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

Statistical Analysis Plan

Protocol Number	PEN-221-001
NCT Number	NCT02936323
Date of SAP	21-Jul-2020

[redacted]

Statistical Analysis Plan for Phase I/II Oncology Studies

Sponsor Name: Tarveda Therapeutics, Inc.

Protocol Number: PEN-221-001.

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 Version and Date: Version 8.0 (12-Jul-2019). Includes Amendment 1 (21-Jun-2016), Amendment 2 (16-Dec-2016), Amendment 3 (02-Mar-2017), Amendment 4 (11-Dec-2017), Amendment 5 (03-Aug-2018), Amendment 6 (08-Jan-2019), and Amendment 7 (12-Jul-2019)

[redacted]

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Revision History

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2.0	28-Apr-2020	[redacted]	Updated to include protocol amendments 5, 6 and 7.
3.0	21-Jul-2020	[redacted]	Corrected references section

I confirm that I have reviewed this document and agree with the content.

Approvals		
Syneos Health Approval		
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Tarveda Approval		
[redacted]	[redacted]	21 Jul 2020
[redacted] Sponsor Contact	Signature	Date (DD-Mmm-YYYY)

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[redacted]

1. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation or specialist term	Explanation
[redacted]	
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC8h	Area under the concentration time curve from time zero to 10h
AUCt	Area under the plasma concentration time curve from time zero to time of the last measurable concentration
AUCtau	Area under the plasma concentration time curve from time zero to the end of the dosing interval
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)
CAV	Cyclophosphamide-doxorubicin-vincristine
CBC	Complete blood count
[redacted]	
CI	Confidence intervals
CL	Clearance
Cmax	Maximum plasma concentration

Abbreviation or specialist term	Explanation
CR	Complete response
CT	Computed tomography
[redacted]	
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of Variation
D	Day (as in C1D1 for Cycle 1 Day 1)
DD	Dose-determining
DLT	Dose-limiting toxicity
DM1	Mertansine
DOR	Duration of Response
EA	Efficacy analysis
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EOT	End of treatment
EWOC	Escalation with overdose control
FAS	Full Analysis Set
FDA	Food and Drug Administration
FFPE	Formalin-fixed paraffin-embedded
FOCBP	Females of childbearing potential
GCP	Good Clinical Practice
GEP	Gastroenteropancreatic
GI	gastrointestinal
HCG	Human chorionic gonadotropin
ICF	Informed consent form

Abbreviation or specialist term	Explanation
ICH	International Conference on Harmonisation
IHC	Immunohistochemistry
IP	Investigational product
ITT	Intent-to-treat
IV	Intravenous or intravenously
LCNEC	Large cell neuroendocrine carcinoma
LD	Longest diameter (when used with RECIST and tumor measurements) or limited disease (when used with SCLC cancer staging)
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NA	Not applicable
NCA	Non-compartmental Analysis
NCI	National Cancer Institute
NET	Neuroendocrine tumor
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

Abbreviation or specialist term	Explanation
PR	Partial response
PS	Performance status
PT	Preferred Term
QC	Quality Control
QTc	Corrected QT Interval
RBC	Red blood cells
RECIST	Response Evaluation Criteria in Solid Tumors v1.1
RP2D	Recommended phase 2 dose
SA	Safety analysis
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SARI	Somatostatin analog radioisotope imaging
SCLC	Small cell lung cancer
SD	Stable disease
SE	Standard error
SI	Standard International System of Units
SOC	System Organ Class
SOP	Standard operating procedure
SRC	Safety Review Committee
SSTR	Somatostatin receptor
t½	Elimination half-life
TEAE	Treatment-emergent adverse event
TLF	Table, listing and figure
Tmax	Time to maximum plasma concentration
TSH	Thyroid-stimulating hormone

Abbreviation or specialist term	Explanation
ULN	Upper limit of normal
V	Volume of distribution
Vss	Volume of distribution at steady state
WBC	White blood cells
WHO	World Health Organization

2. INTRODUCTION

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.

Study 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.

The purpose of this statistical analysis plan (SAP) is to ensure that the data listings, summary tables and figures which will be produced, and the statistical methodologies that will be used, are complete and appropriate to allow valid conclusions regarding the study objectives.

[redacted] will perform the statistical analyses and are responsible for the production and quality control of all tables, listings and figures (TLFs) including the Bayesian approach to efficacy endpoints. Development, use, and reporting results of an adaptive Bayesian logistic regression model (BLRM) guided by the escalation with overdose control (EWOC) principle to make dose recommendations and estimate the maximum tolerated dose (MTD) and will be carried out by a 3rd party vendor chosen by Tarveda Other results will be produced by [redacted].

3. STUDY OBJECTIVES

3.1. Phase 1 (Dose Escalation)

3.1.1. Primary

The primary objective of Phase 1 is to:

Investigate the safety and tolerability, determine the MTD, and recommended phase 2 dose (RP2D) of PEN-221 when administered intravenously (IV) on an every 3 week schedule in patients with SSTR2 expressing advanced cancers, including gastroenteropancreaticor lung or thymus or other NETs or SCLC or large cell neuroendocrine carcinomaof the lung.

3.1.2. 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 Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, and duration of response (DOR).

3.1.3. Exploratory

[redacted]

3.2. Phase 2a (Dose Expansion)

3.2.1. 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 (GI) 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 DOR in the following tumor-specific cohort of patients:

- Patients with advanced or metastatic SCLC.

3.2.2. Secondary

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 PFS and OS in the above tumor-specific cohorts of patients whose tumors express SSTR2.
- Evaluate ORR and DOR 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 PK of PEN-221, DM1, and peptide from PEN-221 in the above tumor-specific cohorts of patients whose tumors express SSTR2.

3.2.3. Exploratory

[redacted]

4. STUDY DESIGN

Study PEN-221-001 is a first-in-human, open-label, Phase 1/2a study evaluating the safety, PK, PDc, 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><td>Phase 1

Dose Escalation</td><td>Phase 2a

Expansion</td></tr>
<tr><td>Number of dose cohorts dependent on toxicity results as determined by Bayesian logistic regression model with overdose control</td><td>Patients with advanced or metastatic, well-differentiated, low- or intermediate grade gastrointestinal mid-gut NET

n=3535</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>

4.1. Pre-screening Phase

Each patient must demonstrate a tumor that is positive for expression of SSTR2 using an approved SARI agent within 180 days of Cycle 1 Day 1 (C1D1). If historical data is not available and after provision of written informed consent for pre-screening, patients will have their cancers assessed for SSTR2 expression using an approved SARI agent.

4.2. Screening Phase

After provision of written informed consent for the study and successful demonstration that tumor uptake of SSTR2 analogs is sufficient per inclusion criteria, patients will proceed to the Screening phase of the study. Screening assessments are to be performed within 14 days before the first study drug dose, with the exception of CT (computed tomography) or MRI (magnetic resonance imaging) 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 C1D1 (baseline).

4.3. Treatment Phase (Phase 1 and Phase 2a)

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

The safety, PK, PDc, and anti-tumor activity of PEN-221 will be assessed.

4.3.1. Phase 1

Phase 1 will employ an adaptive 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 sub-therapeutic 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.

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.

4.3.2. 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 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.

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 adverse events (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.

During Phase 2a, approximately 75 patients will be enrolled in the following cohorts: gastrointestinal mid-gut NET (n=35, 25 PRRT-naïve, 10 PRRT-recurrent), 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.

Patients in both phases 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.

Patients may withdraw from the study or at any time for any reason, without prejudice to their medical care. The Investigator also has the right to discontinue treatment with PEN-221 and withdraw patients from the study for reasons detailed in Protocol Section 7.8

The number of centers is to be determined.

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.

4.4. Patient Selection

4.4.1. Inclusion Criteria

See Protocol Section 7.3 for details.

4.4.2. Exclusion Criteria

See Protocol Section 7.4 for details.

4.5. Treatment Assignment & Blinding

This is an open-label study and blinding is not applicable for this study.

4.6. Administration of Study Medication

PEN-221 Concentrate for Solution for Injection is a [redacted] solution containing PEN-221, a DM1-peptide drug conjugate with affinity for the human SSTR2 receptor, [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. Note if a patient does change dose, their data will be summarized under the starting dose.

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.

4.7. Timing of Analyses

4.7.1. Interim Analysis (end of Phase 1):

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 Protocol Section 8.6.1.

An informal analysis of safety, efficacy, and certain PK and PDc endpoints occurred after all patients enrolled in Phase I had discontinued treatment.

4.7.2. Interim Analysis (Phase 2a):

In Phase 2a, no formal interim analysis is planned. However, preliminary efficacy and safety was assessed in approximately the first 10 patients per cohort before deciding whether to proceed to the second stage of each cohort.

4.7.3. Final Analysis (end of Phase 2a):

In April 2020, the SRC concluded that the trial had achieved its objectives and enrollment could be closed. Database lock is planned for Q3 2020 and final analysis will occur after lock.

4.7.4. Schedule of Assessments

Full details can be found in Protocol Table 2 (Phase 1) and Table 3 (Phase 2a).

