Proximagen, LLC

STATISTICAL ANALYSIS PLAN
Protocol Number P311-201

US IND # 127616
EudraCT # 2015-004214-14

A Phase 1/2 Dose-escalation of USL311 as Single Agent and in Combination with Lomustine (CCNU) in Subjects with Advanced Solid Tumors, with Subsequent Single Agent and Combination Phase 2 Cohorts for Subjects with Relapsed/Recurrent Glioblastoma Multiforme (GBM)

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1 List of Abbreviations and Definition of Terms

Abbreviation	Description
AE	Adverse Event
ATC-2	Anatomical Therapeutic Chemical 2nd level
ATC-3	Anatomical Therapeutic Chemical 3rd level
BMI	Body Mass Index
BSA	Body Surface Area
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CR	Complete Response
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of Variation
DCR	Disease Control Rate
DLT	Dose-Limiting Toxicity
DEC	Dose Escalation Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eCTD	Electronic Common Technical Document
FAS	Full Analysis Set
ICH	International Conference on Harmonisation
IV	Intravenous
KM	Kaplan-Meier
KPS	Karnofsky Performance Status
mCRM	Modified Continual Reassessment Method
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
ORR	Objective Response Rate
OS	Overall Survival
PD	Pharmacodynamics
PFS	Progression Free Survival
PFS-6m	6-month Progression Free Survival
PK	Pharmacokinetics
PR	Partial Response
PT	Preferred Term
RAS	Exposure-Response Analysis Set
RES	Response-Evaluable Analysis Data Set
RP2D	Recommended Phase 2 Dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable Disease
SOC	System Organ Class

Abbreviation	Description
TEAE	Treatment-Emergent Adverse Event
WHO	World Health Organization

2 Introduction

This statistical analysis plan (SAP) describes the analysis method for Study P311-201 protocol Amendment 4, dated 02-Aug-2018 with title "A Phase 1/2 Dose-escalation of USL311 as Single Agent and in Combination with Lomustine (CCNU) in Subjects with Advanced Solid Tumors, with Subsequent Single Agent and Combination Phase 2 Cohorts for Subjects with Relapsed/Recurrent Glioblastoma Multiforme (GBM)". This SAP will be finalized and approved prior to clinical database lock for Part 1 of the study.

This SAP is for Part 1, Phase 1 monotherapy dose-escalation, of this study. The SAP for other parts of this study (Part 2, Phase 1 combination; Part 3, Phase 2 monotherapy, and Part 4, Phase 2 combination) will be described in separate SAPs, as applicable. Pharmacokinetics (PK) and Pharmacodynamics (PD) analyses will also be described in a separate SAP.

This SAP supersedes the statistics considerations in the study protocol, and any substantial differences between protocol and SAP are identified. Any deviations to the analysis outlined in this SAP will be outlined in the final study report.

3 Overall Study Design and Objectives

3.1 Study Objectives for Phase 1

3.1.1 Primary Objectives

The primary objective of the Phase 1 dose-escalation is to:

- Determine the maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D) of USL311 as a single agent in subjects with advanced solid tumors for which no standard-of-care treatment is recognized or who have failed or are intolerant to the standard-of-care treatment (Part 1)
- Determine the MTD and RP2D of USL311 in combination with lomustine in subjects with advanced solid tumors for which no standard-of-care treatment is recognized or who have failed or are intolerant to the standard-of-care treatment (Part 2)

The combination with lomustine objectives are outside the scope of this SAP.

3.1.2 Secondary Objectives

The secondary objectives of the Phase 1 dose-escalation are to:

- Assess the safety and tolerability of USL311 as a single agent and in combination with lomustine
- Determine preliminary efficacy parameters such as 6-month progression-free survival rate (PFS-6m), objective response rate (ORR%), disease control rate

(DCR), progression free survival (PFS) and overall survival (OS) of USL311 as a single agent and in combination with lomustine

- Determine the pharmacokinetic (PK) profile of USL311 in plasma and whole blood, and of lomustine in plasma (prior to and with concomitant USL311 administration)
- Evaluate the drug interaction potential between USL311 and lomustine

The combination with lomustine objectives are outside the scope of this SAP. The PK objectives are outside the scope of this SAP.

3.1.3 Exploratory Objectives

The exploratory objectives of the Phase 1 dose-escalation are to:

- Determine effects of USL311 on systemic markers of CXCR4 inhibition, including measurement of CD34+ cells, and white blood cell count
- Measure effects of USL311 on a urine biomarker of phospholipidosis, di-docosahexaenoyl (22:6)-bis(monoacylglycerol) phosphate (BMP)
- Investigate exposure-response relationships for USL311 as a single agent and in combination with lomustine

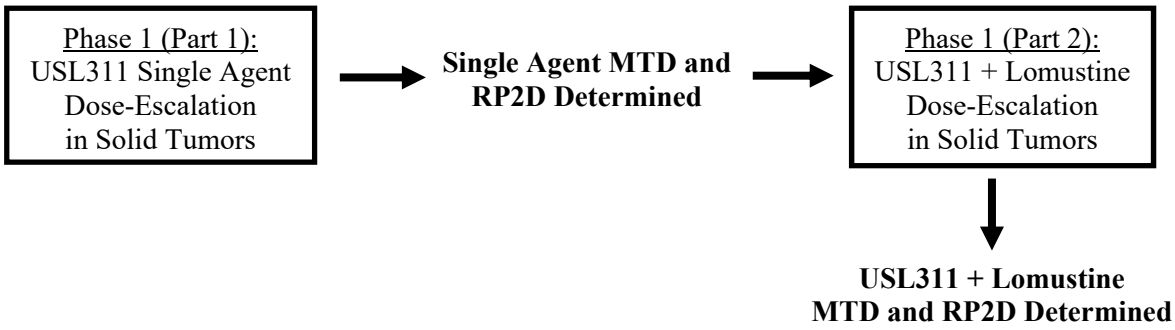
The exposure-response relationship objective is outside the scope of this SAP.

