</th></tr>
<tr><td>Number of dose cohorts dependent on toxicity results as determined by Bayesian logistic regression model (BLRM) with overdose control (EWOC)</td><td>Patients with advanced or metastatic, well-differentiated, low or intermediate grade gastrointestinal mid-gut NET
n=35</td></tr>
<tr><td rowspan="2">etc.
Cohort 4
n=3-6
Cohort 3
n=3-6
Cohort 2
n=3-6
Cohort 1
n=2</td><td>Patients with advanced or metastatic, well-differentiated, low or intermediate grade pancreatic NET
n=20</td></tr>
<tr><td>Patients with advanced or metastatic, small cell lung cancer
n=20</td></tr>
</table>

5.1.1. Pre-screening

Each patient must demonstrate a tumor that is positive for expression of SSTR2, by historical or study-related somatostatin analog radioimaging (SARI). Patients who do not have historical positive SARI will, after provision of written informed consent for the pre-screening assessment, receive SARI. Patients with a historical positive SARI and patients whose pre-screening assessment SARI is positive will enter screening assessments after provision of written informed consent. Patients whose pre-screening assessment SARI is negative will not undergo any further protocol assessments and are not eligible to continue in the study.

Investigators should maintain a log of patients who are consented for pre-screening, including histological type of tumor, stage and grade, anatomical location(s) (primary and metastatic) of tumor, type of SARI used (Octreoscan or ^{68}Ga imaging), and results of screening.

5.1.2. Screening

After provision of written informed consent for the study, patients will be screened for study eligibility within 14 days [and within 28 days for tumor assessments by computed tomography (CT) or magnetic resonance imaging (MRI)] before the first study drug dose.

Investigators should maintain a log of patients who are consented for screening but do not meet eligibility criteria, including histological type of tumor, stage and grade, anatomical location(s) (primary and metastatic) of tumor, and reason for screen failure.

5.1.3. Main Study

5.1.3.1. Treatment Period

Patients who are determined to be eligible, based on screening assessments, and who have provided written informed consent for the study, will begin treatment in the study on Cycle 1 Day 1 (C1D1; baseline). A treatment cycle is 3 weeks in length. All patients will receive PEN-221 administered IV on Day 1 every 3 weeks; the PEN-221 dose received is dependent on the cohort/phase in which the patient is enrolled. During treatment, patients will attend study center visits and have study evaluations performed on D1 of each treatment cycle. D8 and D15 visits will also occur, except that, if after initial dosing or an intra-patient dose escalation, if two cycles are completed with no Grade 2 or higher abnormalities in clinical chemistries or hematology parameters, these visits may be eliminated in subsequent cycles, subject to Investigator discretion (see 9.3.5.1) (Except for C1D1, visits during treatment cycles have a 2-day window.) All study visits are anticipated to be conducted on an out-patient basis, but may be conducted on an in-patient basis per institutional policy.

Safety will be assessed during the study by documentation of adverse events (AEs), clinical laboratory tests, physical examination, neurological examination, vital sign measurements, ECGs, and Eastern Cooperative Oncology Group (ECOG) performance status (PS).

Pharmacodynamic (PDc) and serial blood samples for PK will be collected from all patients.

All sites of disease will be assessed by CT. If the anatomic region cannot be adequately imaged by CT, MRI may be used instead. For SCLC and LCNEC of the lung patients, tumor measurements are to be repeated within 7 days prior to the first study drug dose in every other cycle, starting in C3, and at the Progression Follow-up visits. For all other patients, tumor measurements are to be repeated within 7 days prior to the first study drug dose in every third cycle, starting in C4, and at the Progression Follow-up visits. Repeat assessments should use the same radiographic methods as used at baseline. Disease response is to be assessed by the Investigator using RECIST guidelines, version 1.1 (Eisenhauer 2009). Patients who achieve a partial response (PR) or complete response (CR) by RECIST are to have repeat assessments performed approximately 6 weeks later (and no sooner than 4 weeks from the prior assessment) to confirm the response. Following the confirmatory assessment, the response assessment schedule will resume at intervals of every other cycle for SCLC and LCNEC patients, and every third cycle for all other patients.

5.1.3.2. End of Treatment

Patients who discontinue treatment for any reason (see Section 7.8) should have an EOT visit. The EOT visit should occur within 3 days from the event resulting in treatment discontinuation (i.e. disease progression, AE, withdraw consent).

5.1.4. Follow-up Period

5.1.4.1. Safety Follow-Up

All patients discontinuing treatment or withdrawing from the study will have physical examination, laboratory, AE, and concomitant medication assessments performed as part of a safety follow-up visit 28 days (±3 days) after their last dose of study drug.

5.1.4.2. Progression Follow-Up

For patients that discontinue treatment for reasons other than radiographic progression of disease, tumor assessments should be performed approximately every 6 weeks from previous scan for SCLC and LCNEC of the lung patients and every 9 weeks from previous scan for all other patients, or as clinically indicated, until radiographic progression of disease is observed.

5.1.4.3. Survival Follow-Up

Upon disease progression, all patients will be followed approximately every 3 months to assess survival status and the date and cause of death (if known) will be recorded for patients who died. Survival follow-up will occur every 3 months until death, lost to follow-up or consent withdrawal.

5.1.5. Starting dose

The PEN-221 selected starting dose of 1.0 mg IV every 3 weeks is based upon international guidance for starting dose selection for agents in cancer patients (ICH S9 2010 Guidance for Industry). ICH S9 recommends that a starting clinical dose for a first-in-human study should be either 1/10th of the severely toxic dose (STD_{10}) in rodent toxicity studies or 1/6th of the highest non-severely toxic dose (HNSTD) in non-rodent toxicity studies.

Based on the findings in the 6-week rat repeat dose IV toxicity (PEN-221-TX-006), the STD_{10} for PEN-221 following single or repeat dose administration to rats was determined to be 1.00 mg/kg. Based on these data, the dose of one-tenth the rat STD_{10} gives a Human Equivalent Dose (HED) of 0.016 mg/kg informing the PEN-221 first-in-human starting dose (Table 4). The calculation based on the dog HNSTD (PEN-221-TX-007) is shown in Table 5 and results in a higher HED of 0.022 mg/kg substantiating that rat is the more sensitive species. The human starting dose of 0.016 mg/kg is equivalent to 0.60 mg/m^2 (Table 5). Assuming an average weight of 60 kg in human, the starting dose translates to 0.96 mg or using an average body surface area of 1.7 m^2, the starting dose calculates as 1.02 mg. Hence, we have selected a starting dose of 1.0 mg IV every 3 weeks.

Based on tumor bearing mouse xenograft studies (PEN-221-PHARM-023), the minimum biologic effective dose in mice is 0.33 mg/kg. Applying the mouse to human conversion factor of 12.3 and assuming an average human weight of 60 kg, the human equivalent minimum effective dose is estimated to be 1.6 mg.

Table 4: Human Starting Dose Calculation

Rat STD_{10} mg/kg	1/10 Rat STD_{10} mg/kg	Rat 1/10 STD_{10} mg/m^2	Calculation of Human Starting Dose	
			HED mg/kg	HED mg/m^2
1.0	0.10[a]	0.6[b]	0.016[c]	0.60[c]

[a] As the rodent is the most sensitive species, starting dose was calculated as 1/10 the Severely Toxic Dose in 10% of the animals (STD_{10}) in rodents. (ICH Topic S9 Nonclinical Evaluation for Anticancer Pharmaceuticals, March 2010).

[b] BSA (Body Surface Area, m^2) = mg/kg dose in rat multiplied by 6 to calculate mg/m^2 dose in rat. (FDA Guidance for Industry, Estimating Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers, July 2005).

[c] The human equivalent dose (HED = animal dose in mg/kg × (animal weight in kg/human weight in kg)$^{0.33}$) or alternatively this can be calculated, for HED for rat dose, divide the rat dose in mg/kg by 6.2, assumes 60 kg human. Starting dose HED using 1/10 the STD_{10}, as rat is most sensitive species. To convert the human mg/kg dose to the BSA (mg/m^2) dose, multiply the mg/kg human dose by 37 = human mg/m^2. (FDA Guidance for Industry, Estimating Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers, July 2005).

Table 5: HNSTD in Dog for Comparison to Rat STD_{10}

Dog HNSTD mg/kg	1/6 Dog HNSTD mg/kg	Dog 1/6 HNSTD mg/m^2	Human Equivalent Dose	
			HED mg/kg	HED mg/m^2
0.24	0.04[a]	0.8[b]	0.022[c]	0.82[c]

[a] Highest Non- Severely Toxic Dose (HNSTD). If the non-rodent is the most sensitive species then 1/6 the Highest Non- Severely Toxic Dose (HNSTD) is considered an appropriate start dose. (ICH Topic S9 Nonclinical Evaluation for Anticancer Pharmaceuticals, December 2008).

[b] BSA (Body Surface Area, m^2) = mg/kg dose in dog multiplied by 20 to calculate mg/m^2 dose in dog. (FDA Guidance for Industry, Estimating Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers, July 2005).

[c] The human equivalent dose (HED = animal dose in mg/kg × (animal weight in kg/human weight in kg)$^{0.33}$) or alternatively this can be calculated by dividing the dog dose in mg/kg by 1.8, assumes 60 kg human. To convert the human mg/kg dose to the human BSA (mg/m^2) dose, multiply the mg/kg dose by 37 = human mg/m^2. (FDA Guidance for Industry, Estimating Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers, July 2005).

5.1.6. Phase 1 (Dose escalation)

Phase 1 will employ an adaptive Bayesian logistic regression model (BLRM) with 2 parameters guided by the EWOC principle to make dose recommendations and estimate the MTD.

To minimize the number of patients treated at potentially subtherapeutic dose levels, the first dose cohort will enroll 2 patients, whereas subsequent cohorts will enroll a minimum of 3 and up to 6 patients. The initial patient in Cohort 1 will receive PEN-221 administered IV over 1 hour at the starting dose of 1.0 mg on an every 3 week cycle. This patient will be followed for 7 days, including assessments during the scheduled visit on C1D8, prior to allowing additional patients to begin treatment with PEN-221. If PEN-221 is tolerated by the initial patient for at least 7 days,

then the first cohort will be opened to treatment of 1 additional patient. The first 2 patients will be assessed for safety and dose limiting toxicity (DLT) for at least 4 weeks (including C2D1 and C2D8 assessments) before enrollment in the second cohort may begin.

The SRC will convene to review all data from the first 2 patients in Cohort 1 through C2D8. Providing there are no safety concerns after completion of the first cohort, subsequent cohorts of patients will be dosed as suitable patients are identified. However, the SRC may choose to stagger dosing in the second cohort and likewise for subsequent cohorts.

In each dose escalation cohort following the first cohort, a minimum of 3 patients within a cohort are required to have completed C1 and have been assessed for safety and DLT for at least 3 weeks (including C2D1 pre-dose assessments) before enrollment of the next cohort may begin.

The Safety Review Committee (SRC) will review the safety and tolerability of PEN-221 of each cohort to decide the next dose level to be tested. Statistical modeling will be performed using all safety data and will guide the SRC's selection of dose levels to be tested. In addition, pharmacokinetic (PK) and pharmacodynamics (PDc) data may be used to inform dose selection. Dose escalation increments will be the decision of the SRC. PEN-221 dose cohorts will be enrolled sequentially after the SRC reviews safety data collected during C1 (and through C2D8 for Cohort 1) from the patients enrolled in the current dose level. Dose escalation will continue until the MTD is determined.

During Phase 1, if a patient is tolerating PEN-221 without significant evidence of disease progression, the patient may, beginning with C3 or subsequent cycles, have the dose increased to a dose that has already been established as tolerable by the SRC, and with the agreement of the SRC.

The starting dose of PEN-221 is 1.0 mg. The planned dose levels are summarized in Table 6 .

Table 6: Planned PEN-221 Dose Levels

Dose Level	% Increment from Prior Dose Level	PEN-221 Dose (mg)
−1	(50% decrease)	0.5
1	Starting dose	1
2	100%	2
3	100%	4
4	67%	6.7
5	50%	10
6	33%	13.3
7	25%	16.6
8	25%	20.8

*Actual dose increments will be the decision of the SRC but will not exceed a doubling of dose from the prior dose level. The doses assigned will be the decision of the SRC and will be guided by the updated results of BLRM.

In cohort 1, each patient must have received PEN-221 in C1 and C2 and completed follow-up safety evaluations through C2D8 to be evaluable for the assessment of DLT. In all subsequent cohorts, each patient in a dose cohort must have received PEN-221 in C1 and completed follow-up safety evaluations through C2D1 to be evaluable for the assessment of DLT. Patients who discontinue from the study for reasons other than DLT before completing C1 are to be replaced. See Section 8.9 for definition of evaluable patient.

If a DLT necessitates enrollment of additional patients into a cohort, the SRC will review all safety data for that cohort after all patients have received PEN-221 in C1 and completed follow-up safety evaluations through the end of C1. Based on the interim evaluation of the safety and tolerability data of the previous dose level, it may also be decided that accrual will take place at an intermediate dose level. The SRC may be convened earlier at the discretion of the Sponsor if important safety issues arise requiring the attention of the committee.

Toxicities are to be graded by the Investigator using the National Cancer Institute (NCI) Common Terminology for Cancer Adverse Events (CTCAE), version 4.03.

Although decisions regarding dose escalation will be made based on review of data from C1, safety data will also be collected from all patients continuing treatment and this will be reviewed periodically by the SRC. Any detected cumulative toxicity may require later dose reductions or other action as appropriate, including further refinement of the RP2D.

5.1.7. Phase 2a

In Phase 2a, PEN-221 will be evaluated using the recommended Phase 2 dose (RP2D) identified by the SRC.

Phase 2a may begin once a RP2D is identified in Phase 1 of the study. The RP2D will be the decision of the SRC and will be based on the findings of the safety, tolerability, PK, and PDc profile of PEN-221 during Phase 1. The recommended Phase 2 dose may be the same as the MTD, or may be below the MTD. In the event that the MTD is higher than the dose determined by the SRC to have an acceptable safety and tolerability profile after multiple cycles of administration, the SRC may select a RP2D that is below the MTD.

Phase 2a may, at the discretion of the Sponsor, begin once all patients have been enrolled in Phase 1 and have been assessed for safety through and including C2D1, and the SRC has reviewed all safety data and recommends continuing with Phase 2a.

If one or more DLTs are observed at any time up until 6 patients across any of the three cohorts have been treated for at least 1 cycle in Phase 2a, the BLRM may be re-run to confirm the estimated MTD. The SRC will convene to determine whether it is safe to proceed with dosing at the RP2D or whether an alternative lower dose is to be considered for subsequent patients. If an alternative lower dose is selected, the SRC will reconvene after at least 6 patients have been treated at this new dose to review the data and confirm whether subsequent patients be enrolled into the study at this new dose.

In addition, at any time during Phase 2a, the BLRM may be re-run to confirm the estimated MTD and verify that the dose under study still satisfies the overdose criterion. If the dose fails to satisfy the criterion a change to the dose under study may be decided by the SRC, guided by the Bayesian model recommendation, after review of the clinical data. The SRC decision to change dose may also be spurred by other safety and tolerability considerations (e.g. frequency of lower

grade AEs or events in later treatment cycles). Subsequent patients may then be enrolled at this new dose until at least 6 patients are treated at this new dose level and upon SRC review of the data, the SRC will decide whether the new dose level is appropriate for continued study.

5.2. Justification for the Study Design

Goals of Phase 1 oncology studies include estimation of the MTD and initial assessment of safety and tolerability of a study drug, determination of a recommended range of doses for evaluation in future clinical studies (Ahn 1998; Dillman 1992; Gatsonis 1992; International Conference on Harmonization 1997), and an initial characterization of the PK profile in humans. The objectives of the current study are consistent with those typical of Phase 1 oncology studies.

This first-in-human study is designed as a Phase 1 dose escalation and a Phase 2a expansion phase once the MTD and RP2D have been defined.

The primary objective of the dose escalation phase of the study is to determine the MTD. Dose escalation will be guided by an adaptive BLRM following the EWOC principle. The use of BLRMs for Phase 1 studies has been advocated by the European Medicines Agency (EMA) and by (Rogatko 2007). This design uses all accumulating toxicity data to assign enrolling patients to escalating doses of study drug, while controlling the risk of excessive toxicity.

Once the MTD and RP2D has been determined, the study will proceed in to Phase 2.

The primary objective of Phase 2a is to evaluate the potential anti-tumor activity of PEN-221. The activity of PEN-221 at the MTD or RP2D, as identified in Phase 1, will be evaluated in Phase 2a in patients with specific tumor types to determine whether the activity seen is sufficiently promising to evaluate PEN-221 in patients with those particular tumor types in future clinical studies.

5.3. Criteria for Study Termination

The Sponsor reserves the right to terminate the study or particular study center at any time. If the Sponsor or Investigator discovers conditions arising during the study that suggest the study should be halted, then study termination can occur only after appropriate consultation between the Sponsor and Investigators. Conditions that may warrant study or study center termination include, but are not limited to:

- The discovery of any unexpected, significant, or unacceptable risk to the patients enrolled in the study.
- Failure of the Investigator to enter patients at an acceptable rate.
- Insufficient adherence to the protocol requirements.
- A decision on the part of the Sponsor to suspend or discontinue development of study drug.

Should the study be closed prematurely, all study materials (study drug, etc.) must be returned to the Sponsor or designee (or disposed of after consultation with the Sponsor or designee, as directed by the Sponsor or designee).

5.4. Benefit/Risk Assessment

PEN-221 is a novel peptide-drug conjugate that is specifically designed as a targeted anticancer agent for patients with advanced cancers that overexpress SSTR2. Significant antitumor activity has been seen in multiple SSTR2 positive xenograft models, including complete regressions.

PEN-221 in this first in human study is being tested in the patient population who is considered most likely to benefit from the study medication, namely, those with advanced cancers that overexpress SSTR2. These cancers include gastroenteropancreatic and lung and thymus NETs, NETs of unknown primary, SCLC and LCNEC of the lung, and other tumors of neuroendocrine origin, namely, paraganglioma, pheochromocytoma, medullary thyroid carcinoma, Merkel cell carcinoma, and high grade extrapulmonary neuroendocrine carcinoma (NEC). The somatostatin receptor is known to be overexpressed in the majority of NETs, and approximately 40% of SCLC (Hofland 2001; Lehman 2015; Mato 1998; O'Byrne 1994; Pisarek 2009; Wangberg 1997).

Effective treatment options for patients with these cancers in the advanced setting are extremely limited and new therapies are urgently needed. To improve the possibility that patients enrolled in this Phase 1/2a study might benefit from PEN-221, patients must meet eligibility criteria that include tumor expression of SSTR2 as assessed by a noninvasive, approved imaging modality.

The primary objective of the Phase 1 dose escalation portion of this Phase 1/2a study is to investigate the safety and tolerability and determine the maximum tolerated dose (MTD) of PEN-221. The nonclinical toxicology studies have not identified any risks that would preclude investigation of PEN-221 in the advanced cancer setting, although at high exposures, significant toxicities known to be associated with DM1, antibody-drug conjugates that contain DM1, and other microtubule disrupting agents were observed. Based on the identified and potential risks associated with PEN-221 treatment, this clinical study protocol incorporates mandatory and thorough safety monitoring procedures and additional guidance documents to assist with early diagnosis and rapid management of potential treatment related toxicities. The safety monitoring plan takes into consideration the results of PEN-221 GLP toxicology studies as well as published reports of other targeted conjugates that contain DM1 including ado-trastuzumab emtansine, an approved agent for the treatment of women with previously treated, HER2-positive, metastatic breast cancer (Poon 2013; Verma 2012) and other antibody-drug conjugates in early phase development (Amiri-Kordestani 2014; Galsky 2008; Rodon 2008; Shah 2016).

The Phase 1 dose escalation portion of the study is designed to maximize safety while minimizing the number of patients treated at subtherapeutic dose levels. The starting dose cohort will enroll only 2 patients, whereas subsequent cohorts will enroll a minimum of 3 and up to 6 patients. The first patient treated with PEN-221 in the first cohort will be observed for 7 days prior to allowing additional patients to begin treatment with PEN-221. If PEN-221 is tolerated for at least 7 days by the first patient, then the first cohort will be opened to treatment of 1 additional patient. After the first 2 patients have been assessed for safety and dose limiting toxicity (DLT) for at least 4 weeks (up until C2D8), enrollment in the second cohort may begin. Dose escalation will be guided by an adaptive BLRM following the EWOC principle. The use of BLRMs for Phase 1 studies has been advocated by the European Medicines Agency (EMA) (Committee for Medicinal Products for Human Use (CHMP) 2006) and by Rogatko (2007). This design uses all accumulating toxicity data to assign enrolling patients to doses that have a higher chance of targeted toxicity (close to the MTD), while controlling the risk of excessive toxicity.

During Phase 1, if a patient is tolerating PEN-221 without significant evidence of disease progression, the patient may, starting on D1 of C3 or subsequent cycles, have the dose increased to a dose that has already been established as tolerable by the SRC, and with the agreement of the SRC. This intra-patient dose escalation may allow patients a greater possibility of benefit from treatment with PEN-221 than might be achieved at the starting dose in his/her assigned dose cohort.

Risks specific to patients who have provided written informed consent to undergo an optional tumor biopsy during screening include pain and tenderness at the tumor biopsy site and potential bleeding complications, which will be minimized by inclusion of patients who have at least 1 site of tumor that is accessible to biopsy and that is considered by the Investigator to be low risk and of sufficient size to undergo a biopsy procedure, and monitoring per institutional practice.

No reproductive toxicology, genotoxicity, or carcinogenicity studies have been conducted with PEN-221 to date. Both women and men should be fully informed of the lack of reproductive toxicology testing. Women of childbearing potential and men must agree to use highly effective contraception (as defined in inclusion criterion 6) prior to study entry and for the duration of study participation. Women must have a negative pregnancy test prior to enrollment. It is unknown whether the drug is excreted in human milk, and women who are breast feeding are excluded from the study.

The study design for this first in human Phase 1/2a dose escalation/expansion study of PEN-221 aims to minimize potential risks and offer the potential to benefit patients whose tumors overexpress the SSTR2 target of this anticancer agent. Although the potential benefits to patients are unknown at this time, nonclinical data demonstrate evidence of potent anti-tumor activity in tumor models that overexpress SSTR2. The benefit/risk assessment for this Phase 1 study appears acceptable based on the lack of effective alternative treatments, the limited life expectancy of the patient population, and the strength of the nonclinical data in support of potent antitumor activity.

6. STUDY OBJECTIVES AND ENDPOINTS

6.1. Phase 1

6.1.1. Primary Objective

The primary objective of Phase 1 is to:

- Investigate the safety and tolerability, determine the maximum tolerated dose (MTD), and RP2D of PEN-221 when administered IV on an every 3 week schedule in patients with SSTR2 expressing advanced cancers, including GEP or lung or thymus or other NETs or SCLC or LCNEC of the lung.