Scheduled visits are Pre-screening, Screening, treatment cycles – D1, D8 and D15, End of Treatment (EOT), Safety Follow-up (last dose of study drug + 28 Days) and a Progression Follow up.

Day 8 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, 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.

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. 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).

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).

4.7.5. 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.

4.7.6. 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. ANALYSIS POPULATIONS

The patient populations will be summarized in the disposition table. The following patient populations will be evaluated and used for presentation and analysis of the data:

5.1. The Full Analysis Set (FAS)

The FAS (intent-to-treat (ITT)) population comprises all patients enrolled into the study and who receive any amount of study drug. Patients will be analyzed according to treatment received. Unless specified otherwise, this population will be used for summaries of patient disposition, demographics and baseline characteristics, efficacy endpoints PFS and OS, PEN-221 exposure, medications and significant non-drug therapies and patient listings.

5.2. The Efficacy Analysis (EA) Population

The efficacy analysis (EA) population comprises all enrolled patients who receive any amount of study drug and have at least 1 post-baseline efficacy assessment (RECIST 1.1). Patients will be analyzed according to treatment received. Unless specified otherwise, this population will be used for summaries of efficacy endpoints ORR and DOR. This is the primary efficacy analysis population.

5.3. The Safety Analysis (SA) Population

The safety analysis (SA) population comprises all enrolled patients who receive any amount of study drug and have at least 1 post-baseline safety evaluation (AE, clinical laboratory assessments, vital signs, ECG (electrocardiogram), ECOG (Eastern Cooperative Oncology Group) scores, physical examination). Patients will be analyzed according to treatment received. The SA will be used for all analyses of safety endpoints.

5.4. The Per-protocol (PP) Population

The per-protocol (PP) population comprises all enrolled patients who receive at least 1 cycle of study drug, have at least 1 post-baseline efficacy assessment, and have no major protocol violations, as defined by the medical monitor and sponsor (see SAP Section 5.8). Patients will be analyzed according to treatment received. The PP population will be used for all analyses of ORR and DOR. This is the secondary efficacy analysis population.

5.5. The Dose-determining (DD) Population

The dose-determining (DD) population comprises all enrolled patients who receive any amount of study drug in Phase 1 and either experienced a DLT or have been followed for the full DLT evaluation period and has at least 1 post-baseline safety evaluation. The DD population will be used to determine the MTD of PEN-221.

5.6. The Pharmacokinetic (PK) Population

The PK population comprises all enrolled patients who receive any amount of study drug and have at least one measured post-dose concentration for at least one of the PEN-221 relevant analytes as described in the Section 9 of the SAP. Patients with major protocol violations will be assessed on a

patient-by-patient basis for inclusion in the PK population. The PK population will be used for all analyses of PK endpoints.

5.7. The Pharmacodynamic (PDc) Population

The PDc population comprises all patients who have at least one measured PDc biomarker value at either screening or post-dose. Patients with major protocol violations will be assessed on a patient-by-patient basis for inclusion of the post-dose data in the PDc population. The PDc population will be used for all analyses of PD endpoints.

5.8. Protocol Deviations

Deviations will be managed as detailed in Protocol Deviation and Non-compliance Management Plan.

Deviations are entered directly into the eCRF and categorized as follows:

- Inclusion/exclusion criteria violation.
- Discontinuation criteria violation.
- Study drug administration.
- Use of prohibited concomitant medication(s).
- Non-compliance.
- Safety evaluation(s) not done.
- Efficacy evaluation(s) not done.
- Procedural deviation.

All protocol deviations will be classified as major or minor by the medical monitor and sponsor prior to the final analysis as detailed in Protocol Deviation and Non-compliance Management Plan.

All protocol deviations will be provided in a by-patient listing.

6. STATISTICAL METHODOLOGY

See SAP Section 16 for general programming considerations.

6.1. General Methods

[redacted] will be responsible for reporting the demographic, safety, efficacy and PK/PDc data including the development, use and reporting results of a Bayesian model to calculate CBR and ORR. A 3rd party vendor will be responsible for the development, use and reporting of the Phase 1 primary objective (determining MTD and RP2D) based on the adaptive BLRM in conjunction with EWOC.

SAS version 9.4 or later will be used.

Phoenix WinNonLin version 6.4 or higher will be used for PK parameters derivation.

Categorical variables will be summarized using number of observations (n), frequency, and percentages of patients, unless stated otherwise. Unless stated otherwise, the calculation of percentages will be based on the total number of patients in the population of interest. Thus counts of missing observations will be included in the denominator and presented as a separate category.

Continuous variables will be summarized using the number of observations (n), mean, standard deviation, median, minimum, and maximum, unless stated otherwise.

In cases where n≤1 patient, no summary table/figure will be produced but the data for this patient will be listed.

Time to event data (DOR, PFS and OS) will be analyzed using Kaplan-Meier survival estimates. Summary statistics will include median, 25th, and 75th percentile survival times and corresponding 95% confidence intervals.

Unless otherwise specified, all disposition, demography, baseline characteristics and safety summaries will be presented by total and study phase as follows:

- 'Study Total' (Phase 1 and Phase 2a combined).).
- 'xx.x mg' (dose 1, dose 2 etc - a column for each dose level in Phase 1).
- For Phase 2a, tumor types will be summarized on separate pages by the following by-lines (sub-headings): 'Overall', 'GINET (PRRT Naive)', 'GINET (PRRT Recurrent)', 'GINET (Total)', 'PNET' and 'SCLC'
    - '< 8.8 mg/m sq'
    - '8.8 mg/m sq'
    - '> 8.8 mg/m sq'
    - 'Total'

Efficacy tables will be as described above but without the 'Study Total' column.

For Phase 2a, dose level in mg/m sq is determined using the first dose of PEN-221 in mg received on C1D1. Body surface area (BSA) will be determined using the Du Bois formula:

BSA (m sq) = 0.007184 x (patient height in cm)$^{0.725}$ x (patient weight in kg at C1 D1)$^{0.425}$

The total number of patients in the dose level (for Phase 1), or by tumor-specific cohorts/dose level (for Phase 2a) (N) will be used as the denominator for percentage calculations, unless stated otherwise in the table shell.

Listings will also be provided for Phase 1 and Phase 2a combined. In general, the listings will be sorted by phase (C1D1 dose level within Phase 1 and Phase 2a combined), patient number and assessment date (and time), if applicable. The listings will be presented as follows (see shells for further details):

Example for Phase 1, 'Phase 1 xx.x mg'.

Example for Phase 2a, 'Phase 2a PNET 8.8 mg/m sq'

Missing records will be omitted from the listings, and missing data within a record will be left blank.

Reasons why scheduled visits were not completed will be listed when known.

Multiple assessments at a given time point (planned, repeat) will not be included in summary tables unless specified otherwise, but will be included in the listings. If there are multiple results at a given visit, eg a repeated laboratory test within a visit, the earliest value will be used in the tables.

In general, unscheduled visit data will be listed but not included in the summary tables by time point. Unscheduled data will be included to identify the worst case post first PEN-221 dose for safety shift tables.

The study day is the day relative to the date of first dose of PEN-221 study medication, where Day 1 is the day of first dose of PEN-221 study medication.

The first dose date is defined as the first non-missing date where a non-zero dose of PEN-221 study medication was recorded.

The last dose date is defined as the last non-missing date where a non-zero dose of PEN-221 study medication was recorded. For patients ongoing at time of analysis, last dose date will be considered the date of the most recent study visit in the database for that patient where a non-zero dose of PEN-221 study medication was recorded.

Unless otherwise specified, baseline is the last non-missing observation before the start of PEN-221 study drug medication, which is expected to be Day 1 of Cycle 1 (pre-dose), or screening if the Day 1 data are not available.

6.2. Visit Windows

There are no plans to derive visit windows; visits will be used in the analyses as reported on the electronic Case Report Form (eCRF).

6.3. Handling of Dropouts and Missing Data

There will be no imputation of missing data except partial diagnosis dates (see SAP Section 7.5). Missing data will be treated as missing except for AEs where toxicity and relationship to study drug are missing (see SAP Section 12.1). SAP Section 7.4.2 describes how to determine if a medication is concomitant if partial dates exist. Similarly, SAP Section 12.1 describes how to determine if an adverse event is treatment emergent where partial dates exist.

6.4. Pooling of Investigative Sites

As it is anticipated that accrual will be spread thinly across centers and summaries of data by center would be unlikely to be informative, data from all participating centers will be pooled prior to analysis.

6.5. Subgroups

There are no plans for any subgroup analysis for the efficacy and safety endpoints. SAP Sections 9 and 10 detail subgroup analysis of the PK and PDc endpoints.

6.6. Determination of Sample Size

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.

6.6.1. 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 Protocol Section 15) 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.

6.6.2. 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,177Lu-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 1 provides more probability statements about the true ORR based on number of responses observed in 20 patients, and Table 2 provides probability statements about the true CBR based on the number of patients with clinical benefit observed in 20 patients

Table 1: 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 2 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.

Note at the time of the SRC decision to close the trial to enrollment, the number of patients enrolled in the GINET cohort was 31, (25 PRRT naïve, 6 PRRT recurrent). For the PNET cohort 15, and for the SCLC cohort 17.