Note: Phase 2 objectives are described in detail in the protocol.

3.2 Trial Design and Study Procedures

This is a Phase 1/2 first-in-human, open-label, multicenter study. Phase 1 of the study is described below. The Phase 1 portion of the study consists of two parts, Part 1 and Part 2. Part 1 study the dose escalation of single-agent USL311 (IV for Part 1a or oral for Part 1b) in subjects with advanced solid tumors. As of the date of protocol amendment 4, a total of 13 subjects were enrolled in Part 1a and treated with IV USL311 at doses of 60, 120, 180, and 250 mg/m^2. Even though no DLT was observed, the Dose Escalation Committee halted Part 1a dose escalation due to dose-related increase in QTcF prolongation that was not ameliorated by increasing infusion time. Part 1b studies dose escalation of oral USL311 in subjects with advanced solid tumors. Part 2 studies dose escalation of oral USL311 in combination with lomustine in subjects with advanced solid tumors. Subjects will only participate in one part of the study. Phase 1 (Parts 1 and 2) will be conducted at approximately 4 study sites. Additional sites may be added depending on study recruitment.

Figure 1. Phase 1 Study Components Flow Diagram



Dose-escalation components will 1) assess safety, PK/PD and preliminary efficacy of USL311 as a single agent in subjects with advanced solid tumors for which no standard-of-care treatment is recognized or who have failed or are intolerant to the standard-of-care treatment, and 2) assess safety, PK/PD and preliminary efficacy of USL311 in combination with lomustine in subjects with advanced solid tumors for which no standard-of-care treatment is recognized or who have failed or are intolerant to the standard-of-care treatment.

The dose-escalation component of Part 1 will determine the MTD and RP2D of single agent USL311.

Study assessments of Part 1 of the study will be performed at the visits outlined in the Schedule of Visits and Assessments in Tables 1 (for Part 1a) and Table 2 (for Part 1b) of the protocol.

3.3 Treatments and Assignment to Treatments

3.3.1 Part 1a – Dose-Escalation in Advanced Solid Tumors of Single Agent IV USL311

Subjects in Part 1a (IV USL311) were treated with weekly single agent US311 by IV infusion and participated in the following visits:

- Screening Visit (within 28 to 2 days of Cycle 1, Day 1)
- Baseline Visit (Day -1)
- Treatment Phase Visits for Cycle 1 (Visits on Day 1, Day 2, Day 3, Day 5, Day 8, and Day 15)
- Treatment Phase Visits for Cycle 2+ (Visits on Day 1, Day 8, and Day 15)
- End of Treatment Visit (within 14 days of decision to discontinue on-study treatment)
- Follow-up Visit (within 28 days of last dose on USL311; may be same visit as End of Treatment Visit)
- Long Term Follow-up Visits (quarterly visit or phone call until subject death or study termination)

During the Treatment Phase, treatment was administered once every week in 3-week (21-day) cycles. In Protocol Amendment 3, the duration of infusion for USL311 was increased from 120 minutes (2 hours) to 240 minutes (4 hours). As of Amendment 3, USL311 was administered as an intravenous (IV) infusion over 240 minutes (4 hours) on Days 1, 8, and 15 of a 21-day cycle. Subjects were monitored by study staff for at least 8 hours after the start of the infusion for their first dose of USL311.

Dosing with the 4 hour infusion was initiated at the highest safe dose of USL311 as determined from subjects who received USL311 via a 2 hour infusion (viz., prior to Amendment #3). Subjects who were previously enrolled and were actively participating at the time Protocol Amendment #3 was activated will continue study participation according to Protocol Amendment #2.

As of the date of protocol amendment 4, a total of 13 subjects were enrolled in Part 1a and treated with IV USL311 at doses of 60, 120, 180, and 250 mg/m^2. Even though no DLT was observed, the Dose Escalation Committee halted dose escalation of IV USL311 due to dose-related increase in QTcF prolongation that was not ameliorated by increasing infusion time.

Tumor assessments are carried out at Cycle 3 Day 1 and every 6 weeks (±7) thereafter.