6.1.2. Secondary Objectives

The secondary objectives of Phase 1 are to:

- Characterize the safety and tolerability of PEN-221, including both acute and chronic toxicities.
- Characterize the PK of PEN-221, DM1, and peptide from PEN-221, when administered IV in patients with SSTR2 expressing advanced cancers, including GEP or lung or thymus or other NETs or SCLC or LCNEC of the lung.
- Assess the potential of PEN-221 to induce anti-PEN-221 antibodies in the serum when administered IV in patients with SSTR2 expressing advanced cancers, including GEP or lung or thymus other NETs or SCLC or LCNEC of the lung.
- Assess preliminary anti-tumor activity of PEN-221 in patients with SSTR2 expressing advanced cancers, including GEP or lung or thymus or other NETs or SCLC or LCNEC of the lung, using tumor response criteria as defined by RECIST 1.1, and duration of response.

6.1.3. Exploratory Objectives

[redacted]

6.2. Phase 2a

6.2.1. Primary Objective

The primary objective of Phase 2a is to:

- Assess the efficacy of PEN-221 as a single-agent when administered IV using clinical benefit rate (CBR) as defined as the proporation of patients with the best overall response of complete response (CR), partial response (PR), or stable disease (SD) using tumor response criteria as defined by RECIST 1.1 in the following tumor-specific cohorts:
  - Patients with advanced or metastatic, well-differentiated, low or intermediate grade gastrointestinal mid-gut NETs.
  - Patients with advanced or metastatic, well-differentiated, low or intermediate grade pancreatic NETs.
- Assess the efficacy of PEN-221 as a single-agent when administered IV using objective response rate (ORR) defined as the proportion of patients with best overall response of CR or PR using tumor response criteria defined by RECIST 1.1 along with duration of response in the following tumor-specific cohort of patients:
  - Patients with advanced or metastatic SCLC.

6.2.2. Secondary Objectives

The secondary objectives of Phase 2a are to:

- Confirm the MTD identified during the dose-escalation phase, and further investigate the safety and tolerability of the RP2D and schedule of PEN-221 when administered IV in patients with SSTR2 expressing advanced GEP NETs or SCLC.
- Evaluate progression-free survival and overall survival in all the above tumor-specific cohorts of patients whose tumors express SSTR2.
- Evaluate ORR and duration of response for gastronintestinal mid-gut NET and pancreatic NET.
- Evaluate the safety and tolerability of PEN-221 administration in the above tumor-specific cohorts of patients whose tumors express SSTR2.
- Characterize the PK of PEN-221, DM1, and peptide from PEN-221, in the above tumor-specific cohorts of patients whose tumors express SSTR2.

6.2.3. Exploratory Objectives

[redacted]

7. SELECTION AND WITHDRAWAL OF PATIENTS

7.1. Number of Patients

A total of approximately 105 patients are planned to be enrolled in the study.

7.1.1. Phase 1

It is estimated that approximately 30 patients will be enrolled in Phase 1. After 2 patients are treated in the starting dose cohort, a cohort size of 3 to 6 patients will be treated at each dose level. An adaptive BLRM guided by the EWOC principle will be employed to make dose recommendations and estimate the MTD. Approximately 4 to 6 dose escalation cohorts are anticipated. The total number of patients to be enrolled is dependent upon the observed safety profile as well as the number of dose escalation cohorts required to achieve the MTD and establish the RP2D of PEN-221.

Each patient will participate in only 1 dose cohort with respect to assignment of starting dose. At least 6 patients will be treated at the MTD.

7.1.2. Phase 2a

Approximately 75 patients will be enrolled as follows: gastrointestional mid-gut NET (n=35, 25 PRRT-naïve, 10 PRRT recurrent), pancreatic NET (n=20), and SCLC (n=20). These cohort sample sizes are considered sufficient to obtain an early assessment of efficacy of PEN-221 in patients with distinct tumor types.

7.2. Consent

Patients who undergo any study-related assessment or study-related modification of medical care must, of their free will, give fully considered, written informed consent to those assessments or modifications. Consent is not considered given simply by the patient signing an approved form. The patient's medical record must also clearly indicate that the Investigator, or a qualified health care provider under the direction and designation of the Investigator, had a comprehensive discussion with the patient about the risks, benefits, and responsibilities of participation, ensuring the patient understood the contents of the informed consent form (ICF), and offering the patient sufficient time to consider details and discuss with others if they desire.

In the event that the partner of a patient becomes pregnant, the partner must provide voluntary, fully considered, written informed consent to the use of any information collected about them, the fetus, or any resulting birth before such information can be collected or used in the study.

7.3. Patient Inclusion Criteria

All patients must meet all of the following criteria to be eligible to participate:

1. Provision and understanding of signed and dated, written informed consent prior to any mandatory study-specific procedures, sampling, analysis.
2. Male or female aged ≥ 18 years.
3. ECOG PS of 0 – 1.
4. Adequate organ function within 14 days before C1D1, defined as follows:

- Bone marrow: Absolute neutrophil count (ANC) ≥ 1.5×10^9/L, platelet count ≥ 100×10^9/L, and hemoglobin ≥ 9 g/dl.
- Hepatic: total bilirubin ≤ 1.5× the upper limit of normal (ULN) and alanine ALT and AST ≤ 2.5× ULN.
- Renal: If serum creatinine concentration ≥ 1.5× ULN, then estimated creatinine clearance must be ≥ 50 mL/min (Cockroft-Gault formula)

5. Serum potassium, calcium, magnesium and phosphorus within normal limits. If values are low on the initial screening assessment, supplements may be given and values repeated to confirm within normal limits.
6. If a female of childbearing potential, negative serum pregnancy test within 3 days before C1D1, or in the event of a positive serum pregnancy test, exclusion of pregnancy as assessed by transvaginal ultrasound overseen by a health care professional with experience in investigating and diagnosing early pregnancy, as human chorionic gonadotropin (HCG) can be secreted by neuroendocrine tumor. A female of childbearing potential must agree to the use of highly reliable, physician-approved contraception from 14 days before C1D1 through 3 months after the last study drug dose. Highly reliable contraception means 2 of the following: (1) established use of oral, injected, or implanted hormonal methods of contraception, (2) placement of an intrauterine device, (3) condom or occlusive cap (diaphragm or cervical vault cap with spermicidal gel, foam, film, cream, or vaginal suppository), (4) male sterilization with verified absence of sperm in ejaculate post-vasectomy. Alternatively, true abstinence is acceptable when it is the preferred and usual lifestyle of the individual. Calendar, symptothermal, post-ovulation, coitus interruptus, spermicides only, and lactational amenorrhea are not acceptable methods of contraception.
7. If male, is surgically sterile or agrees to use a condom from C1D1 through 3 months after the last study drug dose. Alternatively, true abstinence is acceptable when it is the preferred and usual lifestyle of the individual.
8. SSTR2 positive tumor as assessed using a SARI agent and as defined as follows:

   - For SCLC patients, tumor uptake equal to or greater than liver update
   - For all other patients, tumor uptake greater than liver uptake.

   SARI performed during the Pre-screening phase must be obtained using an agent that is approved for use by the regional regulatory authority. Documented results of SARI performed as part of a patient's routine diagnostic assessments prior to the Pre-screening Phase and within 180 days of C1D1 may be used in place of a Pre-screening phase SARI assessment.

9. Patients in Phase 1 must have a histologically- or cytologically-confirmed solid tumor in 1 of the following categories:
   - Advanced SCLC or LCNEC of the lung having progressed after 1 or more prior lines of anticancer chemotherapy, or
   - Advanced low or intermediate grade GEP or lung or thymus NET, or NET of unknown primary, having progressed after 1 or more prior lines of anticancer therapy, unless no standard treatments are available or unless such treatments are deemed not appropriate, or

- Advanced paraganglioma, pheochromocytoma, medullary thyroid carcinoma, Merkel cell carcinoma, or high grade extrapulmonary NEC having progressed after 1 or more prior lines of anticancer therapy, unless no standard treatments are available or unless such treatments are deemed not appropriate.

Anticancer therapies include liver-directed intra-arterial therapy, cytotoxic chemotherapy, everolimus, targeted inhibitors, MIBG, and immunotherapies, but does not include somatostatin analogs.

For patients who provide written informed consent to undergo an optional tumor biopsy during the Screening phase, such patients must meet the following additional criterion before undergoing a biopsy procedure:

10. Patient must have at least 1 site of tumor that is accessible to biopsy and that is considered by the Investigator to be low risk and of sufficient size to undergo a biopsy procedure.

Patients in Phase 2a must meet the following additional criteria:

11. Measurable disease per RECIST 1.1 (i.e., at least 1 measurable lesion ≥ 20 mm by conventional techniques or ≥ 10 mm by spiral CT scan or MRI), with the last imaging performed within 28 days before C1D1 and documented radiographic disease progression.
12. Patients in Phase 2a must have a histologically- or cytologically-confirmed, advanced or metastatic solid tumor, in 1 of the following categories:
    - Well differentiated, low or intermediate grade, gastrointestinal mid-gut (arising from the lower jejunum, ileum, appendix, cecum, and proximal colon) NET with documented disease progression within 6 months prior to start of study treatment (i.e. maximum of 24 weeks from documentation of progression until study entry) and evidence of radiographic disease progression based on scans performed not more than 15 months apart. Patients may have received 1 or more prior lines of anticancer therapy, such as somatostatin analogues, targeted agents, or liver-directed intra-arterial therapy, but are NOT eligible if they have received prior systemic cytotoxic chemotherapy.
    - Well differentiated, low or intermediate grade, pancreatic NET with documented disease progression within 6 months prior to start of study treatment (i.e. maximum of 24 weeks from documentation of progression until study entry), and evidence of radiographic disease progression based on scans performed not more than 15 months apart. Patients may have received 1 or more prior lines of anticancer therapy, such as somatostatin analogues, targeted agents, or liver-directed intra-arterial therapy, and up to 1 prior line of systemic cytotoxic chemotherapy, but are NOT eligible if they have received more than 1 prior line of systemic cytotoxic chemotherapy or if they have received prior peptide receptor radionuclide therapy (PRRT).
    - SCLC after having received up to three prior lines of anticancer therapy.

7.4. Patient Exclusion Criteria

Patients meeting any of the following criteria are not eligible for study participation

1. Treatment with anticancer therapy (as defined in inclusion criterion 9 and 12) or an investigational drug or device within 3 weeks (6 weeks for mitomycin C and nitrosoureas) or 5 half-lives of the agent (whichever is shorter) before C1D1. In addition, any drug-related toxicity, with the exception of alopecia, must have recovered to ≤ Grade 1.
2. Any other malignancy known to be active or treated within 3 years of the start of screening, with the exception of cervical intra-epithelial neoplasia, superficial (non-invasive) bladder cancer, and non-melanoma skin cancer.
3. One or more of the following cardiac criteria:
    - Unstable angina
    - Myocardial infarction within 6 months prior to screening
    - New York Heart Association Class II – IV heart failure
    - Corrected QT interval (QTc) >470 msec obtained as the mean from 3 consecutive resting ECGs using the Fredericia formula
    - Clinically important abnormalities in rhythm, conduction, or morphology of resting ECG (e.g., complete left bundle branch block, third degree heart block)
    - Congenital long QT syndrome
    - Symptomatic orthostatic hypotension within 6 months prior to screening
    - Uncontrolled hypertension.
4. Stroke or transient ischemic attack within 6 months prior to screening
5. Grade >1 peripheral neuropathy
6. Patient requires medication with a strong CYP3A4 inhibitor, e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, and voriconazole.
7. History of leptomeningeal disease or spinal cord compression.
8. Brain metastases unless asymptomatic on a stable low dose of steroids.
    - Patients with SCLC or LCNEC of the lung only: CT or MRI of the brain required during screening. If positive for brain metastases, patients must have undergone radiotherapy prior to initiating treatment with PEN-221. If whole brain radiotherapy is performed, a 14-day washout is required prior to treatment with PEN-221. If stereotactic radiosurgery or stereotactic radiotherapy is performed, a 7-day washout prior to treatment with PEN-221 is required.
9. Major surgery within 28 days prior to C1D1.
10. Female who is pregnant or breast-feeding.
11. As judged by Investigator, evidence of severe or uncontrolled systemic disease, active bleeding diatheses, renal or liver transplant, or active infection including known hepatitis B, hepatitis C, or human immunodeficiency virus (HIV).
12. Hypersensitivity or history of anaphylactic reaction to octreotide or other somatostatin analogs.
13. Hypersensitivity or history of anaphylactic reaction to maytansinoids or their derivatives.

14. Any medical, psychological, or social condition that would interfere with the patient's participation in the study.

7.5. Patient Restrictions During Treatment

From the first dose of PEN-221, C1D1, patients must adhere to the following restrictions:

- Male patients must not donate sperm for 3 months after the last study drug dose, and those who have not been sterilized with verified absence of sperm in ejaculate post-vasectomy must use a condom from C1D1 through 3 months after the last study drug dose. Alternatively, true abstinence is acceptable when it is the preferred and usual lifestyle of the individual.
- Female patients of childbearing potential must practice the use of highly reliable, physician-approved contraception from 14 days before C1D1 through 3 months after the last study drug dose. Highly reliable contraception means 2 of the following: (1) established use of oral, injected, or implanted hormonal methods of contraception, (2) placement of an intrauterine device (3) condom or occlusive cap (diaphragm or cervical vault cap with spermicidal gel, foam, film, cream, or vaginal suppository), (4) male sterilization with verified absence of sperm in ejaculate post-vasectomy. Alternatively, true abstinence is acceptable when it is the preferred and usual lifestyle of the individual. Calendar, symptothermal, post-ovulation, coitus interruptus, spermicides only, and lactational amenorrhea are not acceptable methods of contraception.
- All patients must follow concomitant medication provisions in Section 8.12.1.
- Patient hematology and blood chemistries must continue to meet Inclusion Criteria 4 and 5 for patients to continue receiving PEN-221.

7.6. Source of Patients

This will be a multi-center study. Each study center is required to obtain Institutional Review Board (IRB) or Ethics Committee (EC) approval to conduct the study before enrollment of patients may begin. Patients meeting the entry criteria will be eligible for enrollment.

7.7. Patient Identification and Enrollment

To ensure accurate and timely monitoring of patient enrollment, the following procedures will be implemented:

- Patients who are candidates for enrollment into the study will be assigned a sequential and unique patient number by the Investigator after the patient has provided written informed consent into the Screening phase. Once a patient number has been assigned, it cannot be reused.
- Patients who have provided written informed consent will be evaluated for eligibility by the Investigator to ensure that the entry criteria (see Section 7.2 and Section 7.4) have been satisfied and that the patient is eligible for participation in this clinical study.

- The Investigator or the Investigator's research staff will provide eligibility information to the Medical Monitor.
- Patients who are enrolled but not treated will be replaced. Furthermore, during Phase 1, patients who discontinue from the study before completing C1 for reasons other than DLT will be replaced.
- Investigators will be notified by the Sponsor when enrollment in a given dose cohort / study phase is closed and enrollment into the next dose cohort / study phase can begin. Investigators will be consulted in all dose escalation decisions.
- Investigators will be notified by the Sponsor if the study is placed on administrative hold, when it is completed, or is closed to further patient enrollment.

7.8. Patient Withdrawal Criteria

Patients may withdraw from the study at any time for any reason, without prejudice to their medical care. The Investigator also has the right to discontinue treatment with PEN-221 or withdraw patients from the study for any of the following reasons:

- Progression of disease
- AE
- Life threatening or other unacceptable toxicity
- PEN-221 cycle delay for > 3 weeks due to study drug-related toxicity
- Patient requires use of a prohibited concomitant medication or therapy
- General or specific changes in the patient's condition unacceptable for further treatment within the study parameters, in the Investigator's opinion
- Severe non-compliance
- Lost to follow-up
- Patient withdrawal of consent
- A decision to modify or discontinue development of the drug

The EOT visit is to be completed within 3 days from the event resulting in treatment discontinuation (e.g., disease progression, AE, consent withdrawal, etc.). A Safety Follow up visit is to be completed 28 days after the last study drug dose. End of study (EOS) occurs when the patient is no longer being followed up for progression or survival (i.e. death, lost to follow-up, withdrawal of consent). The primary reason for a patient's discontinuation from treatment and withdrawal from the study is to be recorded in the electronic case report form (eCRF).

7.9. Withdrawal of Consent for Use of Donated Samples

Patients may withdraw consent for use of any tissue, fluid, or other biological samples they provide, without prejudice to their medical care, and without necessarily having to withdraw from the whole study.

If patients withdraw consent for use of donated samples, the Investigator must immediately notify the Sponsor or designee and ensure that any samples stored at the study site are disposed of or destroyed in a manner consistent with institutional policy, as promptly as possible, and such actions are recorded. The Sponsor or designee will, as promptly as possible, ensure that any samples stored outside of the study site are similarly disposed of or destroyed, document this action, and provide a copy of that documentation to the study site.

7.10. Incorrectly Enrolled Patients

If it is determined that any patient does not meet all inclusion criteria, or that any patient meets any exclusion criteria, or both, the patient should NOT receive any study drug, and should not receive any study assessments from that point on aside from those used to ensure patient safety.

If an ineligible patient has entered the study but has not yet received any study drug, the patient is to be withdrawn from the study, and may be replaced.

If an ineligible patient has entered the study and has received any amount of study drug, the Medical Monitor must be notified by the Investigator immediately. The SRC will convene to assess the specific patient risks and benefits of the case. The patient must be withdrawn from the study if the SRC determines it is in the patient's best interest.

7.11. Safety Review Committee

The SRC will consist of the Medical Monitor, who will chair the committee, and the Principal Investigator or delegate from each active study center. The study statistician will participate in the SRC during Phase 1. *Ad hoc* participants such as the clinical pharmacology scientist, and clinical operations leader may be invited as appropriate. Additional experts may be consulted by the SRC as needed. The SRC Charter for this study will define the exact membership and who should be present for decisions to be made.

The SRC has the responsibility for monitoring the clinical study's progress and the safety of the participating patients. After there are at least 2 evaluable patients for the first cohort and 3 evaluable patients for subsequent cohorts at each dose level during Phase 1 of the study, the SRC will review and assess all available safety data from the cohort together with available PK data and recommendations from the BLRM to make a decision on the dose for the next cohort of patients. The decision may be to:

- Proceed with dose escalation
- Expand the cohort to a maximum of 6 evaluable patients
- De-escalate the dose to a lower dose level (up to a maximum of 6 evaluable patients) or to an intermediate lower dose level
- Stop the dose escalation

When there are other patients that are ongoing at the time of this review, the SRC may decide to defer their decision until these further patients become evaluable.

Any patient started on treatment in error, i.e., he or she failed to comply with all of the selection criteria but meets the criteria of an evaluable patient, will be reviewed on a case by case basis by

the SRC to determine if the patient should be included or excluded in the decision for dose escalation.

The decisions and decision-making of the SRC on the next dose level will be documented by the Sponsor or designee and provided to the Investigators before dosing any new patients.

After identification of the MTD, the SRC will periodically review all safety data and available PK data to confirm that no unexpected, significant, or unacceptable risk to patients enrolled in the study has been discovered.

7.12. Investigator Compliance

Study centers that deviate significantly from the protocol without prior approval from the Sponsor and regulatory authorities may be discontinued from the study. The Investigator at each study center is responsible for ensuring the accuracy and completeness of all research records, the accountability of study drug, and the conduct of clinical and laboratory evaluations as outlined in the protocol.

7.13. Patient Adherence to Protocol Schedule

All patients are required to adhere to the protocol-specified visit schedule.

Permissible visit windows are specified in Table 2 and Table 3. Visit windows may be lengthened for administrative reasons (e.g., holidays) after consultation with the Medical Monitor.

On D1 of each cycle (i.e., study drug administration days), patients are to present to the study center, ideally within approximately 2 hours before study drug administration for pre-treatment assessments.

Additional study center visits may be scheduled, as deemed necessary based on the patient's clinical status.

An EOT visit should be conducted within 3 days of the event resulting in treatment discontinuation. A Safety Follow-up visit should be conducted 28 days (±3 days) after the last dose of study drug. Progression follow-up visits will occur until objective disease progression. Following disease progression, survival follow-up will occur every 3 months until death, lost to follow-up or consent withdrawal.

Failure to attend scheduled study visits within the protocol-specified windows may result in discontinuation from the study.

8. TREATMENT OF PATIENTS

8.1. Study Drug Supply

PEN-221 Concentrate for Solution for Injection/Infusion is a [redacted] solution containing PEN-221, a DM1-peptide drug conjugate with affinity for the human SSTR2 receptor, [redacted]

8.2. Study Drug Packaging and Labeling

Study drug labels will not bear any statement that is false or misleading in any manner or represents that the study drug is safe or effective for the purposes for which it is being investigated. The content of the labeling will be in accordance with applicable regulatory specifications and requirements.

8.3. Study Drug Storage

PEN-221 Concentrate for Solution for Injection/Infusion is to be stored [redacted], with temperature range per local guidance: In the United States, store per the USP guidance between [redacted]. In the United Kingdom, store per the ICH guidance between [redacted]. PEN-221 is [redacted]. PEN-221 is to be stored in a locked area, accessible only to appropriate study personnel.

8.4. Study Drug Accountability

Regulatory authorities require accounting of all investigational drug received by each study center. Records of drug disposition required include the date received by the center, date administered, quantity administered, and the patient to whom study drug was administered. The Investigator is responsible for the accountability of all used and unused study drug containers and unused study drug.

Each study center is to use a study drug accountability log to document study drug disposition. All items on this form are to be completed in full. A clinical research associate (CRA) representing the Sponsor is to approve the area where study drug is to be stored and accountability records are to be maintained.

The Investigator identification number and patient initials and identification number are to be recorded on each study drug accountability log. Each time study personnel dispense study drug for a patient, he or she is to record the date dispensed, amount of study drug dispensed, and his or her initials. Study personnel are to monitor the inventory of clinical supplies and maintain a count of all used and unused study drug. The CRA is to review study drug accountability records and remaining drug supplies during routine monitoring visits.

Partial vials left over after preparing patient treatments should be destroyed locally at site. A third party supplier for return and destruction should only be used where specific country regulations or local procedures state this is not possible.

8.5. Study Drug Dose Preparation

The PEN-221 dose is dependent on the cohort / study phase in which the patient is enrolled; see Section 8.6.1.

Refer to the Pharmacy Manual for details regarding study dose preparation and administration.