7. PATIENT CHARACTERISTICS

7.1. Patient Disposition

A tabulation of patient disposition, including the number of patients enrolled in each patient population and the number of protocol violations. The table will also include the number that withdrew prior to completing the study, and the primary reasons for withdrawal. The number of patients completing treatment, and the primary reasons for treatment discontinuation will also be summarized. A patient listing of study/treatment completion information, including the reason for premature study withdrawal/treatment discontinuation, if applicable, will be presented. The FAS will be used for the summary tables.

A listing of protocol deviations will be provided including category of deviation as recorded on the eCRF and whether the deviation was considered major or minor as determined by the medical monitor.

A listing of analysis populations will be provided.

Eligibility criteria will be listed including patient consent data.

7.2. Background and Demographic Characteristics

Demographic and other baseline data, including age, sex, race, ethnicity, height (cm), weight (kg) and baseline ECOG performance status will be listed individually by patient and summarized. The FAS will be used.

The following derivations will be used:

- Age at C1D1 = (C1D1 visit date - date of birth + 1) / 365.25 and truncated to complete years.
- Height (in cm) = height (in inches) * 2.54
- Weight (in kg) = weight (in lbs) * 0.4536

Demographic data and baseline characteristics will be listed for all enrolled patients.

7.3. Treatment Exposure and Compliance

Patients will receive PEN-221 administered IV over 60 minutes on Day 1 every 3 weeks.

The extent of exposure will be examined by summarizing the variables below:

- Actual dose (mg) ('Dose Administered (mg)' on eCRF) and BSA dose (mg/m sq) of PEN-221 administered overall and in each cycle.
- PEN-221 dosage interrupted or not in each cycle.
- Duration of exposure (weeks (wk)) for PEN-221. This is calculated as: (Last administration date – first administration date) + 1 / 7

- Number of cycles started (where a non-null value for 'Dose administered (mg)' is captured on Day 1. Presented as a categorical and continuous variable. Categories are '1 – 2 Cycles', '2 – 4 Cycles', '> 4 Cycles'.
- Dose intensity (mg/wk) overall and in each cycle. Computed as the ratio of actual dose received and actual cycle duration. Cycle duration (wk) is calculated as:

  (Administration date of Cx+1) – (administration date of Cx) + 1 / 7

The last cycle duration will be set to 3 weeks.

- Relative dose intensity (%) overall and in each cycle. Computed as the ratio of dose intensity and planned dose received (BSA Dose mg/m sq)/planned duration (3 weeks): 100 * dose intensity (mg/wk) / planned dose intensity (mg/wk).

A relative dose intensity of 100% indicates that the drug was administered at the correct dose within the planned timeframe (e.g. every 21 days).

All study drug administration data captured on the eCRF will be listed.

7.4. Prior and Concomitant Medications and Therapies

All medications will be documented from 30 days before first study drug dose on C1D1 through to the Safety Follow-up visit. Medications will be presented in tabular form using Anatomical Therapeutic Chemical (ATC) level 2 (therapeutic main group) and ATC level 4 (chemical subgroup) via the latest World Health Organization Drug classification Dictionary (WhoDRUG). All medications will be sorted by descending order of occurrence in the study total group for ATC level 2, then ATC level 4 terms. The number and percentage of patients who took at least 1 drug within each specific ATC level 4 will be presented. Patients will only be counted once if they are taking more than 1 medication or take the same medication more than once.

All prior and concomitant medications will be listed including the derived study day (for both start and stop dates) and a flag for prior medications.

7.4.1. Prior Medication

A medication is considered prior if the medication stop date is before treatment start date. Prior medications will be summarized. The FAS will be used.

Prior medications will be listed with the concomitant medications for all enrolled patients. Prior medications will be flagged in the listing.

7.4.2. Concomitant Medication

All medications will be considered concomitant unless the medication stop date is before treatment start date.

Medications with incomplete start dates will be considered concomitant if the:

- Day and month are missing and the year is equal to or after the year of the first dose date;
- Day is missing and the year is after the year of the first dose;
- Day is missing and the year is equal to the year of the first dose date and the month is equal to or after the month of the first dose date;
- Year is missing; or
- Complete date is missing.

Concomitant medications will be summarized. The FAS will be used.

Concomitant medications will be listed with the prior medications for all enrolled patients.

7.4.3. Other Therapies

Prior therapies (including systemic therapies, radiation and surgeries) will be summarized using the FAS and listed for all enrolled patients.

Concomitant procedures will be listed for all enrolled patients.

7.5. Medical Histories

Medical histories/active symptoms will be coded using the latest Medical Dictionary for Regulatory Activities (MedDRA), and coded system organ class (SOC) and preferred terms (PTs) will be used for the summary table. All medical histories will be sorted by decreasing order of occurrence in the study total group for SOC and decreasing order of occurrence of PT within the SOC. The FAS will be used.

Medical history conditions/active symptoms will be listed for all enrolled patients.

7.5.1. Cancer-Related Medical History

Cancer diagnosis and history and SSTR tumor imaging will be summarized. Length of time since diagnosis (months) will be derived as follows:

Time since diagnosis at C1D1 = (C1D1 visit date - date of initial diagnosis + 1) / 30.5.

If partial dates exist for initial diagnosis date, the date will be imputed to the 15th of the month (for missing day) or 01JUL (for missing day and month).

The FAS will be used.

Cancer diagnosis and history and SSTR tumor imaging will be listed for all enrolled patients.

8. EFFICACY

Unless otherwise specified, the EA population will be used for the efficacy analyses except PFS and OS where the FAS will be used.

8.1. Primary Efficacy Endpoint and Analysis

Tumor measurements and disease response assessments are to be performed for all patients. Tumor evaluations 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.

Note for efficacy endpoints based on RECIST 1.1, 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.

8.1.1. Primary Analysis of the Primary Efficacy Endpoints

Note for Phase 1, the primary endpoint is the frequency of DLTs associated with a single administration of PEN-221 during the first cycle of treatment. The 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). This is determined based on an adaptive BLRM in conjunction with EWOC as described in Protocol Section 12.6.1 and will be reported separately by a 3rd party vendor. The DD population will be used.

For Phase 2a, the primary endpoint for gastrointestinal mid-gut NET and pancreatic NET is CBR 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, the primary endpoint is ORR 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.

8.1.1.1. Clinical Benefit Rate for Gastrointestinal Mid-gut NET and Pancreatic NET

Clinical benefit rate 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 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.

8.1.1.2. Objective Response Rate (ORR) for SCLC

Objective response rate is defined as the proportion of patients with a best overall CR or PR as defined by RECIST 1.1 using the investigator assessment captured on the eCRF. Both tumor responses without confirmation as well as confirmed tumor responses (by second assessment at least 4 weeks after first assessment) will be used for efficacy evaluation.

ORR will be estimated and presented with 95% confidence intervals (CIs) based on the exact binomial distribution. Confirmed responses and a row including all responses (confirmed and unconfirmed) will be presented in the summary table. Similarly, rates of individual categories of response (i.e. CR, PR, SD and progressive disease (PD)) will be presented. The best overall response per patient will be presented (order from best to worst is CR, PR, SD, PD). Confirmed best response and all responses (confirmed and unconfirmed) will be summarized separately. All response, target lesion, non-target lesion and new lesion data will be listed.

Additionally, a waterfall plot for best percentage change from baseline in the sum of target lesion longest diameters will be provided. The Y axis will be percent change from baseline and patient number on the X axis. A positive result indicates an increase in tumor size; a negative result indicates a decrease (shrinkage).

In addition, for each tumor-specific cohort, a Bayesian approach will be used to estimate the ORR and its 95% credible interval based on the posterior distribution. An equal tailed 95 % credible interval will be calculated. 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. This analysis will be completed for confirmed responders and all responders (confirmed and unconfirmed responses) separately.

8.1.1.3. Duration of Response (DOR) for SCLC

Duration of response is defined as the time from first documented response (CR or PR), as assessed by the investigator, 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 (months) = ([Date of progression/death due to underlying cancer – date of first response] + 1) / 30.5

DOR analyses will be performed using investigator lesion assessments (for RECIST v1.1 criteria) collected in the eCRF.

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.

8.1.2. Secondary Analysis of the Primary Efficacy Endpoints

The analysis will be repeated using the PP population (with the exception of the Bayes analysis which will be based on the EA population only). The analysis using the EA population will be considered the primary analysis.

8.2. Secondary Efficacy Endpoint(s) and Analyses

8.2.1. Tumor Response and Duration of Response for Phase 1

Objective response rate, best overall response and DOR will be analyzed as for the primary analysis for Phase 1 using dose level with the exception that the Bayesian approach will not be used.

8.2.2. Progression Free Survival (PFS)

PFS (months) = ([Date of progression / death – date of first dose] + 1) / 30.5

PFS analyses will be performed using investigator lesion assessments (for RECIST v1.1 criteria) collected in the eCRF.

PFS will be analyzed and presented using the Kaplan-Meier method, along with the estimated median (in months) with 95% CIs, 25th and 75th percentiles. Separate curves will be produced for Phase 1; Phase 2a will be presented on a separate page from Phase 1 and separate curves will be produced for 'GINET (PRRT Naive)', 'GINET (PRRT Recurrent)', 'GINET (Total)', 'PNET' and 'SCLC'. The FAS will be used.