3.3.2 Part 1b – Dose-Escalation in Advanced Solid Tumors of Single Agent oral USL311

Subjects in Part 1b (oral USL311) are treated with oral daily single agent US311 and are participated in the following visits:

- Screening Visit (within 28 to 2 days of Cycle 1, Day 1)
- Baseline Visit (Day -1)
- Treatment Phase Visits for Cycle 1 (Visits on Day 1, Day 2, Day 8, and Day 15)
- Treatment Phase Visits for Cycle 2+ (Visits on Day 1, Day 8, and Day 15)
- End of Treatment Visit (within 14 days of decision to discontinue on-study treatment)
- Follow-up Visit (within 28 days of last dose on USL311; may be same visit as End of Treatment Visit)
- Long Term Follow-up Visits (quarterly visit or phone call until subject death, lost to follow-up or study termination)

During the Treatment Phase, treatment will be administered in 3-week (21-day) cycles at a starting dose of 40 mg once daily. Treatment cycles will be repeated every 21 days until disease progression, unacceptable toxicity, withdrawal of consent, Investigator decision to discontinue treatment, or Sponsor decision to terminate the study. The MTD will be determined for single agent USL311, and all available safety, PK, and PD data will be reviewed by the DEC and Sponsor prior to confirming the optimal starting dosage for Part 2 (USL311 administration in combination with lomustine) and prior to determining the RP2D. The RP2D of single agent USL311 will be determined by the DEC and

Sponsor after considering the safety, PK/PD, and preliminary efficacy outcomes and may be equal to or lower than the MTD.

3.3.3 Dose-Escalation Strategy

During Phase 1 dose-escalation, subjects will receive study drug USL311 in Part 1a and 1b at increasing doses. Decisions on dose-escalation will be made according to the mCRM design and reviewed by a dose escalation committee (DEC). Complete details of the mCRM model and its operating characteristics are provided in the Appendix 1 of the protocol. The target dose-limiting toxicity (DLT) rate is 33%. The MTD will be defined as the highest safe dose, where safe is defined by having at least a 50% probability that the DLT rate is less than 33%. This definition for safety is consistent with the maximum likelihood estimate for the probability of DLT. If the DLT rate is estimated to be exactly 33%, the probability the DLT rate is less than 33% will be equal to 50%. Therefore, doses with a mean estimated DLT rate less than 33% will be considered safe by this definition and doses with a mean estimated DLT rate greater than 33% will be considered unsafe by this definition. Subjects may never be assigned to a dose that is considered unsafe according to this definition.

A dose-toxicity model will be used to determine which doses are safe and to assign subjects to doses, i.e. to assign subjects to the highest safe dose. However, assignment of dose levels is also governed by rules concerning the speed of dose escalation and rules that determine whether an untried dose level may be skipped. When the dose is escalated, it may only escalate to the highest safe dose that is no more than a 100% increase over the current dose level. If the dose must be de-escalated, the dose will de-escalate to the highest safe dose regardless of how large a decrease in dose level. As long as no DLT has yet been observed, there must be complete DLT information through Cycle 1 on at least 2 subjects in order to escalate. Once the first DLT is observed in the study, there must be complete DLT information through Cycle 1 on at least 3 subjects in order to escalate. A DLT is defined in Section 3.2.5 of the protocol.

In the dose-toxicity model, non-DLT toxicity events (i.e. grade 2 toxicities) will inform the probalility of DLT at each dose level. The DLT observation period, for the purpose of dose-escalation, is one (1) cycle. Once a subject has completed this first cycle DLT observation period, the subject will be considered to have complete DLT information for the purposes of making dose escalation decisions for the next subject enrolling into the study (Part 1a and Part 1b). However, DLTs may also appear in later cycles. If a DLT appears at any time through subsequent cycles of treatment, a subjects DLT status and mCRM model will be updated to reflect the late cycle DLT.

The first three subjects will be enrolled as a dosing cohort in Part 1. There must be complete DLT information on these three subjects in order to enroll the 4th subject. Starting with the 4th subject enrolled, there will be open enrollment to the study meaning that subjects can be enrolled as they become available for the study, however, there may be no more than 3 subjects enrolled in the study (Part 1a and Part 1b) with unknown DLT information at any time.

This study will be monitored for safety and for success in identifying the MTD. If no doses are safe, dose escalation will stop and no MTD will be declared. Alternatively, dose escalation may be stopped early when there are sufficient confidence the MTD has been identified. This is characterized by having either estimated the MTD with high probability, or by having a sufficient number of subjects with complete DLT information at and around the MTD. If the dose escalation is not stopped early for safety or for success in identifying the MTD it will continue to the maximum sample size of 40 subjects for Part 1b. More detailed information regarding the stopping rules and determination of the MTD for dose-escalation is provided in Appendix 1 of the protocol.

No intra-subject dose-escalation will be allowed until the MTD is established, at which time subjects who have received at least 12 weeks of study drug(s) without evidence of progression may receive study drug up to RP2D, at the discretion of the Investigator and with approval of the Sponsor.

3.3.4 Dose Escalation Committee (DEC)

During dose-escalation for Phase 1 (Parts 1 and 2), the safety data, any available PK/PD data, and other relevant subject data will be reviewed by the DEC. The DEC will comprise, at a minimum, Sponsor Chief Safety Officer (or designee), Contract Research Organization (CRO) Medical Monitor and the study site Investigator(s) (or designee). Other representatives may be involved in data review and the dose-escalation decision, as appropriate. All dose modification steps and dose schedule and infusion duration recommendations will be agreed upon by the DEC before dosing at the next dose level or determining the MTD and RP2D. Detailed information is provided in the Dose Escalation Management Plan.

3.4 Number of Subjects Planned

The total number of subjects in Part 1 will depend on the number of dose levels assessed in Phase 1 (Parts 1a and 1b). A total of 13 subjects were enrolled in Part 1a. It is expected that approximately 6-40 subjects with advanced solid tumors be enrolled for Part 1b single agent dose-escalation**.** There is no formal hypothesis testing in this trial, thus no sample size calculations were performed.