8.6. Study Drug Administration

Patients will receive PEN-221 via IV infusion over [redacted] on D1 of each treatment cycle. [redacted]

Clinicians should be prepared for an infusion-related reaction to occur during each PEN-221 drug administration, with frequent monitoring of vital signs, medical equipment, and supplies readily available and standing orders in place for immediate intervention. Patients must be monitored closely during the infusion and for at least 60 minutes following the end of the infusion, which may be characterized by fever, chills, dyspnea, hypertension or hypotension, tachycardia, or other symptoms associated with infusion-related reactions. See section 8.11.3.5 on dose modifications for infusion-related reactions, hypersentivity reactions.

Patients must be monitored closely during PEN-221 administration at the site of infusion for possible subcutaneous infiltration and related signs and symptoms.

8.6.1. Phase 1

8.6.1.1. Starting Dose and Dose Escalation Levels

The starting dose and dose escalation levels are presented in Section 5.1.3.1.

8.6.1.2. Dose Escalation Process (Phase 1)

The following procedure will be used for dose escalation/de-escalation decisions during the study.

1. The study will begin with a cohort size of 2 evaluable patients at dose 1 mg. All subsequent cohorts will have a size of at least 3 and up to 6 evaluable patients. The increase in dose between cohorts will be ≤100%.
2. Patients in Cohort 1 will be considered evaluable for dose determination if they experience a DLT from C1D1 through C2D8 or meet the minimum treatment and safety evaluation requirements from C1D1 through C2D8. Patients in subsequent cohorts will be considered as evaluable for dose determination if they experience a DLT during C1 or meet the minimum treatment and safety evaluation requirements through C1.
3. After completion of the DLT observation period by 2 patients for Cohort 1 and by at least 3 and up to 6 evaluable patients for subsequent cohorts, the 2-parameter BLRM with EWOC will be used to make recommendations about the next dose level, with the following exception:

If 2 patients in a cohort experience a DLT, further enrollment to the study will be suspended and the Bayesian model will be updated with this new information. If the Bayesian model supports enrolling the next cohort at the same dose level, or at a higher dose level, the relevant data and rationale will be discussed and agreed upon at the SRC. If the SRC agrees that it is medically appropriate to enroll an additional cohort at the same dose level, or at a higher dose level, the data and rationale supporting this decision will be provided to regulatory agencies, IRBs and ECs for their review and approval before proceeding with enrollment at the same or higher dose level.

4. Following the principle of EWOC, after each cohort of patients the recommended dose is the 1 with the highest posterior probability of the DLT rate falling in the target toxicity interval [0.16, 0.33) among the doses fulfilling the EWOC criteria. Per EWOC it should be unlikely (<25% posterior probability) that the DLT rate at the dose will exceed 0.33.
5. After repeating the preceding steps, the MTD is declared when at least 6 patients have been evaluated at the dose level recommended by the BLRM, and either of the following conditions is met:
    a. The posterior probability of targeted toxicity is at least 60% for this, or
    b. A minimum of 18 patients have already been treated in the study.

8.6.1.3. Dose Selection Process

At the end of each treatment cohort, the SRC will convene for a dose escalation teleconference. The clinical course for each patient in the current dose cohort will be presented and discussed in detail. Updated safety data on other ongoing patients, including data in later cycles, will be discussed as well.

All available toxicity information, PK, PDc, and anti-tumor activity information, as well as recommendations from the BLRM will be evaluated by the SRC in order to make a determine the dose regimen for the next cohort. The SRC must reach a consensus on whether to declare MTD, escalate the dose any further, or whether to de-escalate and/or expand recruitment into particular cohorts.

Dose levels presented in Table 6 are provisional. Dose decisions during escalation are however not limited to these doses. Based on the recommendation of the BLRM regarding the highest dose that is not to be exceeded at any decision point and the maximum increase in dose allowed by the protocol, intermediate doses may be administered to subsequent cohorts of patients.

Dose escalation may be terminated at any time based on emerging safety concerns without establishing the MTD.

The Sponsor or designee will prepare minutes from these meetings and circulate them to each Investigator for comment prior to finalization. Drug administration at the next dose level may not proceed until the Investigator receives written confirmation from the Sponsor or designee that the results of the previous dose level were evaluated and the higher dose level is estimated not to have exceeded the MTD.

8.6.2. Phase 2a

The RP2D will be the decision of the SRC and will be based on the findings of the safety, tolerability, PK, and PDc profile of PEN-221 during Phase 1. The RP2D may be re-evaluated by the SRC at any time based on emerging safety concerns but may not exceed the MTD established in Phase 1. See section 8.10.

8.7. Definition of Dose-Limiting Toxicity

A dose-limiting toxicity (DLT) is defined as any toxicity occurring within the first four weeks (i.e., up until C2D8) for patients in Cohort 1 and within the first three weeks (i.e., up until C2D1) for patients in subsequent cohorts that is not related to the underlying disease, disease progression, intercurrent illness, or concomitant medications, and that meets any of the following criteria:

1. Hematological toxicity:

   Grade 4 neutropenia (ANC < 500 cells/mm^3) lasting longer than 4 consecutive days

   Grade 3 neutropenia (ANC ≥ 500 to < 1000 cells/mm^3) of any duration associated with fever ≥ 38.5°C or systemic infection

   Grade 4 thrombocytopenia (< 25,000/mm^3) or Grade 3 thromobcytopenia (25,000 to <50,000/mm^3) associated with bleeding

2. Non-hematological toxicity ≥ CTCAE Grade 3 including:

   QTc prolongation (> 500 msec)

   Grade 3 increase in total bilirubin, ALT, AST or ALP

   ALT or AST ≥ 3× ULN and concomitant total bilirubin ≥ 2× ULN

   Refer to Section 10.2.2.3, for more detailed information about the review, assessment and reporting of cases that meet the criteria for potential Hy's Law.

3. Any other toxicity that:

   Is greater than that at baseline, is clinically significant and/or unacceptable, does not respond to supportive care, results in a disruption of PEN-221 dosing schedule of more than 2 weeks and/or is judged to be a DLT by the SRC

A DLT excludes:

1. Isolated laboratory changes of any grade without clinical sequelae or clinical significance with the exception of those laboratory changes outlined above
2. Grade 3 nausea, vomiting, diarrhea or dehydration that resolves to < Grade 3 within 48 hours of initiating supportive care treatment specified in Section 8.11.3.2
3. Grade 3 fever (in the absence of neutropenia), or fatigue that resolves to < Grade 3 within 72 hours.

8.8. Definition and Estimation of Maximum Tolerated Dose

The maximum tolerated dose (MTD) is the highest drug dosage not expected to cause dose-limiting toxicity (DLT) in more than 33% of the treated patients in the first 3 weeks of PEN-221 treatment (or in the first 4 weeks of PEN-221 treatment for Cohort 1 only).

A 2-parameter (BLRM) in conjunction with EWOC (Babb 1998; Neuenschwander 2008) will be used during the escalation phase to guide the selection of doses to investigate and for estimation of the MTD.

The general plan is that cohorts of patients will receive escalating doses of PEN-221 until the MTD is reached. Each cohort will consist of newly enrolled patients.

Estimation of the MTD will be based upon the estimation of the probability of DLT in C1 in patients in the dose-determining set (DDS). Details are described in Section 15.

8.9. Definition of Evaluable Patient

An evaluable patient is defined as a patient that has received PEN-221 and either:

- has completed minimum safety evaluation requirements during the first 21-day cycle, or
- has experienced a DLT during the first 21 day cycle.

8.10. Definition of Recommended Phase 2 Dose

The RP2D may be equal to or below the MTD. The RP2D will be determined by the SRC and will take into consideration the safety data from the patients treated in Phase 1, and, if appropriate, the early experience in Phase 2a. Additionally, observations related to PK, and any cumulative toxicity observed after multiple cycles may be included in the rationale supporting the RP2D.

8.11. Dose Modifications

All patients will receive PEN-221 at the prescribed dose in C1. After C1, if, in the Investigator's judgment, a patient experiences a clinical significant and/or unacceptable toxicity including a DLT not attributable to the disease or disease-related processes under investigation, dosing will be delayed and/or the subsequent dose will be reduced, and supportive therapy will be administered as required. Dose adjustments will be based on the organ system exhibiting the greatest degree of toxicity.

For individual patients, treatment for each new cycle will be delayed if the scheduled off-drug periods are not adequate to allow for recovery to ≤ Grade 1 or the baseline status of the patient; with the exception of fatigue, anorexia, and ALT and/or AST elevation that must have recovered to ≤ Grade 2 and be considered tolerable. Alopecia of any grade or duration will not lead to dose modification or treatment delay.

In Phase 1, patients who are at the lowest possible dose, i.e., in Cohort 1 or who have had their dose previously reduced to the Cohort 1 dose and who have demonstrated an acceptable response to dose interruption may re-start at either the provisional Cohort −1 dose level or the Cohort 1 dose level, at the discretion of the Investigator.

Any patient requiring a toxicity-related dose delay of more than 3 weeks from the intended day of the next scheduled dose must be discontinued from study treatment unless there is approval from the Medical Monitor for the patient to continue. Patients who discontinue from treatment should be observed until resolution of the toxicity.

Patients in Phase 1 and Phase 2a can have a maximum of 1 dose modification of study therapy throughout the course of the study for toxicities. Dose-re-escalation is not permitted. Patients who require more than 1 dose modification will be discontinued from the study.

8.11.1. Intra-patient Dose Escalation

During the Dose escalation phase only, if a patient is tolerating PEN-221 without evidence of PD, the patient may have the dose increased, starting on D1 of C3 or subsequent cycles, to a dose that has already been established as safe and tolerable by the SRC, with the agreement of the Medical Monitor. Patients who undergo intra-patient dose escalation will follow the schedule of safety assessments as outlined in C1 and C2, including PK assessments as outlined in C1D1, for the first 2 cycles of PEN-221 administered at the higher dose level.

Dose modification for toxicity will proceed according to guidelines detailed in Section 8.11.2 and Section 8.11.3.

8.11.2. Dose Modifications for Hematological Toxicities

Complete blood counts (CBC) will be monitored prior to treatment of each dose of PEN-221 and at regular intervals throughout the study (see Section 9.3.5.1). If hematological toxicity occurs, treatment should be held, and ANC, platelets and hemoglobin should be monitored at least weekly until recovery.

Hematological toxicities are to be treated as medically indicated. In addition, the measures listed in Table 7 are recommended.

Table 7: Dose Modifications and Management of Neutropenia, Febrile Neutropenia, Infection, Thrombocytopenia, and Anemia

AE	Action to be Taken
Grade 3/4 neutropenia lasting < 5 days	• Resume treatment at 100% dose, on schedule, with prophylactic granulocyte-colony stimulating factor (G-CSF) for subsequent treatment.
Grade 3/4 neutropenia lasting for ≥ 5 days Grade 3/4 neutropenia with oral temperature ≥ 38.5°C Infection (documented with Grade 3/4 neutropenia)	• Delay treatment for up to 3 weeks (i.e., up to 6 weeks after the previous study drug dose) until ANC is ≥ 1.5×10^9/L (and until infection has resolved completely). Once ANC returns to ≥ 1.5×10^9/L, resume study drug at the next lowest dose level with prophylactic G-CSF for subsequent treatment. • If G3/4 neutropenia recurs on the reduced dose or if ANC recovery to ≥ 1.5×10^9/L does not occur within 6 weeks of the previous study drug dose, then study drug is to be discontinued.
Grade 3/4 thrombocytopenia	• Delay treatment for up to 3 weeks until platelet count is ≥ 100×10^9/L. Once platelet count returns to ≥ 100×10^9/L, re-start study drug at the next lowest dose level. • If platelet count does not return to ≥ 100×10^9/L after delaying treatment for up to 3 weeks (i.e., within 6 weeks after the previous study drug dose), then study drug is to be discontinued.
Grade 2/3 anemia	• Delay treatment up to 3 weeks (i.e., within 6 weeks after the previous study drug dose) until hemoglobin returns to ≥ 9 g/dl. Once hemoglobin returns to ≥ 9 g/dl, re-start study drug at the next lowest dose level. • If hemoglobin does not return to ≥ 9 g/dl after delaying treatment for up to 3 weeks (i.e., within 6 weeks after the previous study drug dose), then study drug is to be discontinued.
Grade 4 anemia	• Discontinue study drug.

8.11.3. Dose modification for Non-hematologic Toxicities

8.11.3.1. Hepatic Toxicity

Serum transaminases and total and direct bilirubin will be monitored prior to treatment of each dose of PEN-221 and at regular intervals throughout the study (see Section 9.3.5.1). If elevations of transaminases or total and direct bilirubin are observed, PEN-221 dose delay, dose reduction or treatment discontinuation may be required as per guidelines below.

For ALT or AST > 2.5× ULN to ≤ 5× ULN delay treatment until recovers to ≤ 2.5× ULN and then treat at same dose level.

For ALT or AST > 5× ULN to ≤ 20× ULN (Grade 3) with or without concomitant elevation of bilirubin >1.5 × and < 2 × ULN, delay treatment until ALT/AST recovers to ≤ 2.5× ULN or baseline and bilirubin has returned to baseline, and then reduce 1 dose level.

For ALT or AST or ALP >20× ULN (Grade 4), discontinue treatment.

For total bilirubin > 1.5 to ≤ 3× ULN (Grade 2), delay treatment until recovers to Grade ≤ 1 and then treat at same dose level.

For total bilirubin > 3 to ≤ 10× ULN (Grade 3), and ALT or AST <3 × ULN, delay treatment until recovers to Grade ≤ 1 and then reduce 1 dose level.

For total bilirubin > 10× ULN (Grade 4), discontinue treatment.

For ALT or AST ≥ 3× ULN and total bilirubin ≥ 2× ULN (Hy's Law), discontinue treatment.

Refer to Section 10.2.2.3, for more detailed information about the review, assessment and reporting of cases that meet the criteria for potential Hy's Law.

8.11.3.2. Gastrointestinal Effects

8.11.3.2.1. Nausea and Vomiting

For ≤ Grade 2 nausea and vomiting, manage symptomatically and re-treat with no reduction of PEN-221 dose, on schedule. Refer to Section 8.12.3 for permitted medications.

For ≥ Grade 3 nausea and vomiting, manage symptomatically and delay treatment for up to 3 weeks until resolution to ≤ Grade 2 or baseline. Thereafter, re-start study drug at the next lowest dose level. If nausea and vomiting do not resolve to ≤ Grade 2 after a delay of up to 3 weeks (i.e., 6 weeks after the previous study drug dose), then study drug is to be discontinued.

8.11.3.2.2. Constipation

For ≤ Grade 2 constipation, manage symptomatically and re-treat with no reduction of PEN-221 dose, on schedule. Refer to Section 8.12.3 for permitted medications.

For ≥ Grade 3 constipation, manage symptomatically and delay treatment for up to 3 weeks until resolution to ≤ Grade 2 or baseline. Thereafter, re-start study drug at the next lowest dose level. If constipation does not resolve to ≤ Grade 2 after a delay of up to 3 weeks (i.e., 6 weeks after the previous study drug dose), then study drug is to be discontinued.

8.11.3.2.3. Diarrhea

For ≤ Grade 2 diarrhea, manage symptomatically and re-treat with no reduction of PEN-221 dose, on schedule. Refer to Section 8.12.3 for permitted medications.

For ≥ Grade 3 diarrhea, manage symptomatically and delay treatment for up to 3 weeks until resolution to ≤ Grade 2 or baseline. Thereafter, re-start study drug at the next lowest dose level. If diarrhea does not resolve to ≤ Grade 2 after a delay of up to 3 weeks (i.e., 6 weeks after the previous study drug dose), then study drug is to be discontinued.

8.11.3.3. Peripheral Neuropathy

For ≥ Grade 2 peripheral neuropathy, delay treatment for up to 3 weeks until resolution to ≤ Grade 1. Re-start study drug at the next lowest dose level.

If peripheral neuropathy does not resolve to ≤ Grade 1 after delaying treatment for up to 3 weeks (i.e., within 6 weeks after the previous study drug dose), then study drug is to be discontinued.

8.11.3.4. QTc Prolongation

For QTcF > 470 to ≤ 500 msec on the average of 3 consecutive readings taken pre-dose on any dosing day, delay treatment for up to 2 weeks and repeat QTcF testing on a subsequent day. If ≤ 470msec upon repeat testing on a subsequent day, resume treatment at the same dose level. If QTcF > 470 to ≤ 500 upon repeat testing, discontinue treatment.

If QTcF > 500 msec on the average of 3 consecutive readings taken at any time point during study, discontinue treatment.

8.11.3.5. Infusion-related Reactions, Hypersensitivity Reactions

Mild to moderate infusion-related reactions (i.e., NCI CTCAE Grades 1 and 2 and infusion reactions that do not involve symptoms of anaphylaxis) should be managed with temporary interruption of the infusion and medical management of symptoms, as per institutional guidelines. After all symptoms have resolved, re-challenge with a reduced infusion rate and additional premedication is permitted.

Severe infusion-related reactions (NCI CTCAE Grade 3 or higher) or reactions with any features of anaphylaxis require immediate discontinuation of the study drug infusion, immediate treatment with epinephrine and antihistamines and additional management per institutional guidelines. Following a severe infusion-related reaction or suspected anaphylaxis, re-challenge with PEN-221 is not permitted; therefore, the patient must permanently discontinue study treatment.

8.11.3.6. Other Non-hematologic Toxicities

For all other Grade 3 – 4 toxicities other than those described above, delay treatment with PEN-221 (max up to 3 weeks) until resolved to ≤ Grade 1 or baseline, and resume at next lowest dose level.

If Grade 3 – 4 toxicity recurs, permanently discontinue treatment.

For all other Grade <3 toxicity, decision to delay PEN-221 for a maximum of 3 weeks is at the Investigator's discretion. PEN-221 will resume at the same dose or at the next lowest dose level prior to interruption, at the Investigator's discretion.

8.12. Concomitant Medications

All prescription and non-prescription medications and therapies, including pharmacologic doses of vitamins, herbal medicines, or other non-traditional medicines, taken from 30 days prior to the first dose of PEN-221 through the EOT visit must be recorded in the eCRF. On PK sample collection days, both the date and time of concomitant medications and therapies must be recorded.

8.12.1. Prohibited Medications

The following medications and treatments are prohibited during study participation.

- Concomitant use of strong CYP3A4 inhibitors (such as ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, and voriconazole). DM1, the cytotoxic component of PEN-221, is metabolized in vitro mainly by CYP3A4 and to a lesser extent by CYP3A5 [(KADCYLA® (ado-trastuzumab emtansine) package insert, Genentech, Inc., South San Francisco, CA]. Therefore, concomitant use of strong CYP3A4 inhibitors is prohibited due to the potential for an increase in DM1 exposure and toxicity. The use of aprepitant (EMEND®), a substrate, moderate inhibitor and inducer of CYP3A4, is **NOT** permitted.
- Any investigational agent or device other than PEN-221, including agents that are commercially available for indications other than the patient's solid tumor that are under investigation for the treatment of solid tumors.
- Any radiotherapy, chemotherapy, anti-neoplastic treatments or investigational agents other than study drug. Radiation for palliation at focal sites may be permitted after discussion between the Investigator and Medical Monitor.
- Live virus and bacterial vaccines should not be administered, e.g., yellow fever, measles, influenza, rubella, mumps, typhoid, mycobacterium tuberculosis (BCG), Yersinia pestis (EV). An increased risk of infection by the administration of these vaccines has been observed with conventional chemotherapy and the effects with PEN-221 are unknown. The administration of killed vaccines is allowed. Examples of killed vaccines are cholera, bubonic plague, polio vaccine, hepatitis A and rabies.

Other medications, other than those described above, which are considered necessary for the patient's safety and well-being, may be given at the discretion of the Investigator and recorded in the appropriate sections of the eCRF.

8.12.2. Medications to be Used with Caution

The following medications should be used with caution during study participation:

- **Anti-hyperglycemic medications**: Somatostatin analogs inhibit the secretion of insulin and glucagon, which may result in hypoglycemia or hyperglycemia. Due to the similarity between somatostatin and the peptide component of PEN-221, dose adjustments of concomitant antihyperglycemic medications may be necessary in patients being treated with PEN-221.
- **Bradycardia-inducing drugs:** Concomitant administration of bradycardia-inducing drugs (e.g., beta-blockers) may have an additive effect on the reduction of heart rate associated with somatostatin analogs. Due to the similarity between somatostatin and the peptide component of PEN-221, dose adjustments of concomitant bradycardia-inducing drugs may be necessary in patients being treated with PEN-221.
- **Orally administered medications:** Somatostatin analogs may reduce the intestinal absorption of concomitant medications. Due to the similarity between somatostatin

and the peptide component of PEN-221, there is a possibility that PEN-221 may reduce the intestinal absorption of concomitant medications.

8.12.3. Permitted Medications

Patients are permitted to receive appropriate supportive care measures as deemed necessary by the treating physician including but not limited to the items outlined below:

- **Nausea/vomiting:** Anti-emetic treatment such as with 5-HT_3 receptor antagonists is to be administered according to the guidelines of the study centers. Patients should be strongly encouraged to maintain liberal oral fluid intake. Strong consideration should be given to the administration of prophylactic anti-emetic therapy according to standard institutional practice, after the first cycle of PEN-221. The use of aprepitant (EMEND®), a substrate, moderate inhibitor and inducer of CYP3A4, is **NOT** permitted.
- **Diarrhea**: Diarrhea should be treated promptly with appropriate supportive care, including administration of an anti-diarrheal agent according to standard practice guidelines. Anti-diarrheal agents should not be taken prophylactically. Patients should be instructed to begin taking anti-diarrheal medication at the first sign of: 1) poorly formed or loose stool, 2) occurrence of more bowel movements than usual in 1 day, or 3) unusually high volume of stool. Anti-diarrheal agents should be deferred if blood or mucus is present in the stool or if diarrhea is accompanied by fever. In this setting, appropriate diagnostic microbiologic specimens should be obtained to exclude an infectious etiology. Patients should also be advised to drink liberal quantities of clear fluids to help prevent dehydration.
- **Constipation:** Contipation may be treated with stool softeners or lubricants. Use of osmotics is allowed with careful monitoring of electrolytes.
- **Anemia:** Transfusions and/or erythropoietin may be used as clinically indicated for the treatment of anemia, but should be clearly noted as concomitant medications. Patients already receiving erythropoietin at the time of screening for the study may continue it providing they have been receiving it for more than 1 month at the time study treatment is started. Prophylactic erythropoietin should not be started during C1 of the study, but may be started during C2 and thereafter.
- **Neutropenia:** Patients who experience Grade 4 neutropenia lasting for ≥ 5 days; Grade 3/4 neutropenia with oral temperature ≥ 38.5°C; or infection with Grade 3/4 neutropenia may receive treatment with colony-stimulating factors as described in Section 8.11.2. Prophylactic use of colony-stimulating factors including G-CSF, pegylated G-CSF or GM-CSF may be used according to institutional standards after the first cycle of PEN-221 therapy.
- **Somatostatin analogs:** Agents such as octreotide, lanreotide, pasireotide, and other somatostatin analogs are permitted if their use is providing benefit in controlling carcinoid symptoms.

