STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 2 Study of Tarloxotinib in Patients with Select Gene Alterations and Non-Small Cell Lung Cancer or Other Advanced Solid Tumors
Study Number:	RAIN-701
Investigational Drug:	Tarloxotinib bromide
Indication:	Treatment of Non-Small Cell Lung Cancer or Other Advanced Solid Tumors
Investigators:	Multicenter
IND Number:	112290
Sponsor:	Rain Therapeutics Inc. 8000 Jarvis Ave Suite 204 Newark, CA, 94560
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RAIN-701

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List of Abbreviations and Definition of Terms

Abbreviation	Description
ADaM	analysis data model
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	Anatomical / Therapeutic / Chemical
BOR	best overall response
CI	confidence interval
CDISC	Clinical Data Interchange Standards Consortium
CM	concomitant medication
CR	complete response
CSR	clinical study report
CT	computed tomography
ctDNA	circulating tumor deoxyribonucleic acids
CTCAE	Common Terminology Criteria for Adverse Events
DCR	disease control rate
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EGFR	epidermal growth factor receptor
EOI	End of infusion
EOT	End-of-Treatment Visit
ERBB2	v-erb-b2 avian erythroblastic leukemia viral oncogene homolog 2
ERBB4	erb-b2 Receptor tyrosine kinase 4
FDA	Food and Drug Administration
HER	human epidermal growth factor receptor
HR	heart rate
ICH	International Council for Harmonisation
IV	intravenous
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NCI	National Cancer Institute
NRG1	neuregulin 1
NSCLC	non-small cell lung cancer
ORR	objective response rate

Abbreviation	Description
OS	overall survival
PAS	Primary analysis set
PD	progressive disease
PET	positron emissions tomography
PFS	progression-free survival
PK	pharmacokinetic
PO	oral
PR	partial response
QTc	corrected QT interval
QTcF	corrected QTc interval as calculated according to Fridericia's formula
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease (tumor response)
SD	standard deviation (statistics)
SOC	system organ class
STEAP4	six transmembrane epithelial antigen of the prostate, family member 4
TEAE	treatment-emergent adverse event
TLF	tables, listings, and figures
WHO	World Health Organization
WOCBP	women of childbearing potential

1 REVISION HISTORY

Version	Date	Document Owner	Revision Summary
1.0	14 October 2022	Inka Leprince	Initial version

2 RELATED DOCUMENTS: PROTOCOL AND CASE REPORT FORMS

Version	Date
Initial Protocol	14Dec2018
Protocol (Amendment 1)	06Mar2019
Protocol (Amendment 2)	17Jun2019
Protocol (Amendment 2.1)	11Nov2019
Protocol (Amendment 3)	24Oct2020
Case Report Forms	22Mar2019

3 COMMITMENT TO GOOD STATISTICAL PRACTICE

3.1 Definition of Good Statistical Practice

The International Council for Harmonisation Guideline on Statistical Principles for Clinical Trials (ICH E9) implicitly defines good statistical practice. Good statistical practice includes both appropriate statistical designs to minimize bias and maximize precision of analysis plus operational excellence to assure credibility of results. The scientific design associated with any clinical trial is found in the protocol and a more detailed, pre-specified statistical analysis plan such as this one presents the final statistical methods.

We interpret the operational side of good statistical practice as a transparent, reproducible, and validated approach to acquiring and analyzing clinical trial data. Reproducible research depends upon process transparency and also provides auditability of the statistical analysis. Analysis transparency requires that a navigable electronic process chain exists from defining the objective of the analysis to creating the results.