4 General Analysis Conventions

Data collected for the Phase I (Part 1a, Part 1b and Part 2) portion of this study will be documented using summary tables and subject data listings. Continuous variables will be summarized using descriptive statistics (number of subjects, mean, median, standard deviation, minimum, maximum, and inter-quartile range). Additional statistics such as geometric mean and coefficient of variation (CV%) may be calculated as warranted. Categorical variables will be summarized using counts and percentages or proportions. Confidence intervals (CIs) will be presented where appropriate. The Clopper-pearson exact method will be used to calculated CI. No formal statistical tests will be performed in this Phase 1 dose escalation study. Time to event variables will be summarized using

Kaplan-Meier estimates and CIs for the 25th, 50th, and 75th percentiles with the standard errors estimated by the Greenwood formula.

Assessments will be displayed separately for Part 1a and Part 1b. Within each part of the study, data will be summarized by dose group and overall.

Study days will be calculated relative to the first dose of USL311 . Day 1 will be the first day of study drug administration in the study, and the day prior to the first dose of study drug administration will be Day -1. There will be no Day 0. Time relative to dose for such endpoints as PK samples, vital signs, and electrocardiograms (ECGs) will be based on the start time of the infusion.

Baseline will be the last assessment prior to the first dose of study drug unless otherwise indicated.

Adverse events, medical history, and surgical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA), Version 19.0. Adverse event intensity will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v 4.03. Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary (March 2016).

4.1 Partial Date Imputation

Partial start dates and end dates for adverse events will be imputed as follows:

Variable	**Missing Day**	**Missing Day, Month**	**Missing Day, Month, Year**
Adverse Event Start Date	Assign first day of month unless it is the month of first dose of study drug. Otherwise, assign date of first dose of study drug. If imputed start date is after end date, assign start date = end date.	Assign January 1 unless the year is year of first dose of study drug. Otherwise, assign date of first dose of study drug. If imputed start date is after end date, assign start date = end date.	Assign date of first dose of study drug. If imputed start date is after end date, assign start date = end date.
Concomitant Medication Start date	Assign first day of month	Assign January 1	No imputation
Concomitant Medication End	Assign last day of	Assign December	No imputation

date	the month	31	

Data for all subjects in the clinical database will be included in the data listings. Calculated (derived) variables will be listed as appropriate. All tables, listings, and figures will be programmed using SAS Version 9.3 or higher.

4.2 Study Periods

The following four study periods are planned for Part 1.

- Screening phase – Screening Visit assessments must be performed within 28 days of Day 1. For part 1a and part 1b, subjects will also have Baseline visit at Day -1.
- Treatment Phase - Treatment phase start at Day 1. Treatment with single agent USL311 will be administered in 21-day cycles.
- The End of Treatment/Follow-up Visit – The End of Treatment Visit will occur ≤ 14 days of the decision to discontinue on-study treatment whereas the Follow-up Visit will occur ≤ 28 days of the last dose of USL311. The End of Treatment visit may be the same as the Follow-up Visit; however, the Follow-up Visit should occur as close to 28 days after the last dose USL311 treatment as possible, per Investigator discretion.
- Long-term Follow-up Phase - All subjects who discontinue from study treatment, and are willing to be contacted, will be followed for survival information (Long-term Follow-up). The Long-term Follow-up Phase will begin after the Follow-up Visit or the End of Treatment Visit, as applicable. If a subject is unable to attend the End of Treatment Visit, the Long-term Follow-up Phase will begin upon investigator determination that the subject has ended the Treatment Phase. Survival follow-up information will be collected via telephone calls and/or clinic visits quarterly (every 3 months ± 1 week) until death, loss to follow-up, End of Study, withdrawal of consent, initiation of subsequent treatment for the target tumor, administrative reasons, or study termination by the Sponsor.

4.3 Visit Windows

Study visits are expected to occur according to the protocol schedule. All data will be tabulated per the evaluation visit as recorded on the electronic case report form (eCRF) even if the assessment is outside of the visit window. Data from unscheduled visits will not be included in summary tables and will only be displayed in listings. No imputation of data will be performed for missed assessments. For time-to-event analyses, evaluations will be based on the actual date of the event rather than on the visit of the event.

5 Analysis Populations

5.1 Full Analysis Data Set (FAS)

The Full Analysis Data Set for Part 1 will include all subjects who receive at least one dose of USL311. This will be the analysis set for efficacy analyses.

5.2 Safety Analysis Data Set

The Safety Analysis Data Set for Part 1 will include all subjects who receive at least one dose USL311 and have at least one post-baseline safety evaluation including adverse event, clinical laboratory data, physical and neurological examination, vital sign, electrocardiogram, Karnofsky performance score. This will be the analysis set for all safety analysis.

5.3 MTD-Evaluable Data Set

The MTD-Evaluable Data Set will include all subjects in Part 1 monotherapy dose-escalation who complete one cycle of treatment and assessment or who discontinue before completing the first cycle because of dose limiting toxicity. This will be the analysis set for MTD determination for Phase I.

5.4 Pharmacokinetic (PK) Analysis Data Set

The PK Analysis Data Set will include all subjects who receive at least one dose of USL311 and have at least one quantifiable post-dose blood or plasma concentration of the drug. Summaries for the PK analysis data set are not described in this SAP.