Data collected at the Survival and Progression Follow-up visits (i.e. patient status (dead, alive, lost to follow up), new anticancer treatments) will be listed.

8.2.3. Overall Survival (OS)

Overall survival 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 (months) = ([Date of death – date of first dose] + 1) / 30.5

OS will be analyzed and presented using the Kaplan-Meier method, along with the estimated median (in months) with 95% CIs, 25th and 75th percentiles. Separate curves will be produced for 'Phase 1'; Phase 2a will be presented on a separate page and separate curves will be produced for 'GINET (PRRT Naive)', 'GINET (PRRT Recurrent)', 'GINET (Total)', 'PNET' and 'SCLC'. The FAS will be used.

8.2.4. 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% 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 RP2D to obtain the posterior distribution of the true ORR. The posterior probability that the true ORR is greater than 20% will be reported.

8.2.5. Duration of Response for Gastrointestinal Mid-gut NET and Pancreatic NET

Duration of response for GINET and PNET will be analyzed as described in SAP Section 8.1.1.3 for SCLC.

9. ANALYSIS OF PHARMACOKINETICS

PK analysis will be done for PK population. PK parameters will be derived using Phoenix WinNonLin version 6.4 or higher. The TLFs including inferential analyses will be done in SAS 9.3. The PK concentrations and parameters will be available for:

- PEN-221.
- Total DM1 (unconjugated from PEN-221 plus DM1 that is still a part of the PEN-221).
- Total peptide (unconjugated from PEN-221 plus peptide that is still a part of the PEN-221).
- Free sulfhydryl DM1 (DM1, that has been unconjugated from PEN-221, but hasn't reacted with anything else);
- Measured Unconjugated DM1 (DM1 that has been unconjugated from PEN-221 and reacted with other thiols in plasma plus free sulfhydryl DM1)
- Calculated Unconjugated DM1. (Calculated Unconjugated DM1 concentration will be estimated by the difference between the total DM1 and PEN-221 to estimate the amount of DM1 not associated with PEN-221 and will be listed and summarized together with other analytes).

9.1. PK Sampling Schedule

The PK samples for PEN-221 related analytes will be collected on Cycle 1 Day 1 and Cycle 3 Day 1 (C3D1 for Phase 1 only) 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 (the 10 hour timepoint applies to Phase 1 only). 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.

The allowable time windows for samples after start of infusion very between ±1 minute to ±10 minutes depending upon the planned time of sample collection. For Phase 2a serial blood samples are to be collected on Day 1 of Cycle 1 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 will 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.

The 'allowable time windows' for samples collection after start of infusion vary between ±1 minute to ±10 minutes depending upon the planned time of sample collection. Additional unscheduled PK sampling will be performed for the intra-patient dose escalation (Phase 1 only). The treatment of these data is described in the Section 9.3.2 and other relevant SAP Sections.

9.2. Plasma PK Endpoint

Following PK parameters will be derived using non-compartmental analysis (NCA) for all analytes (including calculated unconjugated DM1) for Cycle 1 Day 1 Phase 1 and 2a and Cycle 3 Day 1 (C3 D1 Phase 1 only) where possible:

- Cmax - the maximum plasma concentration, (ng/mL).
- Cmax/D – dose normalized Cmax
- tmax - time to Cmax, (h).
- AUCt - area under the plasma concentration time curve from zero to the time of the last measurable concentration (ng/mL*h).
- Clast – last quantifiable concentration for dosing interval (ng/mL)
- Tlast – time of last quantifiable concentration for dosing interval) (h)
- AUC8h – partial area under curve from time 0 to 8 hours post-dose, may require extrapolation (ng/mL*h).
- AUCtau - area under the plasma concentration time curve from zero to the end of dosing interval, may need extrapolation (ng/mL*h).
- AUC∞ - area under the plasma concentration time curve from zero to infinity, (ng/mL*h).
- AUCt/D- dose normalized AUCt
- CL – plasma clearance (PEN-221 only) (L/h).
- Vz the apparent volume of distribution (PEN-221 only) (L).
- CLss at steady state (PEN-221 only) (L/h).
- Vss – volume of distribution at steady state (PEN-221 only) (L).
- λz - terminal rate constant (1/h).
- t½ - terminal elimination half-life (h).
- RCmax, RAUCtau and RAUCt – accumulation ratio assessed as the ratio of Cmax, AUCtau or AUCt C3D1 and C1D1.

Some parameters such as Cmax and AUCt will be also presented as dose normalized for statistical comparisons across the dose levels.

9.3. Presentation of Concentration Data

9.3.1. Handling of Missing Data

Missing concentration data for all patients who are administered scheduled study treatments will be considered as non-informative missing and will not be imputed. No concentration estimates will be provided for missing sample values. All enrolled subjects excluded from the PK analysis population or the PK analysis subset will be described in the PK Report, including reason for exclusion.

For the derivation of PK parameters and for the plasma concentration versus time curves and summary statistics, the following rules will apply:

- Concentration values below the assay's lower limit of quantification (BLQ) in pre-dose samples and in samples taken before the time of the first quantifiable concentration will be treated as zero;
- The sampling time of pre-dose samples relative to dosing will also be treated as zero;
- Post-dose BLQ values after the first quantifiable time point will be set to missing.
- If the actual time of sampling is missing, the samples should be excluded from the NCA and concentration summary statistics.
- Samples taken outside the sampling windows will be used for NCA analysis.

9.3.2. Listing and Presentation of Individual Concentration Data

The actual sampling time of PK blood sample collection will be listed for each patient and will include the deviation in time from the protocol scheduled time, if applicable.

All concentrations will be presented in original units as reported by Bioanalytical lab- nM and recalculated in weight by volume units eg ng/mL using molecular weight (MW) for all analytes:

PEN-221 – 1786.55 g/mol

Total DM1, Measured Unconjugated DM1, Calculated Unconjugated DM1, sulfhydryl DM1 – 738.29 g/mol

Total peptide – 1048.26 g/mol

The formula for calculation $conc\ \left(\frac{ng}{mL}\right) = conc(nM) * FW(\frac{g}{mol})/1000$

Individual patient plasma concentration data for PEN-221, Total DM1, Total peptide, Free sulfhydryl DM1, Measured Unconjugated DM1 and Calculated Unconjugated DM1 will be listed by patient, time point and will be summarized at each time point by cohort.

% ratio of Free sulfhydryl DM1, Measured Unconjugated DM1 and Calculated Unconjugated DM1 to PEN-221 and Total DM1 will be also presented calculated from concentrations in nM units.

The following figures will be produced for individual data for PEN-221:

Individual concentration-time profiles will be presented, for each cohort with all patients in the same figure on linear and log-linear scales vs. actual time for Cycle 1 and Cycle 3 (Phase 1 only) for each analyte separately. Profiles for patients within the same cohort will be combined.

Individual concentration-time profiles will be presented, for each cohort with all analytes in the same figure on linear and log-linear scales vs. actual time for Cycle 1 and Cycle 3 (Phase 1 only) for each patient separately.

Intra-patient dose escalation was performed for some patients after completing planned PK sampling for Cycle 3. The timing of the dose escalation was different for different patients. The intense PK samples were taken at the cycle and day when the dose escalation was implemented. These data will be included in the PK concentration listing and presented as individual profiles with a flag for the additional unscheduled visit and information about dose escalation – original dose and escalated dose.

9.3.3. Summary of Concentration Data

PK concentration data for both types of units (nM and ng/mL) and % molar ratios will be summarized by treatment using the following descriptive statistics: n, number and % BLQ, arithmetic mean, SD, CV%, minimum, median and maximum.

Concentrations for samples on day 8 of cycle 1 will be summarized.

Mean concentrations for PEN-221, Total DM1, Total peptide, Free sulfhydryl DM1, Measured Unconjugated DM1 and Calculated Unconjugated DM1 will not be presented if 50% or more of the actual values at any one time point in the terminal phase are BLQ or missing.

Samples after start of infusion taken more than 10 minutes outside the 'allowable time windows' will be excluded from by-time point concentration summary statistics and mean concentration-time plots The exclusions will be decided based on the review of protocol deviation log and communicated to the sponsor prior to implementation.

Mean ± standard deviation concentration-time profiles and % molar ratio-time profiles will be presented, combining the curves for all dose levels within the same figure, on linear and log-linear scales vs. nominal time separately for each analyte.

Additionally mean ± standard deviation concentration-time profiles and % molar ratio-time profiles will be presented, combining the curves for all analytes within the same figure, on linear and log-linear scales vs. nominal time separately for each dose level.

For the patients with escalated dose levels the trough concentrations, if measured after dose escalation, will not be summarized with the patients from the same cohort. The summaries for intense PK sampling after dose will not be provided unless more than 2 patients had the same dose escalation implemented at the same time relative to start of treatment. For these patients their PK concentrations may be summarized and presented in a separate table and mean plots.