3.2 Use of Standards

Data standards are foundational for creating an environment where tools can be leveraged at different points in the analysis process. Data standards for clinical development of drugs have been defined and are maturing under various initiatives through the Clinical Data Interchange

Standards Consortium (CDISC). RAIN Therapeutics uses raw, source data sets and Analysis Data Model (ADaM) statistical analysis files for producing analysis results. Other applicable standards include regulatory guidance from the Food and Drug Administration (FDA) and ICH:

- ICH Guideline on the Structure and Content of Clinical Study Reports (ICH E3)
- ICH Guideline for Good Clinical Practice (ICH E6)

4 PURPOSE OF THE ANALYSIS PLAN

This statistical analysis plan (SAP) pre-specifies the statistical analysis methods for supporting the completion of the abbreviated clinical study report (CSR) of Study RAIN-701 for investigational product tarloxotinib, a novel drug candidate designed to treat subjects with advanced solid tumors with qualifying genetic mutations and/or fusions. The study intended to enroll up to 215 subjects across 5 cohorts but was discontinued early on the basis of a business decision made by the sponsor. At the time of the database lock for RAIN-701 (23 April 2021), 41 subjects were enrolled. This SAP will be used to conduct a comprehensive safety analysis and summarize the available efficacy data collected during the study. The primary, secondary, and efficacy analyses planned in the protocol may not be appropriate or possible based on the available data. The planned analyses identified in this SAP may be included in future manuscripts.

The analysis methods described in this plan are considered *a posterior*, in that they have been defined after the clinical database lock. Exploratory analyses that are not defined in this SAP may be performed to support the clinical development program. Any post-hoc or unplanned analyses that are performed for the CSR, but not defined in this SAP, will be documented in the CSR. Changes from the planned analyses stated in the study protocol are described in Section 15. Should the SAP and the protocol be inconsistent with respect to any further planned analyses, the language of the SAP is governing.

5 STUDY OBJECTIVE

This study was planned to evaluate the safety and efficacy of tarloxotinib 150 mg/m^2 as a weekly 1-hour intravenous (IV) infusion of up to 40 weeks when administered to subjects with non-small cell lung cancer (NSCLC) whose tumors harbor either an epidermal growth factor receptor (EGFR) exon 20 insertion or a human epidermal growth factor receptor 2 (HER2)-activating mutation (including exon insertions).

5.1 Efficacy Objectives and Endpoints

The primary, secondary, and efficacy analyses planned in the protocol may not be appropriate or possible based on the available data. Additionally, efficacy analyses are unlikely to be significant because the sample size is small and the analyses will be underpowered. In place of formal efficacy analyses, selected efficacy endpoints will be summarized descriptively.

5.1.1 Primary Efficacy

The analysis of the primary objective as outlined in the study protocol will not be performed for the abbreviated CSR, but will instead be summarized descriptively and listed where possible. The primary objective of this study was the evaluation of the objective response rate (ORR), based on subjects who had complete response or partial response, of tarloxotinib according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.

5.1.2 Secondary Efficacy

The analyses of the secondary objectives as outlined in the study protocol will not be performed for the abbreviated CSR, but will instead be summarized descriptively and listed where possible. Secondary objectives include evaluation of the antitumor effect of tarloxotinib on: best overall response (BOR), duration of response (DOR), disease control rate (DCR), progression-free survival (PFS), and overall survival (OS) as measured from the date of first study drug dose to the date of death by any cause. Additional secondary efficacy endpoints such as the exploration of pharmacokinetics of tarloxotinib and tarloxotinib-E; and the determination of whether there is

an association between plasma exposure to tarloxotinib and effects on cardiac repolarization will not be performed because of the limited data basis.

5.1.3 Exploratory Efficacy

The analyses of the exploratory objectives as outlined in the study protocol will not be performed for the abbreviated CSR because of the limited data basis. Exploratory objectives are described in Protocol Section 4.2.3.

5.2 Safety Objective

The safety objective of the study is to evaluate the safety of tarloxotinib subjects with NSCLC using safety assessments described in Section 6.3.2. Safety endpoints include the incidence of treatment-emergent adverse events (TEAEs); changes in clinical laboratory parameters (hematology, serum chemistry, and urinalysis), vital signs, and electrocardiogram (ECG) parameters; physical examination results; and use of concomitant medications (CMs).