5.5 Pharmacodynamic (PD) Analysis Data Set

The PD Analysis Data Set will include all subjects who receive at least one dose of USL311 and have at least one evaluable post-treatment assessment for the given PD measure. Summaries for the PD analysis data set are not described in this SAP.

5.6 Response-Evaluable Analysis Data Set (RES)

The Response-Evaluable Analysis Data Set will consist of those subjects who receive at least one dose of USL311 and have evaluable disease at baseline.

5.7 Exposure-Response Analysis Data Set (RAS)

An Exposure-Response Analysis Data Set may be constructed for each PD or response endpoint to be evaluated for correlation with PK data. If performed, the exposure-response analysis set will consist of all subjects in the PK Analysis Set that also have an evaluable PD/response pretreatment assessment and at least one post-treatment PD/response assessment. The analyses for Exposure-Response Analyses are not described in this SAP.

6 Subject Disposition

Subject disposition will be summarized by dose group and overall for each part (1a or 1b) of the study as well as for overall Part 1. The number of subjects in each population and the number of subjects who complete study will be summarized by dose group and overall for Part 1a, Part 1b and Part 1. The reasons for discontinuing treatment and for discontinuing study will be summarized for the FAS population.

Subjects who are excluded from each population will be presented in a data listing, along with reasons for exclusion.

Inclusion/exclusion data will be presented by subject in a data listing.

7 Protocol Deviations

Protocol deviations categorized as important will be summarized by dose group and overall of Part 1a or Part 1b, respectively and will be presented by subject in a data listing.

8 Demographic and Baseline Characteristics

8.1 Demographic Characteristics

Demographic and baseline characteristics at study entry will be summarized by dose group and overall for Part 1a, Part 1b and Part 1 of the study for the FAS population.

Demographic and baseline characteristics to be summarized are:

- Continuous variables:
  - Age (years)
  - Weight (kg)
  - Height (cm)
  - Body mass index (BMI) (kg/m^2)
  - Body surface area (BSA) (m^2)
  - Time since initial diagnosis (years)

Time since initial diagnosis is calculated as the date the informed consent was signed minus the date of initial diagnosis expressed in years. If the day of initial diagnosis is missing, 15 will be imputed for calculations. If only the year of initial diagnosis is present, time since initial diagnosis is calculated as the year the informed consent was signed minus the year of initial diagnosis.

- Categorical variables:
  - Sex
  - Race
  - Ethnicity
  - Genotype (CYP2D6 and CYP3A), if available
  - Age category (<65, ≥65 years)
  - Karnofsky Performance Status (KPS) Scale (0, 10, 20, 30, …, 100)
  - Stage of disease at diagnosis (as listed on eCRF)
  - Stage of disease at study entry (as listed on eCRF)
  - Type of Cancer (as listed on eCRF)

8.2 Medical History

The number and percentage of subjects with each medical history condition collected on the eCRF will be summarized by MedDRA system organ class (SOC) and preferred term (PT) for the FAS population by dose group and overall for each part of the study.

Medical and surgical history information will be reported by subject in a data listing.

8.3 Prior Cancer Treatment

Prior radiotherapy, surgery, and systemic therapies will be summarized for the FAS population by dose group and overall for each part of the study.

The following variables will be summarized:

- Prior systemic therapy (yes/no)
- Setting of systemic therapy (neo-adjuvant, adjuvant, radio-sensitising, locally advanced, metastatic)
- Number of prior systemic therapy regimens
- Time since last systemic therapy (days)
- Best response to systemic therapy for last systemic therapy
- Prior radiotherapy (yes/no)
- Anatomical site of radiotherapy
- Prior surgery for target tumor (yes/no)

Time since last systemic therapy is calculated as the date the informed consent was signed minus the latest therapy end date expressed in days. If the day of therapy end date is missing, 15 will be imputed for calculations. If only the year is present, time since last systemic therapy will not be calculated.

Results will be summarized by dose group and overall for each part of the study. Continuous variables will be summarized with descriptive statistics (number of subjects, mean, standard deviation, median, range, and inter-quartile range). Number of prior systemic therapy regimens will be summarized using descriptive statistics and will also be categorized and summarized using counts and percentages. All other variables listed above will be summarized using counts and percentages.

Medications reported as prior systemic therapies will be summarized by the WHO Drug Dictionary Anatomical Therapeutic Chemical 3rd level (ATC-3) and preferred name for the full analysis set by dose group and overall for each part of the study. If the 3rd level term is not available, the next available level (e.g., ATC-2) will be used. A subject will only be counted once within each ATC-3 code and within each preferred name.

Prior radiotherapy, surgery, and systemic therapies will be listed by subject in a data listing.

8.4 Prior and Concomitant Medications

Concomitant medication are medications that were taken between the first and last day of study drug administration (i.e., start date < last dose date and end date > first dose date or ongoing). Prior medications are medications with a end date on or before the first day of study drug.

Concomitant or prior medications will be summarized separately by the WHO Drug Dictionary Anatomical Therapeutic Chemical 3rd level (ATC-3) and preferred name for the safety population by dose group and overall for each part of the study. If the 3rd level term is not available, the next available level (e.g., ATC-2) will be used. A subject will only be counted once within each ATC-3 code and within each preferred name.

All prior and concomitant medication data will be listed by subject.