Medications and treatments other than those specified in Section 8.12.1, including palliative and supportive care for disease-related symptoms, are permitted during the study, as appropriate.

9. ASSESSMENT OF PATIENTS

9.1. Demographics and Medical History

9.1.1. Demographics

Patient demographics, including age, sex, race, and ethnicity, are to be documented during screening.

9.1.2. Medical History, Including Cancer History

A complete medical history is to be documented during screening and updated at baseline, prior to administration of the first PEN-221 dose.

The medical history is to include cancer history, including the patient's primary tumor type, current disease stage, date of and disease stage at diagnosis, method of diagnosis, and all previous treatments, including systemic therapy, radiation therapy, and surgeries, as well as response to such treatments.

Each patient's history of somatostatin analog treatment (start and stop dates, agents, doses), and results of any somatostatin analog imaging will be collected.

As part of the patient's cancer history, study centers are to submit a local histology or cytology report obtained prior to enrollment, if available. Furthermore, paraffin blocks (preferred) or a minimum of 10 unstained slides of available archival tumor tissue are to be requested from the patient's local institution and collected, if available.

9.2. Somatostatin Analog Radioisotope Imaging

Those patients who do not have documented results of a historically positive SARI obtained within 180 days of C1D1 will be prescreened by SARI in this study to ensure their neuroendocrine tumors express somatostatin receptor prior to entering screening and prior to receiving PEN-221. This pre-screening must be performed using only SARI with regional marketing authorization to be used for detection and localization of somatostatin-receptor-positive tumors. If multiple kits with marketing authorization are available, any method may be used at the discretion of the Investigator. Patients with documentation of a historically positive SARI (by ^{111}In, ^{68}Ga, ^{99}mTc, or other radioisotope linked to a somatostatin analog) within 180 days of C1D1 to be considered positive for SSTR2 expression, and will not be required to receive SARI during pre-screening in this study.

The current state of neuroendocrine tumor imaging has recently been reviewed by Brabander (2015).

9.2.1. Indium-labeled SARI

Octreoscan™ Kit for the Preparation of Indium In 111 Pentetreotide (pentetreotide scanning) (Mallinckrodt Nuclear Medicine LLC, Maryland Heights MO USA) comprises 2 parts: a 10 ml reaction vial and a 10 ml vial of ^{111}In chloride (Mallinckrodt 2015). The imaging agent is prepared within 6 h prior to use by combining the two components according to package directions to produce ^{111}In pentetreotide. At time of calibration, the kit contains 111 MBq/ml (3.0 mCi/ml) ^{111}In, with a half-life of 2.8 d.

The scan should be performed according to institutional guidelines and manufacturer instructions. FOCBP should be tested for pregnancy and excluded if pregnant. Additional practice guidelines should also be reviewed (Balon 2011). Immediately prior to use, labeling yield must be determined according to package directions. The evening prior to ^{111}In pentetreotide administration, a mild laxative such as bisacodyl or lactulose should be given and continued for 48 h. Both prior to and after administration, patients should be well hydrated, and should be encouraged to drink fluids liberally to reduce radiation dose by flushing out unbound agent through the kidneys as well as to ensure proper bowel cleansing. Although imaging can be performed by both planar and single-photon emission computed tomography (SPECT) cameras, only SPECT imaging should be used for scans performed in this study due to its 3-dimensional capabilities, superior sensitivity, and ability to more precisely allow tumor localization for possible comparision with CT or MRI scans. The recommended radiation dose for SPECT imaging is 222 MBq (6.0) mCi of ^{111}In pentetreotide, and the expected effective dose equivalent is 26 mSv.

Typically, imaging is performed 4 h and 24 h after administration of ^{111}In pentetreotide. In some cases, images taken after 48 h are also useful to aid interpretation. Investigators and designees should follow standard practice for imaging time points.

Scans are to be scored in relation to non-diseased areas of liver as described by Kwekkeboom (2005) and listed in Table 8 .

Table 8: Octreoscan SSTR2 Scoring

Score	Description
1	^{111}In pentetreotide uptake lower than normal liver tissue
2	^{111}In pentetreotide uptake equal to normal liver tissue
3	^{111}In pentetreotide uptake greater than normal liver tissue
4	^{111}In pentetreotide uptake greater than normal spleen or kidney uptake

SCLC patients are considered to have a positive Octreoscan if their score from Table 8 is 2, 3, or 4. All other patients are considered to have a positive Octreoscan if their score from Table 8 is 3 or 4.

According to the manufacturer (Mallinckrodt 2015), the hormonal effect of ^{111}In pentetreotide is 1/10 that of octreotide. Since imaging doses are less than therapeutic doses of somatostatin analogs, the agent is not expected to exert clinically significant somatostatin effects in most cases, although severe hypoglycemia can occur in patients with insulinomas. An IV glucose solution should be administered just before and during administration in patients suspected of having an insulinoma.

In a clinical study, 83 of 87 patients (95%) who received octreotide therapy within 72 h of ^{111}In pentetreotide were successfully imaged. Nevertheless, imaging sensitivity may be reduced in patients concurrently receiving therapeutic doses of short-acting somatostatin therapy, so this should be considered in timing ^{111}In pentetreotide administration.

As ^{111}In pentetreotide is eliminated primarily by the kidneys, use in patients with renal impairment should be considered carefully.

Adverse reactions associated with ^{111}In pentetreotide (<1% in clinical trials of 538 patients) included dizziness, fever, flush, headache, hypotension, changes in liver enzymes, joint pain, nausea, sweating, weakness, a single case of bradycardia, and a single case of decreased hemoglobin and hematocrit.

9.2.2. Gallium-labeled SARI

SARI with ^{68}Ga derivatives of somatostatin analogs has been practiced since at least 2001 (Hofmann 2001). ^{68}Ga-DOTATATE and ^{68}Ga-DOTATOC are commonly used. Compared with PEN-221, they have the following affinity profiles (half-maximal inhibitory concentrations) to various human somatostatin receptors (Table 9):

Table 9: Affinity Profiles (Half-maximal Inhibitory Concentrations) for Various Somatostatin Analogs

	SSTR1	SSTR2	SSTR3	SSTR4	SSTR5
^{111}In pentetreotide[a]	>10 000	22	182	>1 000	237
^{68}Ga-DOTATATE[a]	>10 000	0.2	>1 000	300	377
^{68}Ga-DOTATOC[a]	>10 000	2.5	613	>1 000	73
PEN-221[b]	380	0.042	58	>1 000	24

[a] Data from (Reubi 2000)
[b] Data from internal Tarveda report PEN-221-PHARM-026

^{68}Ga is produced from a cyclotron, or collected from a Ge-Ga generator. It is then combined with somatostatin analogs, for example, as described by Mukherjee (2014). The resulting imaging agent is administered to patients and, almost immediately thereafter, imaged using concurrent positron emission tomography (PET) and CT.

Lesions can be assigned standardized uptake values; however, a patient can be classified as positive overall using the scheme outlined in Table 8 .

9.3. Safety Assessments

9.3.1. Physical Examination

Complete physical examinations are to be performed at the time points designated in Table 2 and Table 3. Complete physical examinations include assessment of the following:

- General appearance
- Head, eyes, ears, nose, and throat
- Cardiovascular system
- Respiratory system
- Chest
- Gastrointestinal system (abdomen)

- Lymphatic system
- Musculoskeletal system
- Skin
- Psychiatric
- Neurological:
  A thorough neurological assessment must be performed as part of the complete physical exam at the time points designated in Table 2 and Table 3 as microtubule disrupting agents including DM1 may be associated with sensory and/or motor peripheral neuropathies and these effects may be cumulative with dose.

  Neurological assessments should include questioning regarding whether the patient is experiencing any numbness, tingling, burning, or pain, or any sensation of weakness or difficulty performing daily activities. Exam to include light touch, sharp touch [skin prick], temperature, proprioception, and vibration sensation testing, as well as testing of deep tendon reflexes. Additional neurological assessments are to be performed as appropriate for the patient's condition, at the Investigator's discretion.

Symptom-directed (i.e., abbreviated) physical examinations are to be conducted at all other study visits.

On dosing days, physical examinations should be completed prior to infusion. Abnormal physical examination findings that are considered by the Investigator to be clinically significant for a particular patient during screening and before dosing on C1D1 are to be reported as part of the patient's medical history. Abnormal, clinically significant examination findings following initiation of dosing on C1D1 are to be reported as an AE, if the finding represents a change from baseline.

9.3.2. Vital Signs

Vital signs, including blood pressure, pulse, respiration rate, and body temperature, are to be measured at the time points designated in Table 2 and Table 3.

During screening, pulse rate and blood pressure will be measured across 3 positions: supine, sitting and standing, after at least 10 minutes rest.

On C1D1 and D1 of subsequent cycles (dosing days), vital signs are to be measured prior to the start of study drug infusion and at 15 minute intervals throughout the infusion and for 1 hour after end of infusion. Pulse rate and blood pressure immediately prior to dosing will be measured across 3 positions: supine, sitting and standing. Other timepoints may be collected in 1 position only. If no notable changes in vital signs are observed, no additional vital sign measurements will be performed subsequent to 1 hour post end of infusion. If notable changes are observed, vital signs will be taken every hour for the next 6 hours, or longer if changes persist.

For any patients on concomitant beta blockers, blood pressure should be monitored carefully and doses of these medications should be adjusted if needed, as somatostatin analogs have been associated with bradycardia.

Abnormal, clinically significant vital signs results are to be reported as AEs, if the finding represents a change from baseline.

9.3.3. Weight and Height

Height is to be measured for all patients during screening.

Body weight is to be measured at the time points designated in Table 2 and Table 3 and at any time the Investigator suspects the patient has experienced a notable change in weight (±10%).

9.3.4. Electrocardiogram

A 12-lead ECG, measuring rhythm, QT, QRS, PR, and R-R intervals, is to be collected with the patient lying face-up at the time points designated in Table 2 and Table 3. Triplicate ECGs are to be collected approximately 5 minutes apart at all time points. On C1D1 (and during Phase 1 only, also on C3D1), ECGs are to be performed immediately prior to the start of study drug infusion, at 30 minutes after the start of the infusion, (±5 minutes), at the end of infusion (±5 minutes), and at all scheduled PK time points thereafter; the date and time of each ECG start and stop are to be documented. On all other dosing days, ECGs should be performed immediately prior to infusion and at end of infusion (±5 minutes). ECGs should be performed after the PK and glucose monitoring.

The Investigator or designated physician will review all ECGs and see that any significant abnormalities are under appropriate management.

9.3.5. Laboratory Assessments

Laboratory assessments for hematology, clinical chemistries, coagulation studies, urinalysis and pregnancy testing will be performed by the local laboratory.

Abnormal, clinically significant laboratory abnormalities are to be reported as AEs, if the findings represent a change from baseline.

9.3.5.1. Hematology and Clinical Chemistries

Blood samples for hematology and clinical chemistries are to be collected at the time points designated in Table 2 and Table 3. If the screening sample is collected within 3 days before C1D1, a sample need not be collected on C1D1. After C1D1, samples may be collected up to 48 hours before scheduled study center visits. Hematology and clinical chemistry results must be reviewed by the Investigator prior to study drug administration. If any clinically relevant hematology or clinical chemistry abnormalities are identified after the patient leaves the study center, the patient is to be contacted and appropriate follow-up performed.

On C1D1, glucose will be monitored pre-dose and at the end of infusion (±3 minute); and 2 hours (±10 minutes), 4 hours (±10 minutes), 6 hours (±10 minutes), and 8 hours (±30 minutes) after the start of study drug infusion and for Phase 1 only at 10 hours (±30 minutes) after the start of study drug infusion (Table 2 and Table 3). If the patient experiences symptomatic hypoglycemia or hyperglycemia, or if any glucose level falls below 55 mg/dL (or below 3.0 mmol/L) or above 250 mg/dL (or above 13.9 mmol/L) at any timepoint on C1D1, additional monitoring may be required per Investigator discretion. When multiple study assessments are scheduled at the same time, glucose monitoring should be done after PK blood collection and prior to ECGs.

For any patients on concomitant anti-hyperglycemic medications, glucose should be monitored carefully and doses of these medications should be adjusted if needed, as somatostatin analogs have been associated with changes in blood glucose levels and regulation.

The following clinical laboratory parameters are to be measured:

Hematology	
RBC count	Platelet count
Hemoglobin	White blood cell count with differential
Chemistry	
Chloride	Bicarbonate
Sodium	Potassium
Calcium	Phosphorus
Blood urea nitrogen (BUN)	Magnesium
Glucose	Creatinine (with calculated creatinine clearance)*
ALP	Albumin
ALT	AST
Total protein	Total and direct bilirubin
Cholesterol and triglycerides (fasting)	Thyroid function (TSH and free T4)
Amylase	Lipase
Cortisol	

*Creatinine clearance is to be estimated using the Cockcroft-Gault formula

For Phase 2a, D8 and D15 evaluations are required for C1. If no Grade 2 or higher abnormalities in clinical chemistries or hematology parameters are observed during C1, then D8 and D15 evaluations are not required for C2 and subsequent cycles. If Grade 2 or higher abnormalities in clinical chemistries or hematology parameters (excluding hyperglycemia in diabetic patients) are observed during C1, the D8 and D15 evaluations are required for C2 and C3. If Grade 2 or higher abnormalities do not recur during C2 and C3, the D8 and D15 evaluations may be eliminated in cycles thereafter, subject to Investigator discretion. If Grade 2 or higher abnormalities occur after C3, evaluations may be performed at a schedule determined by the Investigator, based on the patient's clinical status.

9.3.5.2. Urinalysis

Urine for urinalysis is to be collected at the time points designated in Table 2 and Table 3. If the screening sample is collected within 3 days before C1D1, a sample need not be collected on C1D1.

The following urinalysis parameters are to be determined:

Urinalysis

Specific gravity	Protein
pH	Ketones
Blood	Microscopic examination of sediment
Glucose	

9.3.5.3. Coagulation Studies

Blood samples for coagulations studies, including PT and aPTT, along with international normalized ratio for patients on Coumadin or warfarin only, are to be collected at the time points designated in Table 2 and Table 3. If the screening sample is collected within 3 days before C1D1, a sample need not be collected on C1D1.

9.3.5.4. Peripheral Blood Anti-drug Antibodies

Blood samples for anti-drug antibody assay are to be collected at the time points designated in Table 2 and Table 3.

9.3.5.5. Pregnancy Testing

Serum samples for HCG pregnancy testing are to be collected from females of childbearing potential (FOCBP) at the time points designated in Table 2. and Table 3. If the screening sample is collected within 3 days before C1D1, a sample need not be collected on C1D1. Alternatively, urine dip stick testing can be performed instead, at the discretion of the Investigator and institutional policy.

As HCG can be secreted by neuroendocrine tumors, in the event of a positive pregnancy test, pregnancy is to be assessed by transvaginal ultrasound overseen by a health care professional with experience in investigating and diagnosing early pregnancy.

Pregnancy testing is to be repeated any time pregnancy is suspected.

A FOCBP is defined as any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral oophorectomy, bilateral salpingectomy but not tubal ligaton) or is not postmenopausal (defined as age ≥ 50 years and amenorrheic ≥ 12 consecutive months; or amenorrheic ≥ 12 consecutive months and serum follicle-stimulating hormone, luteinizing hormone and plasma estradiol levels in the postmenopausal range for the institution). Women who are using oral, implanted, or injectable contraceptive hormones or mechanical products, such as an intrauterine device or barrier methods (diaphragm, condoms, spermicides) to prevent pregnancy, are practicing abstinence, or whose partner is sterile (e.g., vasectomy), are considered to be of childbearing potential.

Prior to study enrollment, FOCBP must be advised of the importance of avoiding pregnancy during study participation and the potential risk factors for an unintentional pregnancy. This information will be included in the ICF that must be signed by the patient. In addition, all FOCBP or fertile men with partners of childbearing potential should be instructed to contact the Investigator immediately if they suspect they or their partner might be pregnant (e.g., missed or late menstrual period) at any time during study participation.

Accordingly, the patient must agree to highly effective contraception (as defined in inclusion criterion 6) from 14 days before C1D1 through 3 months after the last study drug dose.

Patients with a positive pregnancy test result during screening or on C1D1 are not eligible for study participation, unless pregnancy is ruled out by transvaginal ultrasound. Patients with positive results any time after the start of study drug administration are to have a transvaginal ultrasound overseen by a health care professional with experience in investigating and diagnosing early pregnancy to confirm or rule out pregnancy, and if positive, study drug is to be permanently discontinued. Refer to Section 10.4 for details regarding management of any pregnancies during the study.

9.3.6. ECOG Performance Status

ECOG performance status is to be determined at the time points designated in Table 2 and Table 3.

The ECOG performance status scale is presented in Table 10.

Table 10: Eastern Cooperative Oncology Group Performance Status Scale

ECOG (Oken 1982)	
Score	Criterion
0	Fully active, able to carry out all pre-disease activities without restrictions
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature eg, light housework, office work
2	Ambulatory and capable of self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled, cannot carry on self-care, totally confined to bed or chair

9.3.7. Adverse Events

Each patient must be carefully monitored for the development of any AEs. This information should be obtained in the form of non-leading questions (e.g., “How are you feeling?”) and from signs and symptoms detected during each examination, observations of study personnel, and spontaneous reports from patients.

Refer to Section 10 for details regarding AE definitions, recording, and reporting.

9.3.8. Concomitant Medications

Patients should be asked at each clinic about the medications they are taking, including any new medications they have started or stopped as well as any missed doses. In addition, the patient’s medical record and records of any hospitalizations should be reviewed to ensure all drugs the patient is taking are listed.

Medications include prescription and over-the-counter medicines, herbal supplements, and vitamin and mineral supplements (excludes once-daily multivitamins).

9.3.9. Evaluation of Safety Information Collected at Each Visit

At the end of each clinic visit, the Investigator or designee must review the safety assessments collected that day that are available (ECGs, vital signs, available blood labs, etc.) to ensure it is safe for the patient to leave the clinic.

9.4. Pharmacokinetic Assessments

For C1D1 (and C3D1 [Phase1 only]), venous blood samples (4 – 6 ml) for determination of PEN-221, the somatostatin analog peptide component of PEN-221 (BT-979), and DM1 (total, unconjugated, and free sulfhydryl) will be taken before the start of the infusion, at 0.5 hours (±5 minutes) after the start of study drug infusion; precisely at the end of infusion (±1 minute); and 1.5 hours (±10 minutes), 2 hours (±10 minutes), 4 hours (±10 minutes), 6 hours (±10 minutes), 8 hours (±30 minutes), (and 10 hours (±60 minutes) after the start of study drug infusion [Phase 1 only]). If the 10 hour time point requires an inpatient admission at the center, the 10 hour time point will not be collected.

For Phase 2a, additional timepoint(s) will be taken on C1D2 within 24 hours (±120 minutes) of treatment initiation, and at any time on C1D8.

If the study drug infusion is interrupted and re-started for any reason, then the time of interruption and re-start of infusion should be recorded, a second pre-dose (time zero) time point should be collected just prior to re-start of the infusion, and subsequent sampling time points should then be adjusted to follow the above schedule in relation to the time of the re-start of the infusion.

When multiple study assessments are scheduled at the same time, PK blood draws should be done prior to glucose monitoring and ECGs. The date and time of collection of each sample will be recorded. Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

9.5. Biomarker and Pharmacodynamic Assessments

[redacted]

[redacted]

9.5.5. Archival Tumor Sample

Whenever available, an archived formalin-fixed paraffin-embedded (FFPE) sample or samples of the patient's tumor prior to treatment with PEN-221 will be collected for retrospective analysis of SSTR2 expression by IHC. If tumor blocks are not available, slides may be provided; 10 slides are requested, if available.

9.5.6. Optional Tumor Biopsy

A biopsy procedure will be performed only for patients who sign the provision of optional tumor biopsy on the Screening informed consent form (ICF) to undergo a tumor biopsy during the Screening phase and who meet the additional eligibility criterion in Section 7.3. Such patients must have at least 1 site of tumor that is accessible to biopsy and that is considered by the Investigator to be low risk and of sufficient size to undergo a biopsy procedure. Consent for this tumor biopsy is voluntary and optional and at the discretion of both the patient and the Investigator. The procedure will be performed during screening (within 14 days prior to C1D1) as indicated in Table 2 and Table 3 and a FFPE sample of the patient's tumor specimen will be collected for retrospective analysis of SSTR2 expression by IHC.

It is requested but not required that two cores be collected during the procedure, if feasible, for the purpose of aiding in the assessment of possible intratumoral heterogeneity of SSTR2 expression. Samples should be provided as FFPE blocks wherever possible.

[redacted]

9.6. Efficacy Assessments

Tumor measurements and disease response assessments are to be performed for all patients. Tumor evaluation studies are to be performed during screening within 28 days before C1D1. For patients with SCLC or LCNEC of the lung, disease response assessments are to be performed within 7 days of the first study drug dose in every other cycle, starting before C3. For all other patients, disease response assessments are to be performed within 7 days of the first study drug dose in every 3rd cycle, starting before C4. All patients that discontinue treatment for reasons other than radiographic progression of disease will be followed for disease progression (Progression follow-up). SCLC and LCNEC of the lung patients will be followed approximately every 6 weeks from their last tumor assessment, or as clinically indicated. Other patients will be followed approximately every 9 weeks from their last tumor assessment, or as clinically indicated. Upon disease progression, all patients will be followed approximately every 3 months from the date of progression to assess survival status and the date and cause of death (if known) will be recorded for patients who died.

All sites of disease should be imaged by CT or MRI. Subsequent assessments should use the same radiographic methods as used during screening. Anatomical measurements (summed across target lesions) will be documented during screening and each subsequent evaluation. When possible, the same qualified physician will interpret results to reduce variability. Radiographic images will be maintained at the study center and test results and Investigator's findings will be filed in the patient's source documents.

Patients in Phase 1 are not required to have measurable disease. Patients in Phase 2a are required to have measurable disease. De-identified results of radiographic tumor evaluations performed prior to study entry and/or during study, such as radiologists' reports or electronic copies of CT and MRI scans may be requested by the Sponsor for independent review of tumor response.

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

Measurable versus non-measurable

- Measurable: lesions that could accurately be measured in at least 1 dimension as ≥10 mm by CT scan or caliper measurement by clinical examination or ≥20 mm by chest X-ray; the longest diameter is to be recorded. For malignant lymph nodes, a node must be ≥15 mm in *short* axis by CT scan
- Non-measurable: all other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) and truly non-measurable lesions.