6 STUDY DESIGN

6.1 Overall Study Design

This was a Phase 2 multicenter, open-label study to evaluate the antitumor effect of tarloxotinib in subjects with NSCLC whose tumors harbors either an EGFR exon 20 insertion or a HER2-activating mutation (including exon 20 insertions) or subjects with advanced solid tumors expressing NRG1/HER-family gene fusions or a HER2-activating. All subjects have received at least 1 prior platinum-based chemotherapy-containing regimen in the advanced/metastatic setting (Cohorts A, B, and B1) or standard of care for cancer (Cohorts C and D). Cohorts B1 and D were not be pursued at the discretion of the Sponsor.

Table 1 RAIN-701 Number of Subjects by Cohort

Cohort	Description	Planned N	Enrolled N
A:	• Subjects with advanced NSCLC harboring an EGFR exon 20 insertion mutation o At least 1 prior platinum-based chemotherapy-containing regimen	43	11
B:	• Subjects with advanced NSCLC with a HER2 activating mutation	43	22

	• Subjects who have received at least 1 prior platinum-based chemotherapy-containing regimen		
B1*	• Subjects with advanced NSCLC harboring a HER2-activating mutation • Subjects who have received at least 1 platinum-based chemotherapy-containing regimen • Subjects who have received prior HER2-directed therapy	43	0
C:	• Subjects with advanced solid tumors who have failed standard therapies appropriate for their tumor type and stage of disease, or, in the opinion of the Investigator, would be unlikely to tolerate or derive clinically meaningful benefit from appropriate standard-of-care therapy • Subjects with tumors harboring an NRG1 gene fusion, EGFR gene fusion, EGFR kinase domain duplication, ERBB2 gene fusion, or ERBB4 gene fusion	43	8
D*:	• Subjects with advanced solid tumors who have failed all standard therapies appropriate for their tumor type and stage of disease, or, in the opinion of the Investigator, would be unlikely to tolerate or derive clinically meaningful benefit from appropriate standard-of-care therapy • Subjects with tumors (excluding NSCLC) harboring a HER2-activating mutation	43	0
Total		215	41

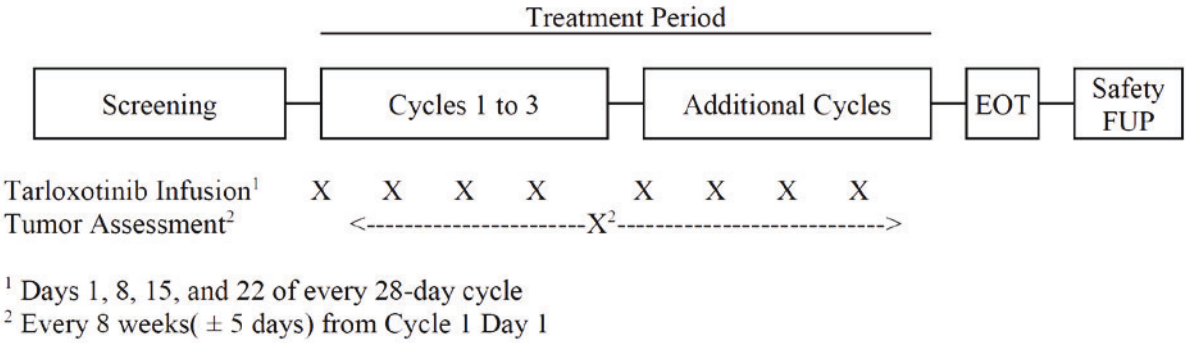
Approximately 248 subjects were planned for enrollment on the study to yield 215 evaluable subjects, 43 subjects per cohort. A total of 41 subjects were enrolled in cohorts A, B and C. No subjects were enrolled on cohorts C and D. All cohorts used a Simon's 2-stage design. In the first stage, 21 subjects were accrued. If more than 3 subjects in a cohort had a partial or complete response, up to 22 additional subjects could have been enrolled to the cohort, for up to a total of 43 subjects per cohort. However, if there were 3 or fewer responses among these 21 subjects, the cohort would be stopped based on futility.