9 Efficacy Variables and Analysis

Efficacy parameters will be determined using RECIST v1.1 or RANO criteria as appropriate. Efficacy variables include the following:

- 6-month progression-free survival rate (PFS-6m)
- Progression-free survival (PFS)
- Objective response rate (ORR)
- Disease control rate (DCR)
- Overall survival (OS)

Efficacy analyses will be summarized with summary statistics for the FAS and RES populations. Results will be summarized by dose group and overall for each part of the study. There is no formal hypothesis testing in this trial for efficacy endpoints.

Six – month PFS rate will be calculated with two-sided 90% confidence interval (CI) using the Kaplan-Meier (KM) product-limit estimate of PFS. Number and percent of patients progressed at 6 months and number of patients censored at 6 months will be summarized descriptively. The analysis will be performed based on both the full analysis set and response-evaluable set. PFS is defined as the interval between the start of USL311 and the earliest documented evidence of disease progression or death due to any cause. Subjects who do not have a documented date of progression or death will be censored at the date of the last adequate assessment. For patient not progressed at six-month, they will be censored at month 6 for PFS-6m analysis. For patients without post baseline tumor assessment and alive at the end of study will be censored at day 1.

PFS will be summarized using KM methodology using 25th, 50th (median), and 75th percentiles with associated 2-sided 90% CIs as well as the number and proportion of censored observations. A KM plot may be provided.

Best overall tumor response will be determined based on all overall tumor responses are collected following the hierarchical order of CR, PR, SD, PD, NE. A confirmed objective

response is defined as a response that persists on repeat imaging for two assessments with a time period of at least 4 weeks between the two assessments (Table 1).

Table 1.

Overall response First time point	Overall response Subsequent time point	BEST overall response
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

[a] If a CR is *truly* met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

ORR is defined as the proportion of subjects with a confirmed complete response (CR) or confirmed partial response (PR) relative to the total number of subjects in the corresponding analysis population. The ORR and 90% CI will be summarized.

DCR is defined as the proportion of subjects who have a confirmed complete response (CR), confirmed partial response (PR), or stable disease (SD). The DCR and 90% CI will be summarized.

Overall survival is defined as the interval between the start of USL311 and date of death due to any cause. Subjects who are still alive or who are lost to follow-up will be censored at the date of last contact. Overall survival will be summarized using KM methodology using 25th, 50th (median), and 75th percentiles with associated 2-sided 90% CIs , as well as the number and proportion of censored observations. A KM plot may be provided.

If central reader imaging analyses are performed, the maximal change of the sum of longest diameters for all target lesions from baseline may be shown in a waterfall plot.

10 Statistical/Analytical Issues

10.1 Handling of Dropouts or Missing Data

No imputation of data will be performed for missed assessments. Imputation rules for missing AE start and end dates are described in Section 3.1.

10.2 Pooling of Centers in Multi-Center Studies

Data will not be summarized by study center or for groupings of study centers.

10.3 Multiple Comparisons/Multiplicity

No formal statistical testing will be performed; therefore, no adjustments for multiple comparisons or multiplicity are planned.

10.4 Examination of Subgroups

No subgroup analyses are planned for this study.

10.5 Interim Analysis and Data Monitoring

No formal interim analysis will be performed in this study. After Part 1, the MTD for single agent USL311 will be determined, if achieved, by the Dose Escalation Committee (DEC). The DEC will also determine the RP2D.

11 Pharmacokinetics/Pharmacodynamics

11.1 Pharmacokinetic analyses

Pharmacokinetic summaries and analyses will be performed according to a separate PK analysis plan and will be reported in a separate PK analysis report. Collection dates and times (both planned and actual) as well as PK concentrations at each timepoint will be listed by subject for all PK samples.

11.2 Biomarker Samples (Pharmacodynamic Analyses)

Blood and urine samples will be collected to evaluate biomarkers of target engagement (WBC and CD34+ cell counts) and phospholipidosis (BMP), respectively.

Biomarkers will be summarized at baseline (the last assessment prior to the first dose of USL311) and at each scheduled post-baseline visit and time point using descriptive statistics. Results will be summarized by dose group and overall for each part of the study. Difference of BMP between cycle 2 day 1 and baseline for the overall part 1 safety population will be analysised using student’s paired t-test.

Additional pharmacodynamic analyses may be performed as warranted following data exploration. If performed, the analyses will be conducted according to a separate pharmacodynamic analysis plan and will be reported in a separate report.

Biomarker data will be presented by subject in a data listing. Collection dates and times (planned and actual) will be listed by subject for all biomarker samples.

11.3 Exposure-Response Analyses

Response data (i.e., efficacy, safety and biomarker data) may be explored for correlations with measures of USL311. If potential exposure-response relationships are suggested, additional analyses may be performed and may be included in the CSR or may be reported in a separate analysis report. Exposure-response analyses, if performed, are outside the scope of this SAP.

12 Safety Analysis

The safety assessments include study drug exposure, adverse events (including DLTs and SAEs), vital signs, physical examinations, neurological examinations, clinical laboratory tests, electrocardiograms (ECG), and concomitant medications. Safety will be summarized by dose group and overall for each part of the study. All safety data will be included in data listings.