9.4. PK parameters derivation

The PK parameters for PEN-221, Total DM1, Total peptide, Free sulfhydryl DM1, Measured Unconjugated DM1 and Calculated Unconjugated DM1 will be estimated using concentrations in ng/ml units as follows:

The apparent Cmax and the corresponding tmax will be read directly from the concentration-time plot (observed data).

Cmax/D will be derived dividing individual values by corresponding dose

AUCt will be calculated using the log-linear trapezoidal interpolation rule for intravenous model.

AUCtau will be calculated using the log-linear trapezoidal interpolation rule for intravenous model with the possible extrapolation to the end of dosing interval if needed.

AUC8h will be calculated using the log-linear trapezoidal interpolation rule for intravenous model with the possible extrapolation to the 8h post-dose if needed. Terminal elimination parameters will be derived if sufficient data are available.

AUC/D will be derived dividing individual values by corresponding dose

The terminal elimination rate constant (λz) will be determined by log linear regression obtained on at least the 3 last quantifiable concentrations and will not include Cmax;t1/2 is calculated by the program as ln2/λz;

The AUC∞ will be calculated by the program as:

AUC∞ = AUCt + AUCextrap where last is the sampling time point of the last measurable concentration (tlast). AUCextrap is calculated by the program as: Clast/λz, where Clast is the observed concentration at time tlast and λz is the elimination rate constant during the apparent terminal elimination phase; AUC∞ will only be presented for patients with a reliable λz;

CL/CLss will be calculated by program as (dose/AUC∞ or dose/AUC0-tau)

VZ will be calculated by the program as (dose/AUC∞)/λz.

Vss will be calculated by program as (MRTinf/CLss) where MRTinf is mean residence time;

RCmax, RAUCtau and RAUCt will be calculated as ratios of the parameters on Cycle 3 day 1 to Cycle 1 day 1 for Phase 1 patients.

The following PK acceptance criteria will be applied to assess the reliability of elimination parameters:

- Number of points to calculate λz is greater than or equal to 3 excluding Cmax point;
- Interval for calculation of λz is longer than half-life;
- The adjusted square of the correlation coefficient (Rsquare adjusted) for the goodness of fit of the regression line through the data points must be ≥0.85;
- AUCextrap ≤30%.

Individual patient PK parameters will be listed for the PK population in a table by patient and will be summarized, by treatment group/cohort. Unreliable PK parameters will be listed but flagged and excluded from summary.

9.4.1. PK Parameters Summarization

Table 2. PK Summary Statistics

Variable	Summarized with:
AUC, Cmax, CL and Vz , t1/2, and λZ	n, arithmetic mean, SD, CV%, minimum, median, maximum, geometric mean and geometric CV%
Tmax (actual time)	n, minimum, Q1 (25% percentile), median, Q3 (75% percentile) and maximum

The following conventions will be used for the presentation of the descriptive statistics of PK parameters and of plasma concentrations:

Table 3. PK Reporting Precision

Statistics	Degree of Precision
Minimum, Maximum	3 significant digits or as needed based on actual measured values (for example PK concentrations)
Mean (arithmetic and geometric), Median	4 significant digits
Standard deviation	5 significant digits
CV and Geometric CV	1 decimal point

For the patients with dose escalation at later cycles the additional unscheduled PK parameters will be calculated and listed with actual dose for the unscheduled visits. The parameters will not be summarized if less than 3 patients will have the same starting and escalated doses at the same time.

9.5. Assessment of Dose Proportionality for PEN-221 Related Analytes

Exploratory dose proportionality for PEN-221 and related analytes will be analyzed with the method originally described by Gough et al. (1995) and modified as described by Smith et al. (2000) and further adapted by Hummel et al. (2009) for Phase 1. Hereby the general model log (Cmax, Cmin, AUCt and AUC∞ for cycles 1 and 3) = μ+ ß log (dose) will be used to investigate the null hypothesis (H0: ß=1). Dose-proportionality will be rejected if the 90% confidence interval (CI) of the estimated slope falls outside the critical interval.

The critical interval will be calculated as follows:

First the ratio (r) of the highest dose level to the lowest dose level will be calculated.
The lower limit of the critical interval will be calculated as: Log (0.5)/log(r) + 1.
The upper limit of the critical interval will be calculated as: Log (2.0)/log(r) + 1.

The r value is based on the ratio between planned highest and lower dose levels of PEN-221 and equals to 20.8 / 1 mg = 20.8

Thus critical interval to declare dose linearity will be 0.77 to 1.23 for 90% confidence interval of the slope estimate for the current dose escalation and will be updated based on actual data. Only cohorts with sufficient number of patients per dose level (n>2) will be included in this analysis.

Additionally PK parameters Cmax, AUCt and AUC∞ for all analytes for Cycles 1 and 3 (C3 Phase 1 only) with total dose, body surface area and body weight adjusted types of dose will be investigated using Pearson correlation analysis to estimate which type of dosing has an effect on pharmacokinetics of PEN-221 and related analytes. Body weight and body surface area adjusted doses will be calculated from demographics data and total dose administered. Body surface area (BSA) will be determined using the Du Bois formula:

BSA (m sq) = 0.007184 x (patient height in cm)$^{0.725}$ x (patient weight in kg at C1 D1)$^{0.425}$

The FISHER option in the PROC CORR statement will be used to estimate confidence limits and p-values for Pearson correlation coefficients based on Fisher's z transformation. Alpha value and a null hypothesis value will be specified for 95% two-sided confidence interval.

Formula for sample Pearson product-moment correlation is

$$r_{xy} = \frac{\sum_i (x_i - \bar{x})(y_i - \overline{y})}{\sqrt{\sum_i (x_i - \bar{x})^2 \sum_i (y_i - \bar{y})^2}}$$

Fisher z transformation is calculated as $z = 0.5 log_e \left(\frac{1+r}{1-r}\right)$

Confidence intervals in addition to p-value will be calculated to demonstrate the validity of correlation.

Dose proportionality will also be explored graphically with plots of Cmax, AUCt and AUC∞ vs. body weight adjusted dose (mg/kg), BSA adjusted dose (mg/m sq) and total dose (mg).

Dose proportionality plots will be presented for PEN-221 and all related analytes PK parameters Cmax, AUCt and AUC∞. Regression/scatter plot in log-log and linear scales of PK parameters vs. dose levels including body weight normalized and total dose will be presented.

The parameters for unscheduled visits obtained as a result in intra-patient dose escalation will not be included.

[redacted]

[redacted]

9.8. Assessment of the Effect of Concomitant Medications on PK of PEN-221

Concomitant medications will be summarized by type of inhibitory or inducing properties for metabolic enzymes such as CYP450 or UGT. Patients with concomitant medications may be included in more than one group. The information about concomitant medications will be reviewed at the end of the study to make a decision on possible grouping if sufficient information available. The comparison of CL and CLss of PEN-221 between different groups of concomitant medications will be done using ANOVA model for log(e) transformed PK parameters. Dose normalized AUCt parameters for C1D1 and C3D1 (C3 Phase 1 only) will be also used for PEN-221 related analytes. SSTR2 expression information may be included in the model as covariates where available.

9.9. Interim Analyses

Informal interim PK data review will be performed by Tarveda for the dosing and safety decisions. This analysis is not within the scope of the SAP.

9.10. Deviation from Analyses Planned in Protocol

Additional PK parameters were added or clarified such as CLss, Vss, AUC/D, Cmax/D and accumulation ratio.

The treatment of the data from unscheduled visits for PK and PD including those arising from intra-patient dose escalation are described.

10. ANALYSIS OF PHARMACODYNAMICS

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

10.1.7. Cardiodynamic Analysis

ECG assessments will be conducted in Phase 1 at C1D1, C3D1, and at visits with dose escalation, prior to infusion, 30 minutes post infusion and at infusion end, then 1.5, 2, 4, 6, 8 and 10 hours post infusion and in Phase 2a at C1D1 prior to infusion, 30 minutes post infusion and at infusion end, then 1.5, 2, 4, 6, and 8 hours post infusion. At other D1 visits, ECG assessments are conducted prior to infusion and end of infusion. The following ECG parameters will be reported: pulse rate (bpm), RR interval (msec), QRS interval (msec), QT Interval (msec), QTcF Interval (msec) and QTcB interval (msec). The details of the summaries for ECG parameters are described in SAP Section 12.4. PK-ECG correlation analysis is described in the SAP Section 10.3.3.

10.2. Presentation of Biomarkers Data

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

10.2.7. Cardiodynamic data

The summary and listing of ECG parameters is described in SAP Section 12.4 and graphic presentation of the data for PK-ECG correlation analysis is presented in SAP Section 10.3.3.

[redacted]

[redacted]

11. ANALYSIS OF IMMUNOGENICITY

Blood samples for anti-PEN-221 antibodies are collected at pre-dose on day 1, pre-dose for Cycle 2 and every odd number Cycle starting from Cycle 3 and end of treatment visit. Note from Cycle 2 onwards, collection can be within 48 hours prior to the scheduled clinic visit.

Immunogenicity sampling times and results will be listed for the Safety population.