Target versus non-target

- Target: all measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, are to be identified as target lesions and measured and recorded at screening. Target lesions are to be selected on the basis of their size (i.e., those with the longest diameter) and suitability for accurate repeated measurement. The sum of the longest diameter for all target lesions is to be calculated and recorded in the eCRF as the baseline sum longest diameter.

- Non-target: all other lesions not classified as target lesions (or sites of disease) are to be identified as non-target lesions and are to be recorded in the eCRF. Measurement of non-target lesions is not required.

Disease response in target and non-target lesions will be assessed by the Investigator using RECIST 1.1, according to the categories and criteria described in Table 11. The best overall response for each patient will be reported as the best response documented over the sequence of objective statuses recorded using the categories and criteria in Table 12.

Table 11 Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 Guidelines for Tumor Response

Disease Response Criteria for Target and Nontarget Lesions	
Evaluation of Target lesions	
Complete Response (CR):	Disappearance of all target lesions.
Partial Response (PR):	At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD.
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.
Progressive Disease (PD):	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of 1 or more new lesions.
Evaluation of Nontarget lesions	
Complete Response (CR):	Disappearance of all nontarget lesions and normalization of tumor marker level.
Incomplete Response/ Stable Disease (SD):	Persistence of 1 or more nontarget lesion(s) or/and maintenance of tumor marker level above the normal limits.
Progressive Disease (PD):	Appearance of 1 or more new lesions and/or unequivocal progression of existing nontarget lesions.

Source: (Eisenhauer 2009) Available at: http://www.eortc.be/recist/documents/RECISTGuidelines.pdf
Key: LD = longest diameter.

Table 12 Overall Response Criteria

Patients with Target and Nontarget Lesions			
Target Lesions	**Non-Target Lesions**	**New Lesions**	**Overall Response**
CR	CR	No	CR
CR	Non-CR / Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not evaluated	Non-PD	No	NE
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

Patients with Nontarget Lesions Only		
Non-Target Lesions	**New Lesions**	**Overall Response**
CR	No	CR
Non-CR / Non-PD	No	Non-CR / Non-PD
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

Source: (Eisenhauer 2009) Available at: http://www.eortc.be/recist/documents/RECISTGuidelines.pdf
Key: CR = complete response; NE = inevaluable; PD = progressive disease.

Any patient with a PR or CR by RECIST 1.1 is to have repeat assessments performed approximately 6 weeks later (and no sooner than 4 weeks from the prior assessment) to confirm the response. Following the confirmatory assessment, the response assessment schedule will resume at intervals of every other cycle for SCLC or LCNEC of the lung patients, and every third cycle for all other patients.

10. ADVERSE EVENT DEFINITIONS, RECORDING, AND REPORTING

10.1. Definition of Adverse Events

10.1.1. Adverse Events

Adverse event (AE) means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related. An AE can therefore be any unfavorable and unintended sign (including abnormal laboratory findings), symptom, or disease temporally associated with the use of an investigational product, and does not imply any judgment about causality.

For the purposes of this study, death and disease progression (i.e., PD) are not considered AEs and should not be reported as such. Death is considered an outcome of 1 or more primary AEs, and PD is considered a worsening of underlying disease and is a criterion for study drug discontinuation. **Events that are unequivocally due to disease progression should not be reported as AEs during the study.**

10.1.2. Unexpected Adverse Event

An AE or suspected adverse reaction is considered "unexpected" if it is not listed in the current Investigator Brochure or is not listed at the specificity or severity that has been observed. "Unexpected" also refers to AEs or suspected adverse reactions that are mentioned in the Investigator Brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

10.1.3. Serious Adverse Event

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

- Death.
- A life-threatening AE. Life-threatening means that, in the view of either the Investigator or the Sponsor, its occurrence places the patient at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.
- In-patient hospitalization or prolongation of existing hospitalization. Hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned prior to study entry are not considered AEs if the illness or disease existed before the patient was enrolled in the study, provided that it did not deteriorate in an unexpected manner during the study (e.g., surgery performed earlier than planned). Additional exclusions to serious adverse event (SAE) reporting include hospitalizations for:
    - Elective procedures.
    - Social/administrative reasons in the absence of an AE.

  - Expected deterioration caused by PD.
- A persistent or significant disruption of a person's ability to conduct normal life functions.
- A congenital anomaly/birth defect.
- An important medical event that may not result in death, be life-threatening, or require hospitalization but may be considered serious when, based upon appropriate medical judgment, it may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this for SAEs. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in in-patient hospitalization, or the development of drug dependency or drug abuse.

All SAEs that occur after signing of study-related informed consent, whether or not the SAEs are related to the study drug, must be reported. (As stated in Section 10.1.1, only PD with an outcome of death is to be reported as an SAE.)

If an Investigator learns of any SAEs, including death, at any time after a patient has completed the study and he/she considers there is a reasonable possibility that the event is related to PEN-221, the Investigator should notify the Sponsor.

10.2. Adverse Event Assessment

10.2.1. Intensity

The intensity of each AE is to be assessed by the Investigator according to the NCI CTCAE, Version 4.03 (see http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf).

10.2.2. Relationship to Study Drug

The Investigator will assess causal relationship between PEN-221 and each AE, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?'

For SAEs causal relationship will also be assessed for other medication and study procedures For SAEs that could be associated with any study procedure, the causal relationship is implied as 'yes'.

10.2.2.1. Adverse Events Based on Signs and Symptoms

All AEs spontaneously reported by the patient or reported in response to the open question from the study personnel or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of a diagnosis is preferred (when possible) to the recording of a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

10.2.2.2. Adverse Events Based on Examinations and Tests

Abnormal, clinically significant laboratory results are to be reported as an AE and must be recorded in the patient's source documents and in the eCRF if the findings represent a change from baseline. If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting Investigator uses the clinical rather than the laboratory term (e.g. anemia versus low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AEs.

Deterioration of a laboratory value, which is unequivocally due to disease progression, should not be reported as an AE/SAE.

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

10.2.2.3. Hy's Law

The Investigator is responsible for determining whether a patient meets potential Hy's Law criteria at any time during the study. Potential Hy's Law criteria are defined as AST or ALT ≥ 3× upper limit of normal (ULN) together with total bilirubin ≥ 2× ULN, irrespective of an increase in ALP, at any point during the study following the start of study medication.

When a case meeting potential Hy's Law is identified, the Investigator will notify the Medical Monitor. The Investigator will also request a new blood draw to repeat the test immediately and will review all previous laboratory data to determine whether potential Hy's Law criteria were met at any study visit prior to or after starting study treatment.

The Investigator will review the case with the Medical Monitor and agree on the approach for the patients' follow-up assessments, which include monitoring the patient until liver chemistry tests and clinical signs and symptoms return to normal or baseline levels, and investigating the etiology of the event including diagnostic tests, as appropriate. The SRC and other subject matter experts may also be involved in the case review and assessment, as needed. Within 3 weeks of detection of the initial laboratory abnormality the Investigator and Medical Monitor will review all available data and agree upon whether there is an alternative explanation for meeting potential Hy's Law criteria other than drug induced liver injury caused by the study drug.

Hy's Law is defined AST or ALT ≥ 3× ULN together with total bilirubin ≥ 2× ULN, where no explanation can be found other than drug induced liver injury caused by the study drug. For potential Hy's Law and Hy's Law, the elevation in transaminases precedes or is concurrent with the elevation in total bilirubin, but there is no specified timeframe within which the elevations in transaminases and total bilirubin occur (FDA 2009).

Standard safety reporting procedures will be followed for reporting AEs and SAEs according to the outcome of the review and assessment. If it is agreed that there is no alternative explanation that would explain the ALT or AST and total bilirubin elevations other than the study drug, then the Investigator is required to report an SAE with the term Hy's Law and the causality assessment of related.

If there is a delay of over 3 weeks in obtaining the information needed to assess whether the case meets Hy's Law criteria then the event should be reported as an SAE with the report term potential Hy's Law and the causality assessment of related, until such time as a reassessment and informed decision is made and the SAE report updated accordingly.

10.2.2.4. Disease Progression

Disease progression can be considered as a worsening of a patient's condition attributable to the disease for which the IP is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. The development of new, or progression of existing metastasis to the primary cancer under study should be considered as disease progression and not an AE. Events that are unequivocally due to disease progression should not be reported as AEs during the study.

10.2.2.5. New Cancers

The development of a new cancer should be regarded as an AE and will generally meet at least 1 of the serious criteria desribed in Section 10.1.3. New cancers are those that are not the primary reason for the administration of the study treatment and have been identified after the patient's inclusion in this study. They do not include metastases of the original cancer.

10.2.2.6. Deaths

All deaths that occur during the study, or within the follow-up period after the administration of the last dose of investigational product, should be reported as follows:

- Death, which is unequivocally due to disease progression, should be communicated to the study monitor at the next monitoring visit and should be documented in the CRF module, but should not be reported as a SAE during the study
- Where death is not clearly due to disease progression of the disease under study, the AE causing the death should be reported as an SAE within 24 hours. The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign a single primary cause of death together with any contributory causes

Deaths with an unknown cause should always be reported as a SAE but every effort should be made to establish a cause of death. An autopsy may be helpful in the assessment of the cause of death, and if performed a copy of the autopsy results should be reported in an expedited fashion to the Sponsor.

10.3. Recording Adverse Events

All AEs (serious and non-serious) will be documented in the patient's source documents and recorded in the eCRF.

The AE term should be reported in standard medical terminology when possible. Also when possible, signs and symptoms indicating a common underlying pathology should be noted as 1 comprehensive event. For each AE, the Investigator will evaluate and report the onset, resolution, intensity, causality, action taken, serious outcome (if applicable), and whether or not it caused the patient to discontinue the study.

10.3.1. Time Period for Collection of Adverse Events

AEs will be collected from the time of signature on pre-screening (if applicable) or screening ICFs throughout the treatment period and including the safety follow-up period. The safety follow-up period is defined as 28±3 days after last dose of study drug. For each AE, the Investigator will evaluate and report the onset, resolution, intensity, causality, action taken, serious outcome (if applicable), and whether or not it caused the patient to discontinue the study. The change in CTCAE v4.03 grade for each event will be recorded in the eCRF.

10.3.2. Follow-Up of Unresolved Adverse Events

Any AEs that are unresolved at the patient's follow-up visit are to be followed up by the Investigator for as long as medically indicated. Additional information for any patient with an ongoing AE at the end of the follow-up period may be requested by the Sponsor, as needed.

If an Investigator learns of any SAEs, including death, at any time after a patient has completed the study and he/she considers there is a reasonable possibility that the event is related to PEN-221, the Investigator should follow the reporting process for SAEs as outlined in Section 10.3.4.

10.3.3. Variables

The following variables will be collected for each AE:

- Adverse event term
- Date when the AE started
- Date when the AE stopped
- CTCAE v4.03 grade and changes in grade during the course of the AE
- Whether the AE is serious or not
- Causality assessment in relation to PEN-221 (yes or no)
- Action taken with regard to PEN-221
- Outcome

In addition, the following variables will be collected for SAEs, if they pertain:

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- Reason AE is serious
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to study procedure(s)

- Causality assessment in relation to other medication(s)
- Description of AE

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 10.1.3. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but is not an SAE unless it meets the criteria shown in Section 10.1.3. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but it will be an SAE when it satisfies the criteria shown in Section 10.1.3.

10.3.4. Reporting Serious Adverse Events

All SAEs, whether or not considered causally related to PEN-221 or to the study procedure(s), have to be reported. All SAEs will be recorded in the eCRF.

The Investigator must report all SAEs to [redacted] within 24 hours of discovery via fax or via secure email only if fax is inoperable using [redacted] SAE reporting form.

[redacted]

Additional follow-up information, if required or available, should be sent to [redacted] within 1 business day of receipt and placed with the original SAE information and kept with the appropriate section of the eCRF and/or study file.

Information on non-serious AEs that become serious must also be reported to [redacted] as soon as it is available.

Investigators must report SAEs and follow-up information to their responsible IRB or EC.

The Sponsor or designee will provide Regulatory Authorities, IRBs, ECs, and PIs with clinical safety updates/reports according to local requirements

10.4. Pregnancy

Pregnancies occurring in the patient or patient's partner while the patient is receiving study drug or within 3 months after the patient's last dose of study drug will be considered neither serious nor an adverse event, but are to be reported using the same procedures as for SAEs described in Section 10.3.1.

Study drug must be discontinued immediately in the event of a pregnancy in the patient. The patient should be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling.

The Investigator will follow the patient/patient's partner until completion of the pregnancy, and must notify the Medical Monitor of the outcome within 5 days. The Investigator will provide this information as a follow-up to the initial report.

If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., spontaneous abortion [any congenital anomaly detected in an aborted fetus is to be documented], stillbirth, neonatal death, or congenital anomaly), then the Investigator should report it as such. All neonatal deaths that occur within 30 days of birth should be reported, without regard to causality, as SAEs. Any infant death after 30 days that the Investigator suspects is related to the *in utero* exposure to the study drug should also be reported.

10.5. Overdose

Signs and symptoms of an overdose should be reported as AEs. Overdoses will not be considered SAEs unless the outcome of the overdose meets seriousness criteria (see Section 10.1.3). However, any overdose must be reported to the Medical Monitor or designee immediately.

The Medical Monitor, in conjunction with the Investigator, will decide whether the patient should continue to participate in the study. All protocol deviations and reasons for such deviations must be documented in the patient's source records.

Any patient receiving a higher dose than intended should be monitored carefully and managed with appropriate supportive care measures.

10.6. Protocol Deviations

Protocol deviations, including protocol waivers (i.e., prospective deviations), are not acceptable. Any protocol deviations and reasons for such deviations must be documented in the patient's source records. The Sponsor will review any protocol deviations and provide additional training to ensure that deviations are not repeated, and, if required, amend the protocol. The Sponsor will notify regulatory authorities of any non-compliance considered a serious breach of GCP or the protocol.

11. DATA REVIEW AND MANAGEMENT

11.1. Study Monitoring

Monitoring and auditing procedures developed by the Sponsor or designee will be followed, in order to comply with good clinical practices (GCP) guidelines.

Before a study center can enter a patient into the study, a representative of the Sponsor or designee will visit the study center to:

- Determine the adequacy of the facilities.
- Discuss with the Investigator(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of the Sponsor or its representatives. This will be documented in a Clinical Study Agreement between the Sponsor and the Investigator.

During the study, a monitor from the Sponsor or designee will have regular contacts with the study center, for the following:

- Provide information and support to the Investigator(s).
- Confirm that facilities remain acceptable.
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the source documents and eCRFs, and that investigational product accountability checks are being performed.
- Perform source data verification. This includes a comparison of the data in the eCRFs with the patient's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each patient (e.g., clinic charts).
- Record and report any protocol deviations not previously sent to the Sponsor or designee.
- Confirm AEs and SAEs have been properly documented in the eCRFs and confirm any SAEs have been forwarded to the Sponsor or designee, and those SAEs that met criteria for reporting have been forwarded to the IRB or EC.

The monitor will be available between visits if the Investigator(s) or other staff needs information or advice.

11.2. Case Report Form Completion

The Sponsor or designee will provide the study centers with eCRFs.

eCRFs will be completed for each study patient. It is the Investigator's responsibility to ensure the accuracy, completeness, and timeliness of the data reported in the patient's eCRF. Source documentation supporting the eCRF data should indicate the patient's participation in the study and should document the dates and details of study procedures, AEs, and patient status.

The Investigator, or designated representative, should complete the eCRF as soon as possible after information is collected, preferably on the same day that a patient is seen for an

examination, treatment, or any other study procedure. Any outstanding entries must be completed immediately after the final examination. An explanation should be given for all missing data.

The Investigator must electronically sign and date the Investigator's Statement at the end of the eCRF to endorse the recorded data.

11.3. Computerized Systems / Medical Records as Source Data

All study data recorded on source documents are to be transcribed into the eCRFs. Any electronic study data are to be entered into a secure, validated data processing system and a backup maintained. Any changes to electronic study data will be documented.

12. STATISTICAL METHODS AND DATA ANALYSIS

12.1. General Statistical Considerations

Protocol PEN-221-001 is an open-label, Phase 1/2a study evaluating PEN-221 in patients with advanced solid tumors expressing somatostatin receptor 2. The study has 2 phases: Phase 1 comprising dose escalation to establish the MTD, and Phase 2a comprising expansion of 3 cohorts, each with distinct, tumor-specific arms. The study objectives and endpoints are listed in Section 6.

Data will be summarized using descriptive statistics (continuous data) and/or contingency tables (categorical data) for demographic and baseline characteristics, efficacy measurements, safety measurements, and all relevant pharmacokinetic and pharmacodynamics measurements.

All data will be summarized by study phase (Phase 1, Phase 2a), cancer indication, and PEN-221 dose received. All data collected will also be presented in patient listings.

Details of the statistical analysis and data reporting will be provided in the SAP document finalized prior to database lock.

12.2. Populations for Analysis

The following patient populations will be evaluated and used for presentation and analysis of the data:

- The Full Analysis Set (intent-to-treat [ITT] population) comprises all patients enrolled into the study and who receive any amount of study drug
- The efficacy analysis (EA) population comprises all patients who receive any amount of study drug and have at least 1 post-baseline efficacy assessment
- The safety analysis (SA) population comprises all patients who receive any amount of study drug and have at least 1 post-baseline safety evaluation
- The per-protocol (PP) population comprises all patients who receive at least 1 cycle of treatment, have at least 1 post-baseline efficacy assessment, and have no major protocol violations, as defined by the Medical Monitor
- The dose-determining (DD) population comprises all patients who receive any amount of study drug and either experienced a DLT or have been followed for the full DLT evaluation period
- The pharmacokinetic (PK) population comprises all patients who receive any amount of study drug and provide adequate PK samples for analysis. Patients with major protocol violations will be assessed on a patient-by-patient basis for inclusion in the PK population.

12.3. Patient Disposition

A tabulation of patient disposition, including the number screened, the number enrolled at each dose of study drug, the number in each patient population for analysis (safety and efficacy), the

number of protocol violations, the number that withdrew prior to completing the study, and reasons for withdrawal.

A by-patient listing of study completion information, including the reason for premature study withdrawal, if applicable, will be presented.

The ITT population will be used.

12.4. Demographics and Baseline Characteristics

Demographic and other baseline data, including age, sex, race, ethnicity, height, weight, baseline ECOG PS, primary diagnosis, disease stage at diagnosis and baseline, prior therapies (including systemic therapies, radiation, and surgeries, etc. will be listed individually by patient and summarized by treatment group using descriptive statistics (continuous data) or contingency tables (categorical data) in the CSR.

The ITT population will be used.

12.5. Treatments and Concomitant Medications

The actual dose and duration in days of PEN-221, as well as the dose intensity (computed as the ratio of actual dose received and actual duration) and the relative dose intensity (computed as the ratio of dose intensity and planned dose received/planned duration) will be listed and summarized by treatment group using descriptive statistics in the CSR.

Concomitant medications and significant non-drug therapies prior to and after the start of the study drug will be listed by patient, and summarized by anatomical therapeutic chemical term and treatment group by means of contingency tables.

The ITT population will be used.

12.6. Primary Objective

The primary objective of Phase 1 is to determine the MTD of PEN-221 when administered IV on a 3 week schedule. The corresponding primary analysis is based on an adaptive BLRM in conjunction with EWOC, as described in detail in Section 12.6.1.

The DD population will be used.

At the conclusion of Phase 1, the final recommended dose for future development will be based on considerations of the MTD estimated by the BLRM, and on an overall clinical assessment of all available safety, tolerability, PK and PDc data from all cycles at all different dose levels tested, in both phases of the study. This dose, which may be lower than the MTD estimated from the BLRM, will be referred to as the recommended phase 2 dose (RP2D).

The primary objective of Phase 2a is to assess the efficacy of PEN-221 with gastrointestinal mid-gut NET and pancreatic NET using CBR as defined as the proportion of patients with the best overall response of CR, PR, or SD using RECIST, version 1.1. For the SCLC cohort, efficacy will be assessed using ORR as defined as the proportion of patients with best overall response of CR or PR using tumor response criteria defined by RECIST, version 1.1, along with duration of response.

The EA population will be used.

12.6.1. Phase 1

12.6.1.1. Definition of MTD and the Primary Variable

The MTD is defined as the highest dose for a given schedule that is not expected by the BLRM to cause DLTs in more than 33% of patients. Estimation of the MTD during the dose escalation phase of the study will be based upon the posterior distribution of the incidence of DLT in C1 in patients in the dose-determining set.

The primary variable is the frequency of DLTs associated with continuous daily administration of PEN-221 during the first cycle of treatment.

12.6.1.2. Statistical Hypothesis, Model, and Method of Analysis

An adaptive BLRM with 2 parameters, guided by EWOC (Babb 1998; Neuenschwander 2008), will be used to make dose recommendations and estimate the MTD during the dose-escalation phase of the study.

The dose-toxicity relationship is modeled by the BLRM:

$$\text{logit}\left(\pi_{(d)}\right) = \log(\alpha) + \beta \log(d/d^*), \alpha > 0, \beta > 0$$

where $\text{logit}\left(\pi_{(d)}\right) = \log(\pi_{(d)}/(1-\pi_{(d)}))$. Doses are rescaled as d/d* with reference dose d*=20.8 mg of PEN-221. The model parameters α and β have the following interpretation:

- α equals the odds of toxicity at the reference dose d*.
- Doubling the dose results in an increase in odds of toxicity by a factor of 2^{β}.

For a dose equal to zero, the probability of toxicity is zero.

12.6.1.3. Prior Specification

The model parameters $(\log(\alpha), \log(\beta))$ are given a weakly informative bivariate normal prior distribution that is guided by guesses from preclinical data and that ensures wide confidence intervals for the DLT rates at each dose, and allows efficient escalation toward the MTD. To tune the prior distribution for the model, *a priori* it is assumed that doses higher than 13.3 mg exceed the EWOC threshold (i.e., greater than 25% probability of excessive toxicity), while doses at or below 16 mg are considered admissible for dose escalation. Such a prior distribution would facilitate initial escalation toward the 6.7 – 13.3 mg range, which includes the predicted MTD of 9 mg based on allometric scaling. Prior parameter values for the bivariate normal distribution of the model parameters are presented in Table 13, and the resulting prior distribution of DLT rates is illustrated in Figure 2. Prior probabilities of excessive toxicity at each dose are shown in Table 14.