12.1 Study Drug Exposure

USL311 exposure will be summarized for the Safety population by dose group and overall for each part of the study. The following variables will be summarized for IV USL311 (part 1a):

- Number of cycles each subject was dosed in. Patient received any dose at a given cycle will be considered as received dose for that cycle
- Number of infusions
- Total cumulative dose over the study (mg and mg/m^2)
- Duration of exposure in weeks, calculated (Date of Last Drug Administration – Date of First Drug Administration + 1 day) / 7 days)
- Treatment compliance of IV USL311 is determined by total cumulative dose over the study/planned dose. Planned dose is equal to duration of exposure in weeks* assigned dose for that subject.

The following variables will be summarized for oral USL311 (Part 1b):

- Number of cycles each subject is dosed in. Patient received any dose at a given cycle will be considered as received dose for that cycle
- Total cumulative dose over the study (mg)
- Duration of exposure in weeks, calculated (Date of Last Drug Administration – Date of First Drug Administration + 1 day) / 7 days)
- Treatment compliance of oral USL311 is determined by total cumulative dose over the study/planned dose. Planned dose is equal to duration of exposure in days* assigned dose for that subject.

Study drug administration data, including BSA, will be presented by subject in a data listing.

12.2 Adverse Events

Adverse events (AEs) will be summarized for the Safety population by dose group and overall for each part of the study. All AEs will be summarized by MedDRA system organ class (SOC) and preferred term (PT). Adverse events will be graded according to the NCI CTCAE v 4.03. An AE that begins on or after the date of first dose of study drug will be considered a treatment-emergent adverse event (TEAE).

Adverse event severity will be classified into 5 categories based on NCI CTCAE 4.03 toxicity grades: Grade 1 = mild, Grade 2 = moderate, Grade 3 = severe or medically significant but not immediately life-threatening, Grade 4 = life threatening or debilitating, and Grade 5 = death related to AE.

The relationship of the AE to USL311 will be classified into 5 categories: related, probably related, possibly related, probably not related, and not related. Treatment-related adverse events are defined as a relationship of related, probably related, or possibly related.

12.2.1 Overview of Treatment-Emergent Adverse Events

An overview summary table of TEAEs will include number and percentage of subjects in each of the following categories, summarized by dose group and overall for each part of the study:

- Subjects reporting at least one TEAE
- Subjects reporting at least one TEAE with CTCAE Grade ≥3
- Subjects reporting at least one TEAE related to USL311
- Subjects reporting at least one treatment-emergent serious AE (SAE)
- Subjects reporting at least one TESAE related to USL311
- Subjects with at least one dose-limiting toxicity (DLT) as defined in the protocol
- Subjects with AE resulting in death on study

12.2.2 Treatment-Emergent Adverse Events

The number and percentage of subjects with the following categories of AEs will be summarized in tables by dose group and overall for each part of the study by system organ class (SOC) and preferred term (PT), with SOCs sorted by decreasing frequency based on the overall populatin, and PTs sorted alphabetically within a SOC by decreasing frequency based on the overall population.

- Any TEAE by SOC and PT.
- Any TEAE by SOC, PT and CTCAE grade
- Any TEAE with CTCAE Grade ≥3 by SOC and PT
- Any TEAE by SOC, PT, and relationship to USL311
- Any treatment-emergent SAE by SOC and PT
- Any treatment-emergent AE resulting in treatment discontinuation by SOC and PT

Each subject will contribute at most one count per summarization category. In other words, if a subject has more than one AE with same SOC or PT, the subject will be counted only once for that SOC or PT. Similarly, if a subject reports multiple toxicity

grades or relationship categories for a PT, only the highest toxicity grade or strongest relationship will be summarized. Missing toxicity grades and relationships will not be imputed.

By-subject listings also will be provided for the following: all AEs, AEs with toxicity grade 3 or above, treatment-related AEs, AEs resulting in death, serious AEs, and DLTs.

12.3 Clinical Laboratory Data

Quantitative clinical laboratory results (hematology [except biomarker white blood cells, which are part of the pharmacodynamics analysis]), coagulation, serum chemistry, and other laboratory tests collected throughout the course of the study) will be summarized at baseline (the last assessment prior to the first dose of study drug), each scheduled post-baseline visit, and change from baseline to each scheduled post-baseline visit using descriptive statistics (number of subjects, mean, median, standard deviation, range, and inter-quartile range). Results will be summarized by dose group and overall for each part of the study.

Shift tables that present changes from baseline to worst on-study values relative to NCI CTCAE v 4.03 classification ranges will be produced by dose group and overall for each part of the study for laboratory parameters. For some lab values, both shift high and shift low are applicable to CTCAE grade.

Hematology

- hemoglobin
- lymphocytes (absolute)
- platelet count
- neutrophils (absolute)
- white blood cells

Coagulation

- activated partial thromboplastin time
- INR

Serum chemistry

- albumin
- alkaline phosphatase
- ALT
- AST
- calcium
- creatinine
- magnesium
- glucose
- potassium
- sodium

Values of laboratory tests with NCI-CTCAE Severity ≥ Grade 3 will be listed by subject; the listing will contain all of a subject's values for parameters meeting the criteria.

All laboratory parameters will be included in data listings, and values outside of the reference range will be flagged in data listings.

12.4 Physical and Neurological Examination

Physical and neurological examination data will be listed by subject.