Immunogenicity endpoints include occurrence of anti-PEN-221 specific antibodies, frequency of occurrence of antibodies by visit and overall by cohort, time of onset immunogenicity and time of resolution of immunogenicity. Time of onset is defined as 1st time point with a positive anti-drug antibody (ADA) result; time of resolution is defined as the 1st time point when previously observed positive ADA result returns to baseline.

Patients developing an antibody response will be listed. The effect of possible antibody responses on PK parameters will be evaluated (only if required i.e., meaningful reports of immunogenic response) by comparison of:

1. Phase 1: CL and dose normalized trough concentration Cmin/D for the Cycle 3 where available for patients with and without ADA.
2. For Phase 2a: AUCt and Cmax where available for patients with and without ADA.

The effect will be analyzed graphically and statistically if sufficient data are available.

Tables summarizing the frequency of the occurrence of ADAs by dose and by time point with overall summary per treatment will be produced. The time of onset of immunogenicity, duration and number of resolved ADA cases will be summarized.

Immunogenicity results will be compared descriptively between treatments using frequency of each type of ADA as main parameter as well as the time of onset of immunogenicity.

Note that the neutralizing antibody assay may not need to be developed given the preliminary results. See associated shells for details.

12. SAFETY ANALYSIS

12.1. Adverse Events / Adverse Drug Reactions

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.

Adverse events will be summarized by the SOC and PT based on the latest MedDRA dictionary (the most current available MedDRA version at database lock should be used).

The CTCAE grades will be summarized by SOC and PT, using the NCI CTCAE version 4.03.

Treatment-emergent adverse events (TEAEs) are 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.

Adverse events with incomplete start dates will be considered to be TEAEs if:

Day and month are missing, and the year is equal to or after the year of the first dose date;

Day is missing and the year is after the year of the first dose;

Day is missing and the year is equal to the year of the first dose date and the month is equal to or after the month of the first dose date;

Year is missing; or

Complete date is missing.

If the relationship to study drug is missing, then the relationship will be counted as related to PEN-221 for the summary tables. Similarly, missing severity will be counted as Grade 3 (severe).

The summary tables will include the number of patients and number of events. For summaries by SOC and PT, a patient is counted once at the SOC level and once at each PT within the SOC level. For summaries by SOC, PT, and maximum intensity, a patient is counted once at the highest intensity level for which the event occurred at the SOC level and the highest intensity level for each unique PT within that SOC level. Therefore, patients may only contribute once to each PT and once to each SOC level.

The summaries presenting frequency of AEs by SOC and PT will be ordered by overall descending frequency of SOC and then, within a SOC, by overall descending frequency of PT. All AE tables will be ordered by descending frequency for the study in total in each SOC.

The following AE tables will be provided:

- An overall summary of the number and percentage of patients reporting TEAEs, serious TEAEs, treatment-related TEAEs, TEAEs leading to discontinuation of study drug and TEAEs leading to death.
- TEAEs overall and by system organ class and preferred term.
- Study-treatment-related TEAEs overall and by system organ class and preferred term
- TEAEs by maximum intensity, overall and by system organ class and preferred term.
- Serious TEAEs, overall and by system organ class and preferred term.
- Study-treatment related TEAEs by maximum intensity, overall and by system organ class and preferred term.
- TEAEs leading to discontinuation of study drug, overall and by system organ class and preferred term.
- TEAEs leading to DLTs, overall and by system organ class and preferred term.
- TEAEs leading to death, overall and by system organ class and preferred term.
- TEAEs by preferred term.

Only the TEAEs will be included in the summary tables; however, all AEs will be included in the AE listing. Note pre-screening adverse events will be listed separately.

Additional listings will be provided for:

- AEs with an outcome of death.
- Serious TEAEs.
- TEAEs leading to discontinuation of study drug.
- TEAS leading to DLTs (Phase 1 only).

The primary cause of death, death date and any autopsy results as recorded on the eCRF 'Death' will be listed.

12.2. Laboratory Evaluations

Protocol Tables 2 and 3 indicates when clinical laboratory assessments are scheduled. Local laboratories will be used.

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.

Parameters include:

Hematology	White blood cell (WBC) count (with differential blood count – neutrophils (bands), lymphocytes, monocytes, eosinophils, basophils), red blood cell (RBC) count, hemoglobin, platelet count
Chemistry	Sodium, potassium, chloride, bicarbonate, blood urea nitrogen (BUN), creatinine, creatinine clearance, glucose, glucose monitoring, albumin, total protein, calcium, alkaline phosphatase (ALP), magnesium, phosphorus, total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), amylase, and lipase
Coagulation parameters	Prothrombin time (PT), activated partial thromboplastin time (aPTT), and International Normalized Ratio (INR)
Urinalysis	specific gravity, pH, blood, glucose, protein, ketones, and microscopic examination: WBC, RBC, epithelial, casts, and crystals
Thyroid function	Free T4, thyroid stimulating hormone (TSH)
Cholesterol and triglycerides	Total cholesterol, and triglycerides
Cortisol levels	Cortisol
Pregnancy Test	Serum samples for HCG (human chorionic gonadotropin) pregnancy testing are to be collected from females of childbearing potential (FOCBP). If the screening sample is collected within 3 days before C1D1, a sample need not be collected on C1D1. Alternatively, urine dip stick testing may be performed instead

All summaries will be based on results in the International System of Units (SI units); conversion will be performed prior to the transfer to INC Biostatistics. High/low classifications will be derived relative to the result and normal range in SI units where normal ranges exist.

Toxicity grading following the NCI CTCAE grades version 4.03 will be summarized for gradable parameters. The frequency of laboratory abnormalities by maximum post-baseline CTCAE grade will be tabulated by cycle and overall. Unscheduled data will be included in overall summaries which will capture a maximum (worst) case across all scheduled and unscheduled visits after the first dose of study treatment. This means that if there are CTCAE grades derived from both unscheduled and scheduled visits data per test per patient then the highest grade will be summarized.

Shift tables also will be produced for these parameters based on the baseline CTCAE grade and the maximum CTCAE grade by cycle and overall. Patients with both a non-missing baseline and at least 1 non-missing post baseline grade will be included in the shift tables.

The following parameters are gradable:

Parameter	NCI-CTCAE Term
WBC	Leukocytosis
WBC	White blood cell decreased
Hemoglobin	Anemia
Hemoglobin	Hemoglobin increased
Platelets	Platelet count decreased
Lymphocytes*	Lymphocyte count decreased
Neutrophils#	Neutrophil count decreased
Sodium	Hypernatremia
Sodium	Hyponatremia
Potassium	Hyperkalemia
Potassium	Hypokalemia
Creatinine	Creatinine increased
Glucose	Hyperglycemia
Glucose	Hypoglycemia
Albumin	Albuminuria
Calcium (corrected for albumin)	Hypercalcemia

Calcium (corrected for albumin)	Hypocalcemia
ALP	Alkaline phosphatase increased
Magnesium	Hypermagnesemia
Magnesium	Hypomagnesemia
Total bilirubin (note that direct bilirubin appear on the eCRF but it is only the Total bilirubin that is gradable)	Blood bilirubin increased
AST	Aspartate aminotransferase increased
ALT	Alanine aminotransferase increased
Amylase	Serum amylase increased
Lipase	Lipase increased
aPTT	Activated partial thromboplastin time prolonged
Cholesterol	Cholesterol high
Triglycerides	Hypertriglyceridemia

* Lymphocytes are collected as a relative value on the eCRF. Absolute values are derived using the absolute value for WBC as follows: (WBC count/100) * relative lymphocyte count.

Relative neutrophils (bands) are currently being collected. Relative values for total neutrophils will be collected, an absolute value will be derived as described for lymphocytes and a CTCAE grade assigned. This change is described in SAP Section 14.

For non-CTCAE gradable tests, a shift table will be provided relative to the normal ranges. This summary of normal range category changes illustrates the number and percentage of patients who fall into specified categories (Decrease to Low, Change to Normal or No Change, Increase to High) by comparing the baseline normal range category to the planned time normal range category and the worst-case on-therapy normal range category. The worst-case post-baseline will be used to summarize the patients' overall worst-case normal range category change during the on-therapy period. The determination of the worst-case during the on-therapy period takes into account both planned and unscheduled assessments. Only laboratory tests which cannot be graded per protocol specified criteria will be included. Patients with missing baseline value are to be assumed to have a normal baseline value. Worst-case can be either High or Low. If a patient has a Decrease to Low and an Increase to High during the same time interval, then the patient is counted in both the 'Decrease to Low' and 'Increase to High' categories. If a patient was High at baseline and Decreases to Low during the time interval, then the patient is counted in the 'Decrease to Low' category. Likewise, if a patient was Low at baseline and Increases to High during the time interval, then the patient is counted in the 'Increase to High' category. Patients are only counted in the 'Change to Normal or No Change' category if they are:

- Normal at baseline and have no values changing to outside the normal range
- High at baseline and do not change to Low during the time interval
- Low at baseline and do not change to High during the time interval

In all cases, patients are only counted once in the total column.

The following parameters are non-CTCAE gradable:

RBC count
Monocytes
Eosinophils
Basophils
Chloride
Bicarbonate
BUN
Creatinine clearance
Total protein
Phosphorous
Direct bilirubin
PT
INR
Free T4
TSH
Cortisol

All worst-case post-baseline summaries will be summarized in a separate table from the by-visit summaries.