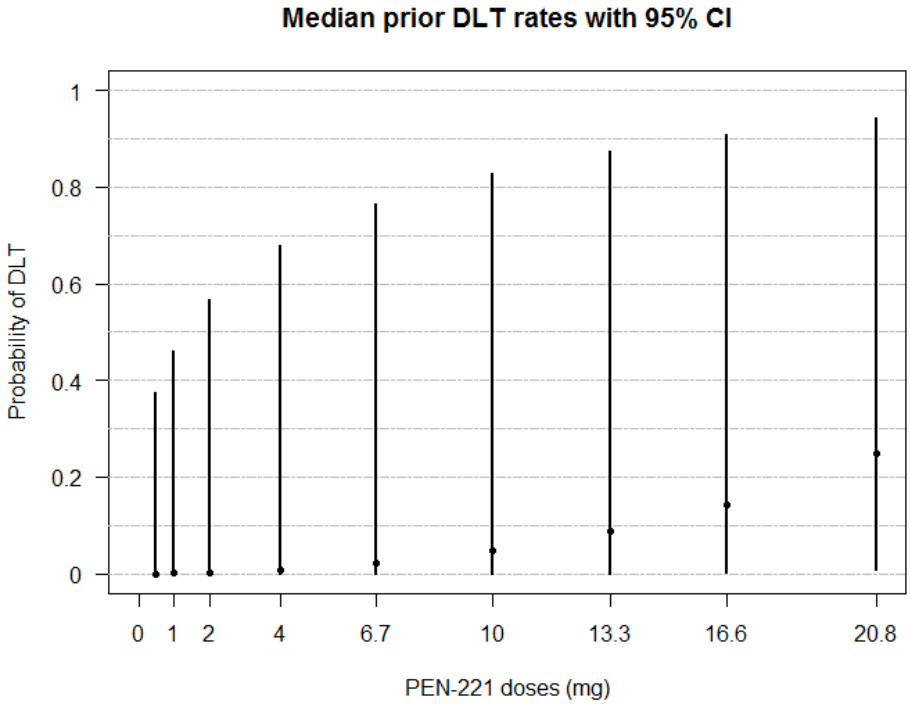
Table 13: Prior parameter values for the bivariate normal distribution of the model parameters

Parameters	Means	Standard deviations	Correlation
$(\log(\alpha), \log(\beta))$	(−1.099, 0.693)	(2, 1)	0

Table 14: Prior probability of excessive toxicity (DLT rate > 0.33)

Dose (mg)	**0.5**	**1**	**2**	**4**	**6.7**	**10**	**13.3**	**16.6**	**20.8**
Probability of excessive toxicity	0.029	0.039	0.056	0.085	0.124	0.175	0.235	0.305	0.422

Figure 2: Prior DLT rates and 95% confidence intervals



12.6.1.4. Dose Recommendation

After each cohort of patients, the posterior distribution for the probabilities of DLT rates at different dose levels are obtained. The results of this analysis are summarized in terms of the estimated probabilities that the true rate of DLT at each dose level will have of lying in each of the following intervals:

- [0, 0.16) under-dosing
- [0.16, 0.33) targeted toxicity
- [0.33, 1] excessive toxicity

The escalation with overdose control (EWOC) criteria is used to guide dose recommendations for each cohort. A dose is not considered admissible for the next cohort unless, given the current

data, there is a small chance (posterior probability < 25%) that this dose is excessively toxic (DLT rate > 33%).

Within the constraints of the EWOC criteria, dose recommendations are based on maximizing the posterior probability that the DLT rate is in the targeted toxicity interval.

The dose recommended for the next cohort is the 1 which has maximum probability of being in the targeted toxicity region (16% – 33% DLT rate), provided it satisfies the EWOC criteria and does not represent more than a doubling (≤ 100% increase) of the current dose.

If the recommended dose satisfying the EWOC criteria is > 100% increase in dose, then escalation will proceed to the highest dose level which is ≤ 100% increase from current dose.

The dose recommended by the BLRM may be regarded as guidance and information to be integrated with a clinical assessment of the toxicity profiles observed at the time of analysis in determining the next dose level to be investigated.

Details of the criteria for dose escalation and determination of the MTD are provided in Section 12.6.1.

12.6.1.5. Stopping Rules

The dose-escalation phase may be stopped in 1 of the following circumstances:

- Stop to declare MTD**:** The study stops with a determination of MTD at dose $\tilde{d}$ if the model's recommended dose for the next cohort is $\tilde{d}$ and the following conditions are met:
  1. At least 6 patients have already been evaluated at dose $\tilde{d}$.
  2. One of the following conditions is satisfied:
     a. The probability of $\tilde{d}$ being in the targeted toxicity region is at least 0.6.
     b. At least 18 patients have been evaluated in the study.
- Stop for over-dosing: The study stops with a declaration that the MTD is below the lowest dose if there are no doses available that satisfy the EWOC criteria.

12.6.2. Phase 2a

12.6.2.1. Clinical Benefit Rate for gastrointestinal mid-gut NET and pancreatic NET

Clinical benefit rate (CBR) is defined as the proportion of patients with a best overall CR, PR, or SD as defined by RECIST 1.1.

For each NET cohort, CBR will be estimated and presented with 95% confidence intervals (CIs)based on the exact binomial distribution.

In addition, a Bayesian approach will be used to estimate the CBR and its 95% credible interval based on the posterior distribution. A vague beta prior distribution with parameters a=1 and b=1 will be used. This translates to a prior mean of 50% with wide uncertainty.

At completion of the study, the prior distribution will be updated with all data available from the evaluable patients at the MTD/RP2D to obtain the posterior distribution of the true CBR. For each NET cohort, the posterior probability that the true CBR is greater than 75% will be reported.

12.6.2.2. Objective Response Rate for SCLC

Objective response rate (ORR) is defined as the proportion of patients with a best overall CR or PR as defined by RECIST 1.1.

ORR will be estimated and presented with 95% confidence intervals (CIs) based on the exact binomial distribution.

In addition, a Bayesian approach will be used to estimate the ORR and its 95% credible interval based on the posterior distribution. A vague beta prior distribution with parameters a=1 and b=1 will be used. This translates to a prior mean of 50% with wide uncertainty.

At completion of the study, the prior distribution will be updated with all data available from the evaluable patients at the MTD/RP2D to obtain the posterior distribution of the true ORR. For the SCLC, the posterior probability that the true ORR is greater than 30% will be reported.

12.6.2.3. Duration of Response for SCLC

Duration of response (DOR) is defined as the time from first documented response (CR or PR) to the date of first documented disease progression or death due to underlying cancer. If a patient has not progressed or died before the analysis cutoff date, DOR will be censored at the date of last adequate tumor assessment.

DOR will be analyzed and presented using the Kaplan-Meier method, along with the estimated median (in months) with 95% CIs, 25^{th} and 75^{th} percentiles.

12.7. Secondary Objectives

12.7.1. Safety Analysis

An objective of all phases of the study is to further characterize the safety and tolerability of PEN-221, including acute and chronic toxicities. This will be based on a comprehensive review of all safety data, including all observed AEs. Data from patients of all study phases will be pooled for analysis according to dose received. All patients who receive any amount of PEN-221 will be included in the final summaries and listings of safety data.

For all safety analyses, the SA population will be used. All listings and tables will be presented by treatment group (dose level) and tumor-specific cohort group.

12.7.1.1. Adverse Events

Summary tables will present the number of patients observed with treatment-emergent adverse events (TEAEs) and corresponding percentages, where treatment-emergent is defined as any AE that occurs after administration of the first dose of study drug and through 28 days after the last dose of study drug, any event that is considered study drug-related regardless of the start date of the event, or any event that is present at baseline but worsens in intensity or is subsequently considered study drug-related by the Investigator.

The denominator used to calculate incidence percentages consists of patients receiving any amount of PEN-221. Within each summary table, the AEs will be categorized according to the Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term. Additional subcategories will be based on event intensity (severity graded according to CTCAE, version 4.03) and relationship to study drug.

Deaths, SAEs, and TEAEs leading to study drug discontinuation will be tabulated on a per-patient basis, as warranted by the data.

For Phase 1, the DLTs, MTD, and RP2D will be identified.

12.7.1.2. Laboratory Anomalies

Change from baseline in clinical laboratory parameters will be summarized across time on study. Furthermore, the frequency of laboratory abnormalities by maximum post-baseline CTCAE grade will be tabulated by cycle and overall for selected laboratory parameters to include at least hemoglobin, white blood cell count, ANC, lymphocytes, platelet count, AST, ALT, total and direct bilirubin, creatinine, ALP, and electrolytes. Shift tables also may be produced for these parameters based on the baseline CTCAE grade and the maximum CTCAE grade by cycle and overall.

12.7.1.3. Vital Signs, ECG, and Other Safety Data

Changes in vital sign parameters (including systolic and diastolic blood pressure and heart rate) and body weight will be summarized over time, and any abnormal values will be tabulated.

The proportions of patients with treatment-emergent clinically significant ECG abnormalities will be tabulated, and changes in ECG findings will be presented in data listing format.

ECOG performance status will be summarized by cycle and worst status overall; ECOG performance status will be presented in data listing format.

Additional safety analyses may be determined at any time without prejudice, in order to most clearly enumerate rates of toxicities and to define further the safety profile of PEN-221.

12.7.1.4. Tolerability

Tolerability will be comprehensively examined based on safety data.

12.7.2. Pharmacokinetic Analysis

All patients who have at least 1 blood sample providing evaluable PK data for PEN-221 will be included in the PK population. The PK population will be used for analysis.

Actual sampling times will be used for the pharmacokinetic analysis of the plasma concentration data for PEN-221, DM1, and peptide from PEN-221. PK parameters will be derived using standard non-compartmental methods. For Phase 2a, additional PK timepoints will be collected on C1D2 and C1D8 to better characterize PEN-221, DM1 and peptide from PEN-221. PK samples on C3D1 are not required for Phase 2a.

The following PK parameters will be calculated: the maximum plasma concentration (C_{max}), time to C_{max} (t_{max}), area under the plasma concentration time curve from zero to the time of the last measurable concentration ($AUC_{(0-t)}$) and from zero to infinity (AUC_{∞}), CL, and the apparent

volume of distribution (V_{ss}; V_z), terminal rate constant (λ_z), and $t_{½}$. The dependency of the pharmacokinetics on multiple dosing will be assessed by the calculation of the ratio of $AUC_{(0\text{-}t)}$ C3D1 and C1D1.

This protocol uses fixed doses. The relationship between CL of PEN-221 and body size, as measured by weight and body mass index (BMI), will be examined as data accrues. If the analysis indicates that CL is dependent on body size, then dosing will be modified to a body-size basis by Safety Review Committee agreement.

The PK may also be characterized by fitting an appropriate compartmental model to aid in evaluation of drug exposure-PDc response relationships and population covariates. The model to be used will be determined from the data and will be parameterized in terms of CL and V_{ss}.

12.7.3. Efficacy Analysis

Evidence of preliminary anti-tumor activity will be assessed by the objective response, as defined by RECIST 1.1. This will be used to summarize the objective response rate (CR+PR), as well as the rates for the individual categories of response, (i.e., CR, PR, SD, and PD).

12.7.3.1. Progression-free Survival

Progression-free survival (PFS) is defined as the time from the date of first dose of PEN-221 to the date of first documented disease progression per RECIST 1.1, or death due to any cause. If a patient has not progressed or died before the analysis cutoff date, PFS will be censored at the date of last adequate tumor assessment.

PFS will be analyzed and presented using the Kaplan-Meier method, along with the estimated median (in months) with 95% CIs, 25^{th} and 75^{th} percentiles.

12.7.3.2. Overall Survival

Overall survival (OS) is defined as the time from the date of first dose of PEN-221 to the date of death due to any cause. If a patient has not died before the analysis cutoff date, OS will be censored at the date of last contact.

OS will be analyzed and presented using the Kaplan-Meier method, along with the estimated median (in months) with 95% CIs, 25^{th} and 75^{th} percentiles.

12.7.3.3. Objective Response Rate for gastrointestinal mid-gut NET and pancreatic NET

For gastrointestinal mid-gut-NET and pancreatic NET, objective response rate (ORR) is defined as the proportion of patients with a best overall CR or PR as defined by RECIST 1.1.

ORR will be estimated and presented with 95% confidence intervals (CIs) based on the exact binomial distribution.

In addition, a Bayesian approach will be used to estimate the ORR and its 95% credible interval based on the posterior distribution. A vague beta prior distribution with parameters a=1 and b=1 will be used. This translates to a prior mean of 50% with wide uncertainty.

At completion of the study, the prior distribution will be updated with all data available from the evaluable patients at the MTD/RP2D to obtain the posterior distribution of the true ORR. The posterior probability that the true ORR is greater than 20% will be reported.

12.7.3.4. Duration of Response for gastrointestinal mid-gut NET and pancreatic NET

For gastrointestional mid-gut NET and pancreatic NET, duration of response (DOR) is defined as the time from first documented response (CR or PR) to the date of first documented disease progression or death due to underlying cancer. If a patient has not progressed or died before the analysis cutoff date, DOR will be censored at the date of last adequate tumor assessment.

DOR will be analyzed and presented using the Kaplan-Meier method, along with the estimated median (in months) with 95% CIs, 25th and 75th percentiles.

12.8. Interim Analyses

No formal interim analyses are planned in Phase 1. However, the dose-escalation design is adaptive by nature, basing ongoing decisions about dose assignment on observed data. Details of this procedure and the process for communication with Investigators are provided in Section 8.6.1.In Phase 2a, no formal interim analysis are planned. However, preliminary efficacy and safety will be assessed in approximately the first 10 patients per cohort before deciding whether to proceed to the second stage of each cohort.

12.9. Sample Size Calculation

No formal statistical power calculations to determined sample size were performed for this study. However, based on the performance characteristics computed and described hereafter, the sample sizes in each phase are adequate to address the study's objectives.

12.9.1. Phase 1

No formal sample size calculations were performed for Phase 1. It is estimated that 30 patients will be enrolled in the dose-escalation phase including at least 6 patients treated at the MTD level. The actual number of patients will depend on the number of dose levels/cohorts that are tested. Based on the simulation study undertaken with the East 6.4 software to evaluate operating characteristics of the BLRM (see Section 15.2) at least 18 patients are expected to be treated in the dose-escalation phase for the model to have reasonable operating characteristics relating to its MTD recommendation.

12.9.2. Phase 2a

No formal sample size calculations were performed for Phase 2a. A total of approximately 75 patients will be enrolled in Phase 2a. This includes the following Phase 2a cohorts: GI mid-gut NETs (n=35), pancreatic NETs (n=20), and advanced or metastatic SCLC (n=20).

For patients with advanced pancreatic NET, approved drugs (beyond somatostatin analogs) include sunitinib and everolimus, both of which improved PFS but are associated with clinical benefit rates of approximately 72% for sunitinib and 78% for everolimus (Raymond 2011; Yao 2011). In the pancreatic NET group, an observed clinical benefit rate of 75% or greater would be considered promising. Given a sample size of 20 patients, if clinical benefit is observed in 15 patients (observed rate of 75%), the posterior probability of the true rate being <65% is 0.20, with the 95% credible interval around the true rate being (52.8%, 88.7%). If only 14 responses are seen (observed clinical benefit rate of 70%), the probability of the true clinical benefit rate being at least 75% is 0.26, while seeing only 13 responses (observed clinical benefit rate of 65%)

would result in that probability being only 0.13. If the true underlying clinical benefit rate is 75%, there is 0.38 probability to observe fewer than 15 patients achieve clinical benefit. This probability drops to 0.20 if the true underlying rate is 80%.

For patients with advanced gastrointestinal NETs, approved drugs (beyond somatostatin analogs) include everolimus, which has been shown to improve PFS but is associated with a clinical benefit rate of 83% (Yao 2016). In a randomized Phase 3 study, ^{177}Lu-DOTATATE plus Octreotide LAR in patients with advanced GI mid-gut NETs was shown to improve PFS and is associated with a clinical benefit rate of 82% (Strosberg 2017; Strosberg 2016 [4th Theranostics World Congress 2016])). In the gastrointestinal mid-gut NET group, an observed clinical benefit rate of approximately 75% or greater would be considered promising. In a sample 35 patients, if clinical benefit is observed in 26 patients (observed rate of 74%), the posterior probability of the true rate being <65% is 0.14, with the 95% credible interval around the true rate being (57.8%, 85.8%). If only 25 responses are seen (observed clinical benefit rate of 71%), the probability of the true clinical benefit rate being at least 75% is 0.27, while seeing only 24 responses (observed clinical benefit rate of 69%) would result in that probability being only 0.17. If the true underlying clinical benefit rate is 75%, there is 0.37 probability to observe fewer than 26 patients achieve clinical benefit. This probability drops to 0.15 if the true underlying rate is 80%. Approximately 25 of the 35 patients in the gastrointestinal mid-gut NET group are expected to be treated at the current RP2D (15mg), and among these patients, approximately 20 are expected to have not received prior PRRT. These two subgroups will be summarized separately. For the subgroup of approximately 20 patients without prior PRRT and who are treated at the current RP2D, the performance characteristics based on a target CBR of 75% (15 patients with clinical benefit out of 20) are the same as those presented in the previous paragraph for the pancreatic NET cohort.

For patients with advanced SCLC, approved drugs in the second-line include topotecan, which has been shown in a randomized Phase 3 study (von Pawel 1999) compared to cyclophosphamide-doxorubicin-vincristine (CAV) to achieve similar time to progression, survival, and response rates (topotecan 24% vs. CAV 18%) in patients who relapsed >90 days after completion of their first line platinum containing chemotherapy regimen, and similar though somewhat lower response rates in the subset of patients who relapsed within 60 to 90 days after completion of the first-line chemotherapy (topotecan 13.6% vs. CAV 4.8%). In the platinum-sensitive SCLC group, a tumor response rate of 30% or greater would be considered very promising. Given a sample size of 20 patients, if 6 responses are seen (observed ORR of 30%), the posterior probability of the true ORR being < 10% is 0.5% and being ≥ 30% is 55%, with the 95% credible interval about the true ORR being (14.6%, 52.2%). For a cohort of 20 patients, if the observed proportion is 0.3, there is 100% probability that the true underlying proportion exceeds 0.05, and 55.0% probability that the true underlying proportion exceeds 0.3. If the true underlying proportion is 0.3, there is 0.1% probability to observe 0 responses. If only 4 responses are seen (observed ORR of 20%) the probability of the true ORR being ≥ 30% drops to 19.8%, while seeing only 2 responses (observed ORR of 10%) would result in that probability being only 2.7%. If the true underlying proportion is 0.3, there is 0.1% probability to observe 0 responses.

Table 15 provides more probability statements about the true ORR based on number of responses observed in 20 patients, and Table 16 provides probability statements about the true CBR based on the number of patients with clinical benefit observed in 20 patients

Table 15: Posterior probability of true ORR based on observed number of responses

Number of Responses out of 20 Patients	Observed ORR	Prob (True ORR>5%)	Prob (True ORR>10%)	Prob (True ORR>20%)	Prob (True ORR>30%)
0	0%	34.1%	10.9%	<1%	<0.1%
1	5%	71.7%	36.5%	5.8%	0.6%
2	10%	91.5%	64.8%	17.9%	2.7%
3	15%	98.1%	84.8%	37.0%	8.6%
4	20%	99.7%	94.8%	58.6%	19.8%
5	25%	100.0%	98.6%	76.9%	36.3%
6	30%	100%	99.7%	89.1%	55.1%
7	35%	100%	99.9%	95.7%	72.3%

Twenty patients will result in 88% and 64% probability of detecting at least one response with a true rate of 10% and 5%, respectively.

Table 16: Posterior probability of true CBR based on observed number of patients with clinical benefit

Number of Patients with Clinical Benefit out of 20 Patients	Observed CBR	Prob (True CBR>60%)	Prob (True CBR>65%)	Prob (True CBR>70%)	Prob (True CBR>75%)
10	50%	17.4%	7.7%	2.6%	0.6%
11	55%	30.9%	16.2%	6.8%	2.1%
12	60%	47.6%	29.4%	14.8%	5.6%
13	65%	65.0%	46.4%	27.7%	13.0%
14	70%	80.0%	64.3%	44.9%	25.6%
15	75%	90.4%	79.9%	63.7%	43.3%
16	80%	96.3%	90.8%	80.2%	63.3%
17	85%	98.9%	96.7%	91.4%	80.8%

Based on the performance characteristics above, the sample sizes are adequate to address Phase 2a objectives.

12.9.3. Primary Analysis Cutoff

For the GI mid-gut NET, pancreatic NET and SCLC groups, the cutoff date for the primary analysis will occur after all patients received the first dose of PEN-221 at least 21 weeks (7 cycles) prior to the analysis cutoff date.

12.10. Replacement of Patients

Patients may only be replaced in 2 instances:

- Patients who are discontinued from the study prior to receiving study drug PEN-221 may be replaced (i.e. lost to follow-up, withdraw consent).
- Patients in the dose-escalation phase who withdraw before completing C1 assessments for reasons other than experiencing a DLT may be replaced.

12.11. Changes to the Planned Statistical Methods

Planned statistical analyses will be documented in a formal Statistical Analysis Plan before database lock. Any changes to the planned statistical methods will be documented in the CSR.

13. ETHICS

13.1. Good Clinical Practice Compliance

The Sponsor, Investigators, and any third party to whom aspects of the study management or monitoring have been delegated will undertake their assigned roles for this study in compliance with US 21 Code of Federal Regulations (CFR) 11, 21 CFR 50, 21 CFR 54, 21 CFR 56, and 21 CFR 312, all applicable local industry regulations, and International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guideline E6.

ICH GCP Guideline E6 is available at:

http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/good-clinical-practice.html

13.2. Institutional Review Board or Ethics Committee

The IRB or EC will review all appropriate study documentation in order to safeguard the rights, safety, and well-being of the patients. The study will only be conducted at study centers where IRB or EC approval has been obtained. The protocol, Investigator Brochure, informed consent, advertisements (if applicable), written information given to the patients (including diary cards), safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB or EC by the Investigator.

The final study protocol, including the final version of the ICF, must be approved or given a favorable opinion in writing by an IRB or EC, as appropriate. Written IRB or EC approval must be received by the Sponsor or designee before a study center can enroll any patient into the study.

The Investigator is responsible for informing the IRB or EC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or EC must approve all advertising used to recruit patients for the study. The protocol (and other amended study documents) must be re-approved by the IRB or EC upon receipt of amendments and annually, as local regulations require. The Investigator is also responsible for providing the IRB or EC with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product. The Sponsor or designee will provide this information to the Investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB or EC according to local regulations and guidelines.

To ensure compliance with GCP and all applicable regulatory requirements, the Sponsor or designee may conduct a quality assurance audit. Please see Section 14.2 for more details regarding the audit process.

13.3. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH GCP, and applicable regulatory requirements.

13.4. Written Informed Consent

The Investigator at each center will ensure that the patient is given full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study. Patients must also be notified that they are free to discontinue from the study at any time. The patient should be given the opportunity to ask questions and allowed time to consider the information provided. This process should be recorded in the patient's source documentation.

The patient's signed and dated ICF must be obtained before conducting any study procedures. Documentation of the consenting process must be recorded in the patient's source documents.

The Investigator must maintain the original, signed ICF. A copy of the signed ICF must be given to the patient, and this must be documented in the patient's source documents.