12.5 Vital Signs

Vital signs data will include systolic blood pressure, diastolic blood pressure, pulse rate, temperature, respiration rate, weight, and BSA. Results will be summarized by dose group and overall for each part of the study at baseline (the last assessment prior to first dose of study drug), at each scheduled post-baseline visit, and change from baseline to each scheduled post-baseline visit using descriptive statistics (mean, median, standard deviation, range, and inter-quartile range).

On the dosing day, vital sign will be summarized pre-dose, post dose and change from pre-dose descriptively.

Vital signs data will be listed by subject.

12.6 Electrocardiogram

12.6.1 Safety Electrocardiograms

Safety ECG data collected at the investigative sites and entered into the eCRF will include heart rate, PR and QRS intervals, QT interval, QT interval corrected for heart rate using Bazett method (QTcB), and QT interval corrected for heart rate using Fridericia method (QTcF). ECG data will be summarized for baseline (pre-dose), each scheduled post-baseline visit, and change from baseline to each post-baseline visit using descriptive statistics (number of subjects, mean, median, standard deviation, range, and inter-quartile range) by dose group and overall for each part of the study. All parameters will be based on ECG triplicate averages (or if fewer, average of ECGs available).

Shift tables will be prepared for the overall interpretation of the ECG. Both the baseline and the worst on study results will be classified into 1 of 3 categories: normal, abnormal – not clinically significant, or abnormal – clinically significant. Baseline will be the worst value at Screening.

The number and percentage of subjects meeting each of the following criteria (based on NCI-CTCAE 4.03) for QTc value will be summarized.

- < 450 msec
- 450 - 480 msec
- 481 - 500 msec
- > 500 msec

Furthermore, subjects meeting the following criteria for change from baseline within each of the above category will also be summarized.

- ≤ 30 msec increase from baseline
- > 30 - 60 msec increase from baseline
- ≥ 60 msec increase from baseline

In addition, a listing of subjects with values meeting each criterion any time after the first dose of study drug will be provided. The listing will contain all of a subject's values for parameters meeting the criteria.

All safety ECG results will be listed by subject.

12.6.2 Extracted Electrocardiograms

Quantitative analysis of the ECG extractions from the holters will be performed and reported separately by the ECG vendor.

ECG data including heart rate, PR and QRS intervals, QT interval, QTcB, and QTcF with respect to the Holter monitor will be listed by subject and summarized similaly as the safety ECG data. In addition, time match change will be listed and summarized for the above extracted ECG data.

12.6.3 Real-Time Bedside ECG and Heartrate Monitoring

Real-time bedside ECG will be monitored by clinic staff from start of USL311 infusion through clinic discharge (up to approximately 6 hours post start of infusion) on days where continuous telemetry monitoring is required. Date of assessment will be captured on the eCRF and will be presented in a data listing.

12.7 Karnofsky Performance Status (KPS) Scale

Performance status will be measured using the KPS Scale (Table 2). The KPS Scale allows subjects to be classified as to their functional impairment. Lower scores represent more impairment.

The number and percentage of subjects with each KPS score will be summarized for baseline (the last assessment prior to first dose of study drug) and for each scheduled post-baseline assessment by dose group and overall for each part of the study.

KPS data will be listed by subject.

Table 1: Karnofsky Performance Status Scale

Karnofsky Performance Status Scale	
Percent	**Description**
100	Normal, no complaints, no evidence of disease
90	Able to carry on normal activity; minor signs or symptoms of disease
80	Normal activity with effort; some signs or symptoms of disease

70	Cares for self, unable to carry on normal activity or to do active work
60	Requires occasional assistance, but is able to care for most of his/her needs
50	Requires considerable assistance and frequent medical care
40	Disabled, requires special care and assistance
30	Severely disabled, hospitalization indicated Death not imminent
20	Very sick, hospitalization indicated Death not imminent
10	Moribund, fatal processes progressing rapidly
0	Dead

12.8 Other Safety and Pharmacodynamic Assessments

Any safety and pharmacodynamics assessments not previously described will be presented in data listings. Additional analyses may be performed if warranted.

13 Quality Control

All data displays and analyses will adhere to the International Conference on Harmonisation (ICH) Harmonized Tripartite Guideline: Structure and Content of Clinical Study Reports (ICH Topic E3).

All analyses will be performed using SAS® Version 9.3 (or later). Covance will follow its standard operating procedures in the creation and quality control of all tables, listings, figures, and analyses. The Sponsor or its designee will review all tables, listings, and figures prior to final database lock. All final SAS programs and associated output files will be transferred to the Sponsor in agreed-upon format at project completion.

14 Changes in Conduct or Planned Analyses from the Protocol

Study P311-201 was terminated early, for non-safety reasons, during Part 1b prior to the determination of the MTD. As a result, the SAP for the protocol has been revised from version 1.0, dated 29Apr2020, of the SAP to report endpoints to support an abbreviated clinical study report focusing on safety. The analyses will include summary tables, supported by listings, for study demographics and safety. Summary tables related to evaluation of efficacy have been removed from the final analysis. A summary of changes to reflect the change in scope of the protocol analyses are as follows:

1. Section 5 Analysis Population: Only Full Analysis data set, Safety Analysis data set, and MTD-Evaluable Data set will be determined.
2. Section 9 Efficacy Variables and Analysis: As there are limited number of patients per dose level in the dose escalation, no efficacy analysis will be completed. Tumor assessment and responses will be included in listings.
3. Section 12.7: Karnofsky Performance Status (KPS) Scale: KPS Scale will only be presented in a listing.