All laboratory results in original and SI units will be included in data listings. Reported units and ranges will be included in the data listings. Tests will be summarized and listed in eCRF order.

12.3. Vital Signs

Vital signs will include measurements of heart rate (beats per minute [bpm]), systolic and diastolic blood pressure (mmHg), body temperature (centigrade) and body weight (kg).

All vital signs data will be listed.

12.3.1. Vital Sign Values of Potential Clinical Importance

The Potential Clinical Importance (PCI) ranges are given in the table below for vital sign results. The values outside these ranges will be flagged on the listings as either 'Low' or 'High' relative to the PCI ranges.

Vital Signs Parameter	PCI Range	Unit
Systolic Blood Pressure	<85 (L) and >160 (H)	mmHg
Diastolic Blood Pressure	<45 (L) and >100 (H)	mmHg

The change from baseline values will be compared to the ranges in the tables below and be flagged on the listings if outside of these PCI ranges.

Vital Signs Parameter	PCI Range	Unit
Systolic Blood Pressure (Change from Baseline)	Increase ≥20 and ≥40	mmHg
	Decrease ≥20 and ≥40	
Diastolic Blood Pressure (Change from Baseline)	Increase ≥10 and ≥20	mmHg
	Decrease ≥10 and ≥20	

12.3.2. Summary of Changes in Heart Rate from Baseline

A summary of changes in heart rate comparing the baseline value to the worst-case post baseline value will be provided.

For heart rate, both an increase and decrease in value are of clinical concern. The worst-case post baseline summary is used to summarize the patients' overall worst-case shifts post baseline. The determination of the worst-case post baseline will take into account both planned and unscheduled assessments.

Patients with missing baseline value are to be assumed to have a normal baseline value. The percentages are based on the number of patients with heart rate data at the specified planned time.

The oncology standard categories of clinical concern are:

Heart Rate (bpm): 'Decrease to <60', 'Increase to >100'

Worst-case can be either High (ie >100) or Low (ie <60). If a patient has a Decrease to Low and an Increase to High during the same time interval, then the patient is counted in both the "Decrease to <60" category and the "Increase to >100" category. If a patient was High at baseline and decreases to Low during the time interval, then the patient is counted in the 'Decrease to <60' category. Likewise, if a patient was Low at baseline and increases to High during the time interval, then the patient is counted in the 'Increase to >100' category.

Patients are only counted in the 'Change to Normal or No Change' category if they are:

- Normal at baseline and have no normal range High and no normal range Low values during the time interval
- High at baseline and do not change to Low during the time interval
- Low at baseline and do not change to High during the time interval

12.3.3. Summary of Increases in Blood Pressure from Baseline

A summary of increases in blood pressure parameters comparing the baseline value to each planned time and to the worst-case post baseline value will be provided. The worst-case post baseline will be summarized separately from the by-visit summaries. These summaries apply to blood pressure parameters where increases in value are of clinical concern. The worst-case post baseline summary is used to summarize the patients' overall worst-case shifts post baseline. The determination of the worst-case post baseline takes into account both planned and unscheduled assessments.

Patients with missing baseline values are assumed to have baseline value below the lowest threshold. The percentages are based on the number of patients in the treatment group with data for the vital sign parameter at the specified planned time.

The oncology standard categories for Systolic Blood Pressure in mmHg are:

- 'Any Grade Increase'
- 'Increase to Grade 2 (140-159)'
- 'Increase to Grade 3 (≥160)'

Note: 'Any Grade Increase' will be footnoted as Grade 0 (<120), Grade 1 (120-139), Grade 2 (140-159), or Grade 3 (≥160).

The oncology standard categories for Diastolic Blood Pressure in mmHg are:

- 'Any Grade Increase'
- 'Increase to Grade 2 (90-99)'
- 'Increase to Grade 3 (≥100)'

Note: 'Any Grade Increase' will be footnoted as Grade 0 (<80), Grade 1 (80-89), Grade 2 (90-99), or Grade 3 (≥100).

Note: Whole numbers are expected for systolic and diastolic blood pressure in mmHg. For values with decimal places in the data the following cut-offs will be used for programming of the oncology standard categories. For systolic blood pressure: Any Increase to ≥120, Increase to ≥140-<160, and Increase to ≥160. For diastolic blood pressure: Any Increase to ≥80, Increase to ≥90-<100, and Increase to ≥100.

An increase is defined as an increase in grade (eg, for diastolic blood pressure, if a patient had Grade 1 hypertension [84 mmHg] at baseline and at week 4 had an increase to 85 mmHg [still Grade 1], this is NOT counted as an increase). However, if the patient had an increase to 101 mmHg (Grade 3) this is counted as an increase and the patient will be counted in the 'Any Grade Increase' and the 'Increase to Grade 3 (≥100)' categories).

For body temperature and weight, summary tables by visit and change from baseline to visit will be provided. Summaries will include data from scheduled assessments only, and all data will be reported according to the nominal visit date for which it was recorded (ie, no visit windows will be applied). If there are multiple results at a given visit, eg a repeated vital signs test within a visit, the earliest value will be used in the tables (see SAP Section 6.1).

12.4. Triplicate 12-lead ECG

At C1D1, C3D1 (Phase 1 only), and at visits with dose escalation, ECG assessments are conducted prior to infusion, 30 minutes post infusion (+/- 5 minutes) and at infusion end (+/- 5 minutes), then 1.5, 2, 4, 6, 8 and 10 hours post infusion (Phase 1 only). At other D1 visits, ECG assessments are conducted prior to infusion and end of infusion. A summary table of pulse rate (bpm), RR interval (msec), QRS interval (msec), QT Interval (msec), QTcF Interval (msec) and QTcB interval (msec) by visit/timepoint and change from baseline to visit/timepoint will be provided. Prior to summary, the mean of the 3 results will be determined per patient per visit/timepoint. Summaries will include data from scheduled assessments only, and all data will be reported according to the nominal visit date and timepoint for which it was recorded (ie, no visit windows will be applied). If there are multiple results at a given visit/timepoint, eg a repeated ECG test within a visit/timepoint, the earliest value will be used in the tables (see SAP Section 6.1).

Central tendency analysis: the change from baseline in QTcF, RR, QRS, QTcB, and pulse rate will be summarized by visit/time point using descriptive statistics including SD and 90% confidence intervals.

A shift from baseline summary table of QTcF CTCAE grade to the worst (highest) value on study (based on individual assessment, not and aggregation of the triplicate readings). The determination of the worst-case post baseline takes into account both planned and unscheduled assessments. Patients with missing baseline values are assumed to have baseline value below the lowest threshold (i.e. less than 450 msec).

A shift from baseline summary table of overall ECG interpretation to each scheduled visit/timepoint will be provided. Prior to summary, the worst of the 3 results will be determined per patient per visit/timepoint. For multiple assessments at the same visit/timepoint, the worst value will be summarized. Order from best to worse is 'Normal', 'Abnormal NCS', 'Abnormal CS'. The percentages are based on the number of patients in the treatment group with data at the specified visit/timepoint. A worst-case post baseline summary will also be included. The determination of the worst-case post baseline takes into account both planned and unscheduled assessments.

A summary table of the following will be presented by visit/timepoint:

- QTcF values > 450 msec and ≤ 480 msec; > 480 msec and < 500 msec; and ≥ 500 msec
- QTcF increase from baseline values ≥ 30 and <60 msec; and ≥ 60 msec
- QRS change from baseline > 25% resulting in QRS > 120 msec
- RR interval change from baseline >25% reaching a value >220 msec
- Pulse rate change from baseline > 25% decrease resulting in a pulse rate < 50 bpm; and pulse rate change from baseline > 25% increase resulting in a heart rate > 100 bpm

The percentages are based on the number of patients in the treatment group with data at the specified visit/timepoint.

Note SAP Section 10.3.3 describes the drug concentration-ECG correlation analysis.

12.5. Physical Examination

Physical examination body system results data will be listed in eCRF order.

12.6. Other Safety

12.6.1. Eastern Cooperative Oncology Group Performance Status

Eastern Cooperative Oncology Group (ECOG) performance status data will be listed. A summary table will be provided with the number and percentage of patients with each ECOG score (0 to 4) by visit. Summaries will include data from scheduled assessments only, and all data will be reported according to the nominal visit date for which it was recorded (ie, no visit windows will be applied). If there are multiple results at a given visit, the earliest value will be used in the tables (see SAP Section 6.1). A summary will also be included summarizing the worst (highest) post-baseline value per patient. An additional summary table will also include the number and percentage of patients with change from baseline, 'Improved', 'No Change' and 'Deteriorated', by visit. The percentages are based on the number of patients in the treatment group with data at the specified visit. An additional summary will also be included summarizing the worst change post-baseline per patient. The determination of the worst-case post baseline takes into account both planned and unscheduled assessments.

13. INTERIM ANALYSIS

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 Protocol Section 8.6.1.

Note for Phase 1, the SRC will review the safety and tolerability of PEN-221 of each cohort to decide the next dose level to be tested. Statistical modeling (provided by a 3rd party vendor) 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.