13.5. Patient Confidentiality

In order to maintain patient privacy, all eCRFs, study drug accountability records, study reports, and communications will identify the patient by initials (as allowed by local regulations) and the assigned patient number. The Investigator will grant monitor(s) and auditor(s) from the Sponsor or designee and regulatory authority(ies) access to the patient's original medical records for verification of data gathered on the eCRFs and to audit the data collection process. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

14. ADMINISTRATIVE REQUIREMENTS

14.1. Retention of Records

The Investigator will maintain all study records according to ICH GCP and applicable regulatory requirement(s). Records will be retained for at least 2 years after the last marketing application approval or 2 years after formal discontinuation of the clinical development of the investigational product or according to applicable regulatory requirement(s). If the Investigator withdraws from the responsibility of keeping the study records, custody must be transferred to a person willing to accept the responsibility. The Sponsor or designee must be notified immediately by telephone or email and the notification confirmed in writing if a custodial change occurs.

14.2. Audits and Inspections

Authorized representatives of the Sponsor, or designee, a regulatory authority, IRB, or EC may visit the study center to perform audits or inspections, including source data verification. The purpose of a Sponsor audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, ICH GCP, and any applicable regulatory requirements.

The Investigator should contact the Sponsor immediately if contacted by a regulatory agency about an inspection.

14.3. Publication Policy

All information regarding PEN-221 supplied by the Sponsor to the Investigator or generated as a result of any clinical studies is privileged and confidential information belonging to the Sponsor. The Investigator agrees to use Sponsor's confidential information solely to accomplish the study and will not use such information for any other purposes without the prior written consent of the Sponsor. It is understood that there is an obligation to provide the Sponsor with complete and accurate data obtained during the study. The information obtained from the clinical study will be used towards the development of PEN-221 and may be disclosed by the Sponsor to regulatory authority(ies), other Investigators, corporate partners, or consultants as required.

It is anticipated that the results of this study may be presented at scientific meetings and/or published in a peer reviewed scientific or medical journal. A Publications Committee, comprised of Investigators participating in the study and representatives from the Sponsor, as appropriate, will be formed to oversee any publication or presentation of the study results, which will reflect the experience of all participating study centers. All publications and presentations must be approved in advance by the Sponsor at its sole discretion. Subsequently, individual Investigators may publish results from the study in compliance with their agreement with the Sponsor.

A pre-publication manuscript is to be provided to the Sponsor at least 30 days prior to the submission of the manuscript to a publisher. Similarly, the Sponsor will provide any company-prepared manuscript to the Investigators for review at least 30 days prior to submission to a publisher. All publications and presentations must be approved in writing by the Sponsor before public disclosure.

15. APPENDIX: PRIOR CALIBRATION AND OPERATING CHARACTERISTIS OF THE BAYESIAN LOGISTIC REGRESSION MODEL

15.1. Introduction

This appendix evaluates the performance of the proposed adaptive BLRM with EWOC via computer simulations. The detailed dose escalation procedure is described in Section 8.6.1 of the study protocol. In brief, the EWOC criteria is used to guide dose recommendations for each cohort. A dose is not considered admissible for the next cohort unless, given the current data, there is a small chance (posterior probability < 25%) that this dose is excessively toxic (DLT rate > 33%). Within the constraints of the EWOC criteria, dose recommendations are based on maximizing the posterior probability that the DLT rate is in the targeted toxicity interval of 16% – 33%.

15.2. Operating Characteristics for Simulation

15.2.1. Dose Levels

The dose levels for simulation are given as 0.5, 1, 2, 4, 6.7, 10, 13.3, 16.6, and 20.8 mg. The starting dose for simulations is 1.0 mg, but a lower dose of 0.5 mg is provided in case a dose reduction from the starting dose is necessary.

15.2.2. Statistical Model

For a dose d, let $\pi_{(d)}$ denote the probability of dose limiting toxicity (DLT) at dose d. For a cohort of size n evaluated at dose d, the number of patients, y, with a DLT is assumed to follow a binomial distribution:

$$y \mid \pi_{(d)} \sim \text{Binomial}(n, \pi_{(d)})$$

The relationship between doses and DLT rates is modeled by the logistic curve

$$\text{logit}(\pi_{(d)}) = \log(\alpha) + \beta \log(d/d^*), \alpha > 0, \beta > 0$$

where $\text{logit}(\pi_{(d)}) = \log(\pi_{(d)}/(1-\pi_{(d)}))$. Doses are rescaled as d/d* with reference dose d*=20.8 mg of PEN-221. The model parameters α and β have the following interpretation:

- α equals the odds of toxicity at the reference dose d*.
- Doubling the dose results in an increase in odds of toxicity by a factor of 2^{β}.

For a dose equal to zero, the probability of toxicity is zero.

15.2.3. Prior Specification

The model parameters $(\log(\alpha), \log(\beta))$ are given a weakly informative bivariate normal prior distribution that is guided by guesses from preclinical data and that ensures wide confidence intervals for the DLT rates at each dose, and allows efficient escalation towards the MTD. To tune the prior distribution for the model, *a priori* it is assumed that doses higher than 13.3 mg exceed the EWOC threshold (i.e., greater than 25% probability of excessive toxicity), while

doses at or below 13.3 mg are considered admissible for dose escalation. Such a prior distribution would facilitate initial escalation toward the 6.7 – 13.3 mg range, which includes the predicted MTD of 9 mg based on allometric scaling. The prior parameter values to be used in this study are given in Table 17, and the resulting prior distribution of DLT rates is illustrated inFigure 3.Prior probabilities of excessive toxicity at each dose are shown in Table 18.

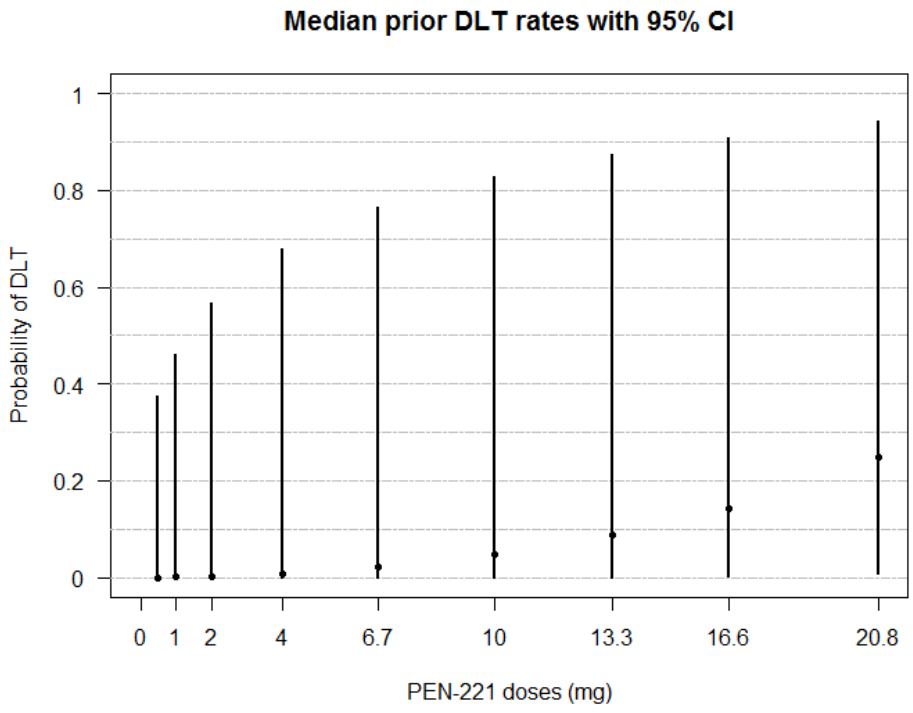
Table 17: Prior parameter values for the bivariate normal distribution of model parameters

Parameters	Means	Standard deviations	Correlation
$(\log(\alpha), \log(\beta))$	$(-1.099, 0.693)$	(2, 1)	0

Table 18: Prior probability of excessive toxicity (DLT rate > 0.33)

Dose (mg)	0.5	1	2	4	6.7	10	13.3	16.6	20.8
Probability of excessive toxicity	0.029	0.039	0.056	0.085	0.124	0.175	0.235	0.305	0.422

Figure 3: Prior median DLT rates and 95% confidence intervals at dose levels used for simulations

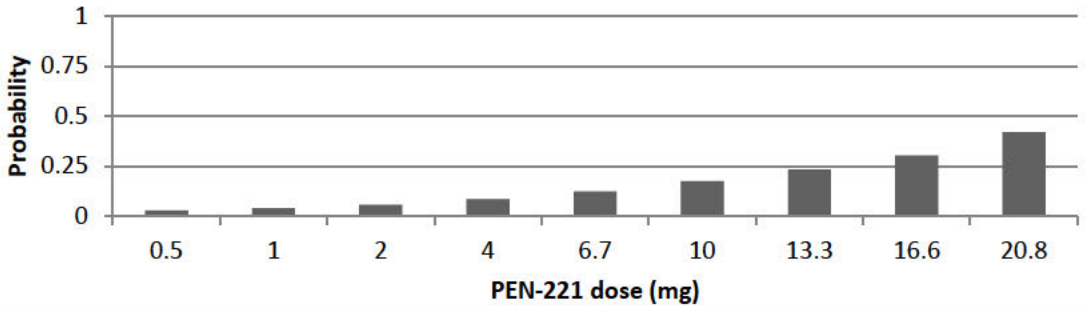


A consideration in tuning the prior parameter values is to produce a model that adapts well to emerging data. To illustrate the proposed model's response to DLTs in early cohorts, Figure 4 shows the prior probabilities of excessive toxicity for each dose along with the posterior probabilities of excessive toxicity after observing a single DLT in cohort 1, 2 or 3. Prior to

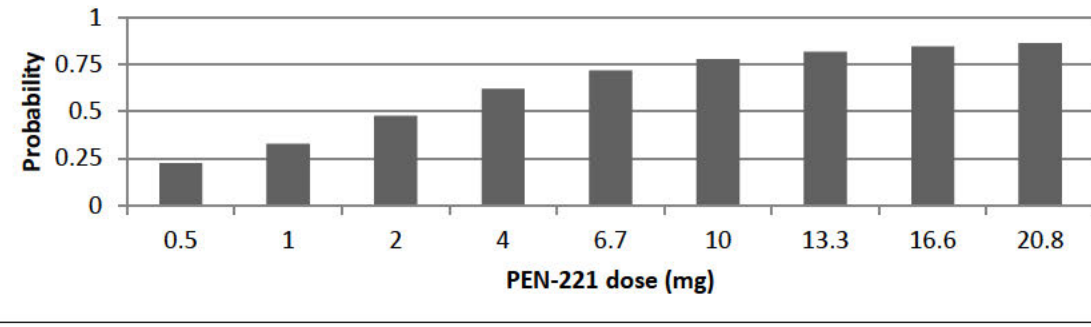
observing any data, the probability of excessive toxicity is low (<25%) for most doses, but this probability increases substantially once a single DLT is observed. For example, if the first DLT occurs in 1 of 2 patients in cohort 1 at 1mg (Figure 4b), then the updated model suggests that a dose of 1mg or higher may be too toxic for the next cohort, and escalation is not permitted per EWOC. Similarly, if the first DLT occurs in 1 of 3 patients in cohort 2 (Figure 4c) then escalation is not permitted for the next cohort. On the other hand, if the first DLT occurs in 1 of 3 patients in cohort 3 at 4 mg then a 67% increase to 6.7mg is permitted (Figure 4d), and if cohort 2 enrolls 6 patients and only 1 of them experiences a DLT, then an increase of 100% to 4mg is permitted (Figure 4e). These examples are evidence that the model makes reasonable recommendations based on observed toxicities during initial cohorts by providing good overdosing control without unduly restricting escalation when the DLT rate is low. Additional early cohort scenarios are presented in Table 21 .

Figure 4: Prior probability of excessive toxicity at each dose and posterior probabilities of excessive toxicity upon observing the first DLT in cohort 1, 2, or 3

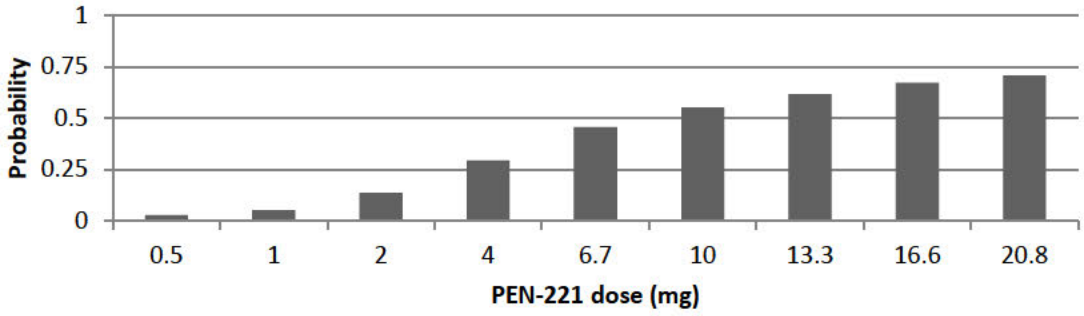
a. Prior probability of excessive toxicity. Doses 13.3 mg and lower are under the EWOC threshold of 0.25 probability of excessive toxicity.



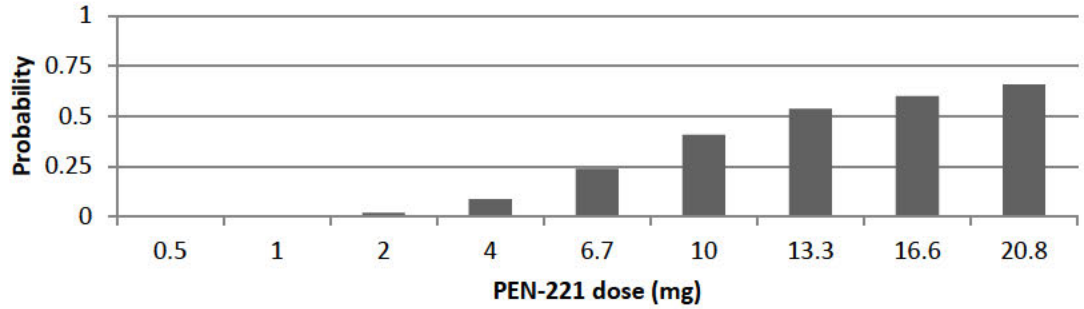
b. Posterior probability of excessive toxicity after observing 1 DLT in 2 patients assigned to 1mg in cohort 1. After updating the model, all doses higher than 0.5mg exceed the 0.25 EWOC threshold for overdosing. The next recommended dose is 0.5mg.



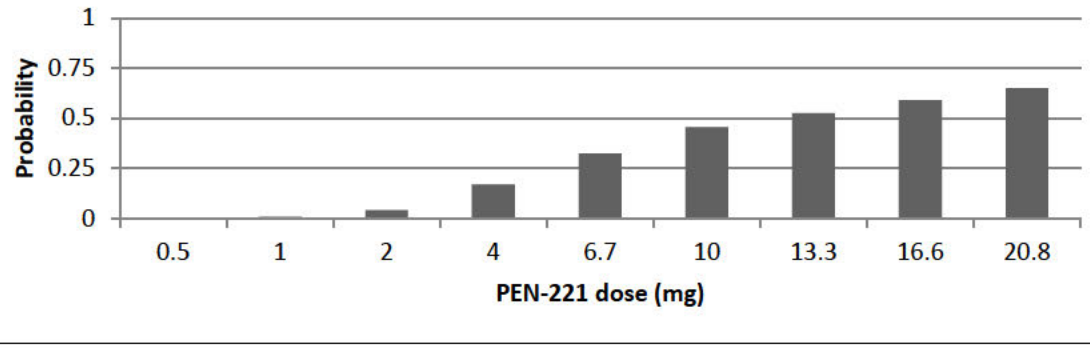
c. Posterior probability of excessive toxicity after observing 0/2 + 1/3 DLTs/Patients in cohorts 1 and 2, assigned to doses 1mg and 2mg respectively. After updating the model, all doses higher than 2mg exceed the 0.25 EWOC threshold for overdosing. Escalation is not permitted, and the next recommended dose is 2mg.



d. Posterior probability of excessive toxicity after observing 0/2 + 0/3 + 1/3 DLTs/Patients in cohorts 1, 2, and 3, assigned to doses 1mg, 2mg, and 4mg respectively. After updating the model, the probability of excessive toxicity at dose 6.7mg is 0.24, which is just below the EWOC threshold for overdosing. Escalation to 6.7mg is permitted.



e. Posterior probability of excessive toxicity after observing 0/2 + 1/6 DLTs/Patients in cohorts 1 and 2, assigned to doses 1mg and 2mg respectively. After updating the model, all doses higher than 4mg exceed the 0.25 EWOC threshold for overdosing. Escalation to the next dose of 4mg is permitted.



15.2.4. Dose Escalation Rules for Simulation

The principle of escalation with overdose control (EWOC) prohibits recommending a particular dose for the next cohort unless, given the current data, there is a small chance (posterior probability < 25%) that this dose is excessively toxic (DLT rate > 33%).

Within the constraints of the EWOC criteria, dose recommendations are based on maximizing the posterior probability that the DLT rate is in the targeted toxicity interval. For simulations, dose escalation proceeds according to the following rules:

- Each cohort has 3 patients.
- The dose recommended for the next cohort is the 1 that has maximum probability of being in the targeted toxicity region (16% – 33% DLT rate), provided it satisfies the EWOC criteria and is does not skip an untried dose.
- If the recommended dose satisfying the EWOC criteria is higher than the next higher dose, then escalate only to the next higher dose.
- **Stop to declare MTD:** The study stops with a determination of MTD at dose $\tilde{d}$ if the model's recommended dose for the next cohort is $\tilde{d}$ and the following conditions are met:
  1. At least 6 patients have already been evaluated at dose $\tilde{d}$.
  2. One of the following conditions is satisfied:
     a. The probability of $\tilde{d}$ being in the targeted toxicity region is at least 0.6.
     b. At least 18 patients have been evaluated in the study.
- **Stop for over-dosing:** The study stops with a declaration that the MTD is below the lowest dose if there are no doses available that satisfy the EWOC criteria.

15.2.5. Hypothetical Dose-Toxicity Relationships for Simulation

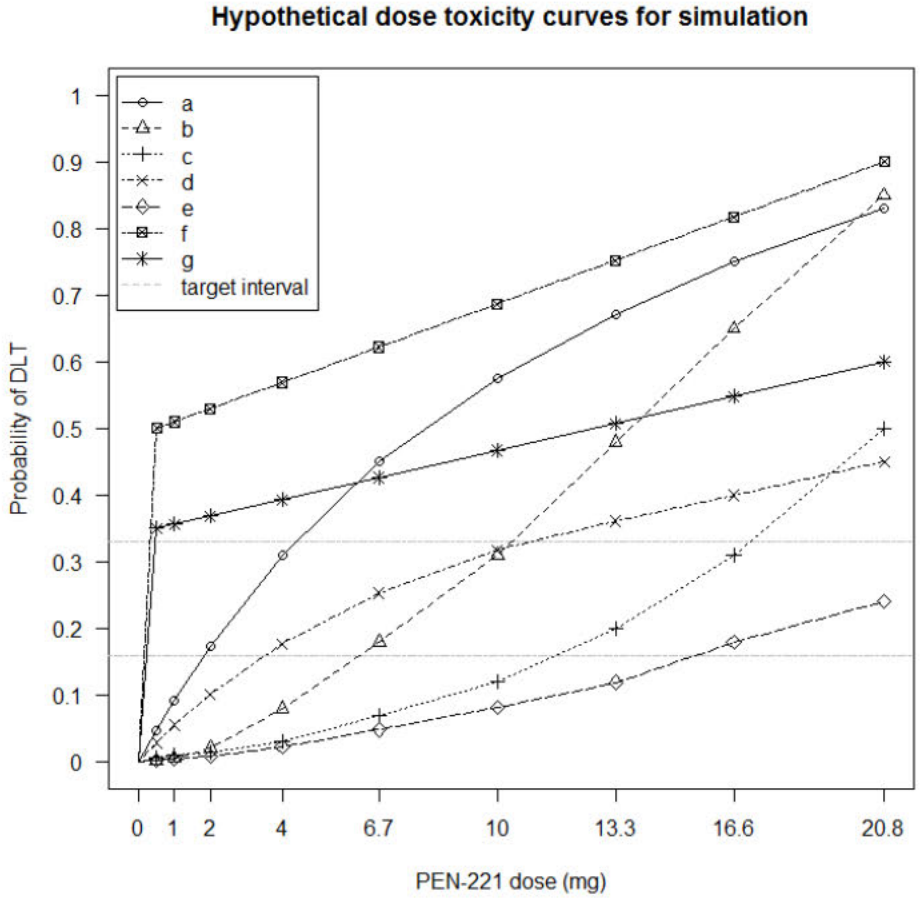
Simulations were performed considering 5 hypothetical dose toxicity curves (Table 19 and Figure 5) which capture a range of potential true underlying dose toxicity relationships.

a. Steep dose toxicity curve and MTD is in the early range of dose levels
b. Steep dose toxicity curve and MTD is in the middle range of dose levels
c. Steep dose toxicity curve and MTD is in the upper range of dose levels
d. Flat dose toxicity curve and MTD is in the middle range of dose levels
e. Flat dose toxicity curve and MTD is in the late range of dose levels
f. Steep dose toxicity curve and all doses are excessively toxic
g. Flat dose toxicity curve and all doses are excessively toxic

Table 19: Hypothetical DLT rates at each dose under 5 different scenarios for simulation

Scenario	DLT rates at different doses (mg) Doses with probability of DLT in the interval [0.16, 0.33) are shaded in gray								
	0.5	1	2	4	6.7	10	13.3	16.6	20.8
a	0.047	0.092	0.174	0.31	0.45	0.575	0.671	0.75	0.83
b	0.001	0.005	0.021	0.08	0.18	0.31	0.48	0.65	0.85
c	0.007	0.01	0.014	0.03	0.07	0.12	0.2	0.31	0.5
d	0.029	0.055	0.102	0.177	0.253	0.318	0.361	0.4	0.45
e	0.002	0.004	0.009	0.022	0.048	0.081	0.119	0.18	0.24
f	0.500	0.510	0.530	0.569	0.622	0.687	0.752	0.817	0.900
g	0.350	0.356	0.368	0.393	0.426	0.467	0.508	0.548	0.60

Figure 5: Hypothetical dose toxicity curves under 5 different scenarios for simulation



15.2.6. Simulation Results

To evaluate the operating characteristics of the BLRM method with the specified prior distribution, simulations were performed in East 6.4 under each of 5 true dose-toxicity scenarios. Results based on 1000 simulated studies per scenario are summarized in Table 20.

Table 20: Operating characteristics of the BLRM design. The toxicity of a dose is classified by its DLT rate as follows: [0,0.16) under dosing; [0.16, 0.33) targeted toxicity; [0.33, 1] excessive toxicity.

Sce-nario	% simulations selecting MTD in interval				Average % of patients receiving a dose with		Average number of DLTs	Ave Sample size	Ave % of patients experiencing DLT
	targeted toxicity	excessive toxicity	under dosing	below lowest dose	targeted toxicity	excessive toxicity			
a	77.6	10.9	8.3	3.2	58.8	12.4	4.2	18.7	23.5
b	79.3	7.5	13.2	0	41.1	8.1	3.4	21.0	16.3
c	62.5	6.5	31.0	0	26.2	3.7	3.1	25.0	12.3
d	72.9	9.7	16.6	0.8	50.6	5.3	3.6	20.7	18.1
e	67.6	-	32.4	0	23.3	-	2.3	26.4	8.7
f	-	6.7	-	93.3	-	100	3.5	7.1	60.3
g	-	35.8	-	64.2	-	100	4.1	11.5	46.0

In scenarios a – e, there is a high chance (62% – 80% probability) that the BLRM method recommends a dose with DLT rate in the target range of 0.16 – 0.33. Across all of these scenarios, there is a low chance of recommending an excessively toxic dose (<11% probability), of assigning a patient to an excessively toxic dose (<13% probability), and of a patient in the study experiencing a DLT (<24% probability). In scenario f, which assumes all doses are highly toxic with DLT rates of at least 50%, it is very unlikely (7% probability) that any dose is recommended. Instead, the MTD would be declared to be below the lowest dose (93% probability). Scenario g also assumes all doses are in the excessive toxicity region, but the early doses are only slightly above the cutoff for excessive toxicity. Table 21 shows the probability of selecting each dose as MTD in scenario g. When a dose is selected as MTD, there is a high probability (95%) that the selected dose is one of 0.5, 1, 2, or 4, all of which have DLT rates 33% – 40%, just above the cutoff for excessive toxicity.

Table 21: Probability that each dose is selected as MTD in scenario g

Dose (mg)	0.5	1	2	4	6.7	10	13.3	16.6	20.8
Probability of selecting dose as MTD	4.6%	13.9%	11.2%	4.3%	1.5%	0.1%	0.2%	0%	0%

For comparison, simulations of the standard 3+3 design were also performed for scenario g. These show worse performance overall as illustrated in Table 22. The MTD was only declared below the lowest dose 17.9% of the time.

Table 22: Probability that each dose is selected as MTD in scenario g using a 3+3 design

Dose (mg)	Below lowest dose	0.5	1	2	4	6.7	10	13.3	16.6	20.8
Probability of selecting dose as MTD	17.9%	21.7%	38.4%	14.1%	6.2%	1.3%	0.3%	0.1%	0%	0%

15.3. Dose Escalation Scenarios in Early Cohorts

Table 23 presents dose escalation scenarios to illustrate dose levels recommended by BLRM via EWOC up to the first 3 cohorts, following the rules described in the previous section. The BLRM performs reasonably in these hypothetical scenarios. The actual dose selected for each cohort will be guided also by medical review of all available clinical data. Notably, if a toxicity is observed in the first cohort, the choice of dose level for the next cohort would largely rely on clinical judgment as the available statistical information would be relatively weak.

Table 23: Possible scenarios up to the 3rd cohort

Scenario	Cohort	Dose assigned (mg)	Number of patients	Number of DLTs	Next provisional dose recom-mended (mg)	Highest acceptable next dose (mg)
1	1	1	2	0	2	2
	2	2	3	0	4	4
	3	4	3	0	6.7	8
2	1	1	2	0	2	2
	2	2	3	0	4	4
	3	4	3	1	6.7	6.9
3	1	1	2	0	2	2
	2	2	3	0	4	4
	3	4	3	2	2	3.3
4	1	1	2	0	2	2
	2	2	3	1	2	3.3
	3	2	3	0	4	4
5	1	1	2	0	2	2
	2	2	3	1	2	3.3
	3	2	3	1	2	2.3

Scenario	Cohort	Dose assigned (mg)	Number of patients	Number of DLTs	Next provisional dose recom-mended (mg)	Highest acceptable next dose (mg)
6	1	1	2	0	2	2
	2	2	3	1	2	3.3
	3	2	3	2	1	1.2
7	1	1	2	0	2	2
	2	2	3	2	0.5	0.9
	3	0.5	3	0	1	1
8	1	1	2	0	2	2
	2	2	3	2	0.5	0.9
	3	0.5	3	1	0.5	0.6
9	1	1	2	0	2	2
	2	2	3	2	0.5	0.9
	3	0.5	3	2	NA*	<0.5
10	1	1	2	1	0.5	0.6
	2	0.5	3	0	1	1
	3	1	3	0	2	2
11	1	1	2	1	0.5	0.6
	2	0.5	3	0	1	1
	3	1	3	1	1	1.2
12	1	1	2	1	0.5	0.6
	2	0.5	3	0	1	1
	3	1	3	2	NA*	<0.5
13	1	1	2	1	0.5	0.6
	2	0.5	3	1	NA*	<0.5

*No available doses satisfying the EWOC criteria

15.4. Dose Recommendation

After at least 3 patients in a cohort become evaluable, the posterior distribution for the probabilities of DLT rates at different dose levels will be obtained. The results of this analysis will be summarized in terms of the estimated probabilities that the true rate of DLT at each dose-level has of lying in each of the following intervals:

- [0, 0.16) under-dosing
- [0.16, 0.33) targeted toxicity
- [0.33, 1] excessive toxicity

The escalation with overdose control (EWOC) criteria will be used to guide dose recommendations for each cohort. A dose will not be considered admissible for the next cohort unless, given the current data, there is a small chance (posterior probability < 25%) that this dose is excessively toxic (DLT rate > 33%).

Within the constraints of the EWOC criteria, dose recommendations will be based on maximizing the posterior probability that the DLT rate is in the targeted toxicity interval.

The dose recommended for the next cohort will be the 1 that has maximum probability of being in the targeted toxicity region (16% – 33% DLT rate), provided it satisfies the EWOC criteria and does not represent more than a doubling (≤ 100% increase) of the current dose.

If the recommended dose satisfying the EWOC criteria is > 100% increase in dose, then escalation will proceed to the highest dose level which is ≤ 100% increase from current dose.

The dose recommended by the BLRM may be regarded as guidance and information to be integrated with a clinical assessment of the toxicity profiles observed at the time of analysis in determining the next dose level to be investigated.

Details of the criteria for dose escalation and determination of the MTD are provided in Section 8.6.1.

15.5. Discussion

The BLRM with EWOC for the dose-escalation phase of the study enables the use of all safety data in the study when making dose-escalation recommendations.

The metrics provided in this section demonstrate that the model is robust to different scenarios of the truth, selecting the MTD with high probability. In general, the model is conservative due to the overdose control criterion. In all scenarios, the probabilities of recommending a dose with excessive toxicity (probability of DLT greater than 33%) are much smaller than the probabilities of recommending a dose with targeted toxicity (probability of DLT between 16% and 33%) as the MTD. In addition, the average proportion of patients receiving a dose with excessive toxicity (probability of DLT greater than 33%) is less than 13%.

On-study recommendation based on the model are consistent with the clinical decision-making process, and should be considered in conjunction with other available clinical information by the SRC in making dose recommendations for purposes of estimating the MTD.

16. LIST OF REFERENCES

Ahn C. An evaluation of phase I cancer clinical trial designs. Stat Med 1998;17:1537-49.

Amiri-Kordestani L, Blumenthal GM, Xu QC, et al. FDA approval: ado-trastuzumab emtansine for the treatment of patients with HER2-positive metastatic breast cancer. Clinical cancer research : an official journal of the American Association for Cancer Research 2014;20:4436-41.

Babb J, Rogatko A, Zacks S. Cancer phase I clinical trials: efficient dose escalation with overdose control. Stat Med 1998;17:1103-20.

Bajetta E, Ferrari L, Martinetti A, et al. Chromogranin A, neuron specific enolase, carcinoembryonic antigen, and hydroxyindole acetic acid evaluation in patients with neuroendocrine tumors. Cancer 1999;86:858-65.

Balon HR, Brown TL, Goldsmith SJ, et al. The SNM practice guideline for somatostatin receptor scintigraphy 2.0. J Nucl Med Technol 2011;39:317-24.

Barbieri F, Bajetto A, Pattarozzi A, et al. Peptide receptor targeting in cancer: the somatostatin paradigm. Int J Pept 2013;2013:926295.

Barok M, Joensuu H, Isola J. Trastuzumab emtansine: mechanisms of action and drug resistance. Breast cancer research : BCR 2014;16:209.

Brabander T, Kwekkeboom DJ, Feelders RA, Brouwers AH, Teunissen JJ. Nuclear Medicine Imaging of Neuroendocrine Tumors. Front Horm Res 2015;44:73-87.

Caplin ME, Pavel M, Cwikla JB, et al. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. N Engl J Med 2014;371:224-33.

Metastatic well-differentiated gastrointestinal neuroendocrine (carcinoid) tumors: Systemic therapy options to control tumor growth and symptoms of hormone hypersecretion. 2016. (Accessed May 12, 2016, 2016,

Committee for Medicinal Products for Human Use (CHMP). Guideline on Clinical Trials in Small Populations. 2006.

Creutzfeldt W, Lembcke B, Folsch UR, Schleser S, Koop I. Effect of somatostatin analogue (SMS 201-995, Sandostatin) on pancreatic secretion in humans. The American journal of medicine 1987;82:49-54.

D'Alessandro M, Mariani P, Lomanto D, Carlei F, Lezoche E, Speranza V. Serum neuron-specific enolase in diagnosis and follow-up of gastrointestinal neuroendocrine tumors. Tumour biology : the journal of the International Society for Oncodevelopmental Biology and Medicine 1992;13:352-7.

de Herder WW, Hofland LJ, van der Lely AJ, Lamberts SW. Somatostatin receptors in gastroentero-pancreatic neuroendocrine tumours. Endocr Relat Cancer 2003;10:451-8.

Dillman RO, Koziol JA. Phase I cancer trials: limitations and implications. Molecular biotherapy 1992;4:117-21.

Duprat JP, Landman G, Salvajoli JV, Brechtbühl ER. A review of the epidemiology and treatment of Merkel cell carcinoma. Clinics 2011;66:1817-23.

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228-47.

Elisei R, Schlumberger MJ, Muller SP, et al. Cabozantinib in progressive medullary thyroid cancer. J Clin Oncol 2013;31:3639-46.

Fasano M, Della Corte CM, Papaccio F, Ciardiello F, Morgillo F. Pulmonary Large-Cell Neuroendocrine Carcinoma: From Epidemiology to Therapy. J Thorac Oncol 2015;10:1133-41.

FDA Guidance for Industry (July 2009) Drug-induced liver injury: Premarketing clinical evaluation. 2009. (Accessed May 21, 2016, 2016, at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf.)

Flyvbjerg A, Marshall SM, Frystyk J, Hansen KW, Harris AG, Orskov H. Octreotide administration in diabetic rats: effects on renal hypertrophy and urinary albumin excretion. Kidney international 1992;41:805-12.

Galsky MD, Eisenberger M, Moore-Cooper S, et al. Phase I trial of the prostate-specific membrane antigen-directed immunoconjugate MLN2704 in patients with progressive metastatic castration-resistant prostate cancer. J Clin Oncol 2008;26:2147-54.

Gatsonis C, Greenhouse JB. Bayesian methods for phase I clinical trials. Stat Med 1992;11:1377-89.

Hadoux J, Pacini F, Tuttle RM, Schlumberger M. Management of advanced medullary thyroid cancer. The Lancet Diabetes & Endocrinology 2016;4:64-71.

Harding M, McAllister J, Hulks G, et al. Neurone specific enolase (NSE) in small cell lung cancer: a tumour marker of prognostic significance? Br J Cancer 1990;61:605-7.

Hatzoglou A, Ouafik L, Bakogeorgou E, Thermos K, Castanas E. Morphine cross-reacts with somatostatin receptor SSTR2 in the T47D human breast cancer cell line and decreases cell growth. Cancer Res 1995;55:5632-6.

Hofland LJ, Lamberts SW. Somatostatin receptor subtype expression in human tumors. Ann Oncol 2001;12 Suppl 2:S31-6.

Hofmann M, Maecke H, Borner R, et al. Biokinetics and imaging with the somatostatin receptor PET radioligand (68)Ga-DOTATOC: preliminary data. Eur J Nucl Med 2001;28:1751-7.

Hou JM, Krebs MG, Lancashire L, et al. Clinical significance and molecular characteristics of circulating tumor cells and circulating tumor microemboli in patients with small-cell lung cancer. J Clin Oncol 2012;30:525-32.

Im H, Shao H, Park YI, et al. Label-free detection and molecular profiling of exosomes with a nano-plasmonic sensor. Nat Biotechnol 2014;32:490-5.

International Conference on Harmonization. E8: General Considerations for Clinical Trials. In: Harmonization ICo, ed.1997.

Jeong S, Park J, Pathania D, Castro CM, Weissleder R, Lee H. Integrated Magneto-Electrochemical Sensor for Exosome Analysis. ACS Nano 2016;10:1802-9.

Kaupmann K, Bruns C, Raulf F, Weber HP, Mattes H, Lubbert H. Two amino acids, located in transmembrane domains VI and VII, determine the selectivity of the peptide agonist SMS 201-995 for the SSTR2 somatostatin receptor. The EMBO journal 1995;14:727-35.

Khan MS, Kirkwood A, Tsigani T, et al. Circulating tumor cells as prognostic markers in neuroendocrine tumors. J Clin Oncol 2013;31:365-72.

Kunz PL. Carcinoid and neuroendocrine tumors: building on success. J Clin Oncol 2015;33:1855-63.

Kwekkeboom DJ, Teunissen JJ, Bakker WH, et al. Radiolabeled somatostatin analog [177Lu-DOTA0,Tyr3]octreotate in patients with endocrine gastroenteropancreatic tumors. J Clin Oncol 2005;23:2754-62.

Lehman J, Hoeksema M, Chen H, Shi C, Eisenberg R, Massion PP. Loss of somatostatin receptor 2 expression and lung cancer growth. J Clin Oncol 2015;33:7569.

Leighton JK. Center for Drug Evaluation and Research Application Number 125427Orig1s000, Pharmacology Review, File for BLA 125427. In: Administration UFaD, ed.2013.

Liapakis G, Fitzpatrick D, Hoeger C, Rivier J, Vandlen R, Reisine T. Identification of ligand binding determinants in the somatostatin receptor subtypes 1 and 2. The Journal of biological chemistry 1996;271:20331-9.

Octreoscan prescribing information. Mallinckrodt Pharmaceuticals, 2015. (Accessed May 13, 2016, at http://www2.mallinckrodt.com/WorkArea/DownloadAsset.aspx?id=501.)

Mamdani H, Induru R, Jalal SI. Novel therapies in small cell lung cancer. Translational lung cancer research 2015;4:533-44.

Massironi S, Conte D, Sciola V, et al. Plasma chromogranin A response to octreotide test: prognostic value for clinical outcome in endocrine digestive tumors. The American journal of gastroenterology 2010;105:2072-8.

Mato E, Matias-Guiu X, Chico A, et al. Somatostatin and somatostatin receptor subtype gene expression in medullary thyroid carcinoma. J Clin Endocrinol Metab 1998;83:2417-20.

McGranahan N, Furness AJ, Rosenthal R, et al. Clonal neoantigens elicit T cell immunoreactivity and sensitivity to immune checkpoint blockade. Science 2016;351:1463-9.

Misumi A, Shiratori K, Lee KY, Barkin JS, Chey WY. Effects of SMS 201-995, a somatostatin analogue, on the exocrine pancreatic secretion and gut hormone release in dogs. Surgery 1988;103:450-5.

Morabito A, Carillio G, Daniele G, et al. Treatment of small cell lung cancer. Critical reviews in oncology/hematology 2014;91:257-70.

Mountain CF. The international system for staging lung cancer. Seminars in surgical oncology 2000;18:106-15.

Mukherjee A, Pandey U, Chakravarty R, Sarma HD, Dash A. Development of single vial kits for preparation of (68)Ga-labelled peptides for PET imaging of neuroendocrine tumours. Molecular imaging and biology : MIB : the official publication of the Academy of Molecular Imaging 2014;16:550-7.

Small Cell Lung Cancer Treatment. 2016. (Accessed April 25, 2016, at http://www.cancer.gov/types/lung/patient/small-cell-lung-treatment-pdq.)

NCCN Clinical Practice Guidelines in Oncology: Neuroendocine Tumors Version 1.2016. National Comprehensive Cancer Network, 2016. (Accessed April 25, 2016,

Neuenschwander B, Branson M, Gsponer T. Critical aspects of the Bayesian approach to phase I cancer trials. Stat Med 2008;27:2420-39.

Nghiem PT, Bhatia S, Lipson EJ, et al. PD-1 Blockade with Pembrolizumab in Advanced Merkel-Cell Carcinoma. N Engl J Med 2016.

O'Byrne KJ, Halmos G, Pinski J, et al. Somatostatin receptor expression in lung cancer. Eur J Cancer 1994;30a:1682-7.

Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. American journal of clinical oncology 1982;5:649-55.

Pisarek H, Stepien T, Kubiak R, Borkowska E, Pawlikowski M. Expression of somatostatin receptor subtypes in human thyroid tumors: the immunohistochemical and molecular biology (RT-PCR) investigation. Thyroid Res 2009;2:1.

Poon KA, Flagella K, Beyer J, et al. Preclinical safety profile of trastuzumab emtansine (T-DM1): mechanism of action of its cytotoxic component retained with improved tolerability. Toxicology and applied pharmacology 2013;273:298-313.

Raymond E, Dahan L, Raoul JL, et al. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. N Engl J Med 2011;364:501-13.

Reubi JC, Schar JC, Waser B, et al. Affinity profiles for human somatostatin receptor subtypes SST1-SST5 of somatostatin radiotracers selected for scintigraphic and radiotherapeutic use. Eur J Nucl Med 2000;27:273-82.

Reubi JC, Waser B, Schaer JC, Laissue JA. Somatostatin receptor sst1-sst5 expression in normal and neoplastic human tissues using receptor autoradiography with subtype-selective ligands. Eur J Nucl Med 2001;28:836-46.

Rinke A, Muller HH, Schade-Brittinger C, et al. Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID Study Group. J Clin Oncol 2009;27:4656-63.

Robben JH, Visser-Wisselaar HA, Rutteman GR, et al. In vitro and in vivo detection of functional somatostatin receptors in canine insulinomas. J Nucl Med 1997;38:1036-42.

Rodon J, Garrison M, Hammond LA, et al. Cantuzumab mertansine in a three-times a week schedule: a phase I and pharmacokinetic study. Cancer Chemother Pharmacol 2008;62:911-9.

Rogatko A, Schoeneck D, Jonas W, Tighiouart M, Khuri FR, Porter A. Translation of innovative designs into phase I trials. J Clin Oncol 2007;25:4982-6.

Shah MH, Lorigan P, O'Brien ME, et al. Phase I study of IMGN901, a CD56-targeting antibody-drug conjugate, in patients with CD56-positive solid tumors. Invest New Drugs 2016;34:290-9.

Strosberg J, Wolin E, Chasen B, et al. 177-Lu-Dotatate Significantly Improves Progression-Free Survival in Patients with Midgut Neuroendocrine Tumors: Results of the Phase III NETTER-1 Trial. 2015 Neuroendocrine Tumor Symposium; 2015; Austin TX. p. C39.

Strosberg J, El-Haddad G, Wolin E, Hendifar A, et al. Phase 3 Trial of 177-Lu-Dotatate for Midgut Neuroendocrine Tumors. N Engl J Med 2017;376;125-135.

Strosberg J, Wolin E, Chasen B, Kulke M, et al. NETTER-1 Phase III in Patients with Midgut Neuroendocrine Tumors Treated with 177-Lu-Dotatate: Efficacy, Safety, QoL Results and Subgroup Analysis. Endocrine Abstracts 2016;47;OC8.

Tamura Y. Study on ectopic calcification in bone marrow of rat tibia caused by vinblastine. The Bulletin of Tokyo Medical and Dental University 1986;33:9-22.

Thake DC, Naylor MW, Denlinger RH, Guarino AM, Cooney DA. Preclinical toxicologic evaluation of maytansine NSC-153858 in dogs and monkeys. In: Battelle CL, Ohio, ed.1975.

van der Zwan WA, Bodei L, Mueller-Brand J, de Herder WW, Kvols LK, Kwekkeboom DJ. GEPNETs update: Radionuclide therapy in neuroendocrine tumors. Eur J Endocrinol 2015;172:R1-8.

Verma S, Miles D, Gianni L, et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. N Engl J Med 2012;367:1783-91.

von Pawel J, Schiller JH, Shepherd FA, et al. Topotecan versus cyclophosphamide, doxorubicin, and vincristine for the treatment of recurrent small-cell lung cancer. J Clin Oncol 1999;17:658-67.

Wangberg B, Nilsson O, Johanson VV, et al. Somatostatin Receptors in the Diagnosis and Therapy of Neuroendocrine Tumor. Oncologist 1997;2:50-8.

Waser B, Tamma ML, Cescato R, Maecke HR, Reubi JC. Highly efficient in vivo agonist-induced internalization of sst2 receptors in somatostatin target tissues. J Nucl Med 2009;50:936-41.

Wells SA, Jr., Robinson BG, Gagel RF, et al. Vandetanib in patients with locally advanced or metastatic medullary thyroid cancer: a randomized, double-blind phase III trial. J Clin Oncol 2012;30:134-41.

Yao JC, Lombard-Bohas C, Baudin E, et al. Daily oral everolimus activity in patients with metastatic pancreatic neuroendocrine tumors after failure of cytotoxic chemotherapy: a phase II trial. J Clin Oncol 2010;28:69-76.

Yao JC, Shah MH, Ito T, et al. Everolimus for advanced pancreatic neuroendocrine tumors. N Engl J Med 2011;364:514-23.

Yao JC, Fazio N, Singh S, et al. Everolimus for the treatment of advanced, non-functional neuroendocrine tumours of the lung or gastrointestinal tract (RADIANT-4): a randomised, placebo-controlled, phase 3 study. The Lancet 2016;387:968-77.

Yoshida H, Sekine I, Tsuta K, et al. Amrubicin monotherapy for patients with previously treated advanced large-cell neuroendocrine carcinoma of the lung. Jpn J Clin Oncol 2011;41:897-901.

Zhang CY, Yokogoshi Y, Yoshimoto K, Fujinaka Y, Matsumoto K, Saito S. Point mutation of the somatostatin receptor 2 gene in the human small cell lung cancer cell line COR-L103. Biochemical and biophysical research communications 1995;210:805-15.