Interim Analysis (end of Phase 1) and for Phase 2a is described in SAP Section 4.7.1 and 4.7.2 respectively.

14. CHANGES TO METHODS PLANNED IN THE PROTOCOL

1. The laboratory parameter relative neutrophil bands are currently collected. Relative total neutrophils will be collected so a CTCAE grade can be assigned.

2. Section 12.9.3 of the protocol states the following: *For the gastrointestinal (GI) mid-gut neuroendocrine tumor (NET), pancreatic NET (PNET) and small cell lung cancer groups (SCLC) groups, the cutoff date for the primary analysis will occur after all 20 patients received the first dose of PEN-221 at least 21 weeks (7 cycles) prior to the analysis cutoff date.* The timing of analysis will occur as described in SAP Section 4.7.3.

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Figure Number	Name	Population
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16. PROGRAMMING GUIDELINES

All tables, data listings, figures (TLFs), and statistical analyses will be generated using SAS® for Windows, Release 9.3 (SAS® Institute Inc., Cary, NC, USA). Computer-generated table, listing and figure output will adhere to the following specifications.

Phoenix WinNonLin version 6.4 or higher will be used for PK parameters derivation.

16.1. General Considerations

A separate SAS program will be created for each output.

Each output will be stored in a separate file.

Output files will be delivered in Word format (rtf).

Numbering of TLFs will follow ICH E3 guidance.

16.2. Table, Listing and Figure Format

16.2.1. General

All TLFs will be produced in landscape format on American letter size, unless otherwise specified.

All TLFs will be produced using the Courier New font, size 8

The data displays for all TLFs will have a minimum 2.5 cm blank margin on all 4 sides.

Headers and footers for figures will be in Courier New font, size 8.

Legends will be used for all figures with more than 1 variable, group, or item displayed.

TLFs will be in black and white (no color), unless otherwise specified.

Specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, will not be used in the TLFs. On some occasions, superscripts 1, 2, or 3 may be used (see below).

Only standard keyboard characters will be used in the TLFs. Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will not be used. Hexadecimal-derived characters will be used, where possible, if they are appropriate to help display math symbols (e.g., µ). Certain subscripts and superscripts (e.g., cm2, Cmax) will be employed on a case-by-case basis.

Mixed case will be used for all titles, footnotes, column headers and programmer-supplied formats, as appropriate.

16.2.2. Headers

All output should have the following header at the top left of each page:

Tarveda Therapeutics, Inc. Protocol PEN-221-001([redacted])

Draft/Final Run ddMMMyyyy

All output should have Page n of N at the top or bottom right corner of each page. TLFs should be internally paginated in relation to the total length (i.e., the page number should appear sequentially as page n of N, where N is the total number of pages in the table).

16.2.3. Display Titles

Each TLF should be identified by the designation and a numeral. (i.e., Table 14.1.1). ICH E3 numbering will be used. A decimal system (x.y and x.y.z) should be used to identify TLFs with related contents. The title is centered. The analysis population should be identified on the line immediately following the title. The title and table designation are single spaced. A solid line spanning the margins will separate the display titles from the

Column headers. There will be 1 blank line between the last title and the solid line.

Table x.y.z

First Line of Title

Second Line of Title if Needed

FAS

16.2.4. Column Headers

Column headings should be displayed immediately below the solid line described above in initial upper-case characters.

In the case of efficacy tables, the variable (or characteristic) column will be on the far left followed by the treatment group columns and total column (if applicable). P-values may be presented under the total column or in separate p-value column (if applicable). Within-treatment comparisons may have p-values presented in a row beneath the summary statistics for that treatment.

For numeric variables, include “unit” in column or row heading when appropriate.

Analysis population sizes will be presented for each treatment group in the column heading as (N=xx) (or in the row headings if applicable). This is distinct from the ‘n’ used for the descriptive statistics representing the number of patients in the analysis population.

16.2.5. Body of the Data Display

General Conventions

Data in columns of a table or listing should be formatted as follows:

alphanumeric values are left-justified;

whole numbers (e.g., counts) are right-justified; and

numbers containing fractional portions are decimal aligned.

Table Conventions

Units will be included where available

If the categories of a parameter are ordered, then all categories between the maximum and minimum category should be presented in the table, even if n=0 for all treatment groups in a given category that is between the minimum and maximum level for that parameter. For example, the frequency distribution for symptom severity would appear as:

Severity Rating	N
Severe	0
Moderate	8
Mild	3

Where percentages are presented in these tables, zero percentages will not be presented and so any counts of 0 will be presented as 0 and not as 0 (0%).

If the categories are not ordered (e.g., Medical History, Reasons for Discontinuation from the Study, etc.), then only those categories for which there is at least 1 patient represented in 1 or more groups should be included.

An Unknown or Missing category should be added to any parameter for which information is not available for 1 or more patients.

Unless otherwise specified, the estimated mean and median for a set of values should be printed out to 1 more significant digit than the original values, and standard deviations should be printed out to 2 more significant digits than the original values. The minimum and maximum should report the same significant digits as the original values. For example, for systolic blood pressure:

N	XX
Mean	XXX.X

Std Dev	X.XX
Median	XXX.X
Minimum	XXX
Maximum	XXX

P-values should be output in the format: “0.xxx”, where xxx is the value rounded to 3 decimal places. Any p-value less than 0.001 will be presented as <0.001. If the p-value should be less than 0.0001 then present as <0.0001. If the p-value is returned as >0.999 then present as >0.999

Percentage values should be printed to one decimal place, in parentheses with no spaces, one space after the count (e.g., 7 (12.8), 13 (5.4)). Pre-determine how to display values that round down to 0.0. A common convention is to display as '<0.1', or as appropriate with additional decimal places. Unless otherwise noted, for all percentages, the number of patients in the analysis set for the treatment group who have an observation will be the denominator. Percentages after zero counts should not be displayed and percentages equating to 100% should be presented as 100, without any decimal places.

Tabular display of data for medical history, prior / concomitant medications, and all tabular displays of adverse event data should be presented by the body system, treatment class, or SOC with the highest occurrence in the study total group in decreasing order, assuming all terms are coded. Within the body system, drug class and SOC, medical history (by preferred term), drugs (by ATC2 code), and adverse events (by preferred term) should be displayed in decreasing order. If incidence for more than 1 term is identical, they should then be sorted alphabetically. Missing descriptive statistics or p-values which cannot be estimated should be reported as “-”.

The percentage of patients is normally calculated as a proportion of the number of patients assessed in the relevant treatment group (or overall) for the analysis population presented. However, careful consideration is required in many instances due to the complicated nature of selecting the denominator, usually the appropriate number of patients exposed. Describe details of this in footnotes or programming notes.

For categorical summaries (number and percentage of patients) where a patient can be included in more than one category, describe in a footnote or programming note if the patient should be included in the summary statistics for all relevant categories or just 1 category and the criteria for selecting the criteria.

Where a category with a subheading (such as system organ class) has to be split over more than one page, output the subheading followed by “(cont)” at the top of each subsequent page. The overall summary statistics for the subheading should only be output on the first relevant page.

Listing Conventions

Listings will be sorted for presentation by phase and part then patient number, visit/collection day, and visit/collection time.

Missing data should be represented on patient listings as either a hyphen ("-") with a corresponding footnote ("- = unknown or not evaluated"), or as "N/A", with the footnote "N/A = not applicable", whichever is appropriate.

Dates should be printed in SAS® DATE9.format ("ddMMMyyyy": 01JUL2000). Missing portions of dates should be represented on patient listings as dashes (--JUL2000). Dates that are missing because they are not applicable for the patient are output as "N/A", unless otherwise specified.

All observed time values must be presented using a 24-hour clock HH:MM or HH:MM:SS format (e.g., 11:26:45, or 11:26). Time will only be reported if it was measured as part of the study.

Units will be included where available

Figure Conventions

Unless otherwise specified, for all figures, study visits will be displayed on the X-axis and endpoint (e.g., treatment mean change from Baseline) values will be displayed on the Y-axis.

16.2.6. Footnotes

A solid line spanning the margins will separate the body of the data display from the footnotes.

All footnotes will be left justified with single-line spacing immediately below the solid line underneath the data display.

Footnotes should always begin with "Note:" if an informational footnote, or 1, 2, 3, etc. if a reference footnote. Each new footnote should start on a new line where possible.

PatientPatient specific footnotes should be avoided, where possible.

Footnotes will be used sparingly and must add value to the table, figure, or data listing. If more than six lines of footnotes are planned, then a cover page may be used to display footnotes, and only those essential to comprehension of the data will be repeated on each page.

The penultimate line of the footnote section will be a standard source line that indicates the listing source (i.e., 'Listing Source: 16.x.y.z').

The last line of the footnote section will be a standard line that indicates the date output was generated (i.e., 'Listing Generation: ddmmmyyyy hh:mm).

The program name will appear as a footer on each page.

17. REFERENCES

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18. APPENDICES

18.1. Table Mock-Ups

See attachment

18.2. Figure Mock-Ups

See attachment

18.3. Listing Mock-Ups

See attachment