Subjects received taroxontinib 150 mg/m^2 administered as a weekly 1-hour IV infusion on Days 1, 8, 15, and 22 of each 28-day cycle until disease progression or unacceptable toxicity (e.g., hepatotoxicity meeting Hy's law criteria or serious arrhythmias of ventricular origin).

* Cohorts B1 and/or D were not pursued, at the discretion of the Sponsor

Subjects were expected to receive up to 10 cycles of treatment. The total study duration was estimated to be 36 months, including approximately 24 months for accrual and approximately 12 months for follow-up after the last subject was enrolled. Upon completion of the end of treatment visit, subjects returned to the clinic within 30 days following their last dose for a Follow-up visit. Clinical visits during the Treatment Period and Follow-up Period included efficacy, biomarkers, safety, and pharmacokinetic (PK) assessments. Figure 1 depicts study visits from Screening Period to Follow-up Period. The maximum duration of Study RAIN-701 per subject was expected to be up to 338 days (i.e., a maximum of 28-day Screening Period, a Treatment Period consisting of a maximum of ten 28-day treatment cycles, and a 30-day safety Follow-up Period). Assessments and procedures for evaluation of safety, efficacy, PK, and biomarkers were conducted per the protocol-specified schedule (see Table 2).

Figure 1 Schema of Study RAIN-701



[1] Days 1, 8, 15, and 22 of every 28-day cycle
[2] Every 8 weeks(± 5 days) from Cycle 1 Day 1

6.2 Study Medication

6.2.1 Tarloxotinib

Tarloxotinib 150 mg/m^2 was administered as a 1-hour IV infusion weekly until progressive disease (PD) or unacceptable toxicity. Tarloxotinib was administered on Day 1, Day 8, Day 15, and Day 22 of every 28-day cycle. All infusions after Cycle 1 Day 1 were administered 7 days ± 1 day after the prior infusion.

6.2.2 Potassium Supplementation

Serum electrolytes (including potassium) were checked prior to each tarloxotinib infusion. Subjects with a pre-infusion serum potassium of < 3.5 mEq/L received potassium replacement

per institutional policy (IV and/or oral [PO]) and have the scheduled tarloxotinib infusion delayed at least 24 hours and potassium levels rechecked within 1 hour prior to the rescheduled infusion. All subjects with a pre-infusion serum potassium levels ≥ 3.5 mEq/L and ≤ 5.0 mEq/L were supplemented daily with 40 mEq/L of potassium replacement per institutional policy (IV and/or PO).

6.2.3 Premedication

All subjects may have received steroid or anti-emetics premedication prior to tarloxotinib infusions. The premedication regimen was determined by the Investigator and may be adjusted at subsequent infusions based on the signs and symptoms observed during or after prior infusions.

6.3 Assessments

Table 2 shows the schedule of events for the study.

6.3.1 Efficacy Assessments

Tumor assessment and imaging was performed according to institutional practice and included computerized tomography (CT) or magnetic resonance imaging (MRI) of the chest and abdomen, brain scan, and bone scan at baseline. The baseline radiographic tumor assessment was required within 28 days prior to the first dose of tarloxotinib, at the Screening assessment. Brain and bone scans did not need to be repeated for subjects with no brain or bone metastases at baseline. Recently completed negative positron emissions tomography (PET) scans could be substituted for baseline bone scans. Subsequent radiographic tumor assessments were every 8 weeks (± 5 days) with respect to Cycle 1 Day 1 (e.g., Cycle 3 Day 1, Cycle 5 Day 1, etc.), until unequivocal PD was documented. The same imaging modality used for baseline imaging (i.e., CT or MRI) was used for subsequent tumor assessments in each subject. In accordance with RECIST v1.1, response (partial response [PR] and complete response [CR]) was confirmed by a second tumor assessment at least 4 weeks after the initial observed response. The scheduling of subsequent tumor assessments may have been adjusted based on the date of the most recent imaging.

6.3.2 Safety Assessments

The objective of the safety assessments was to evaluate the safety and tolerability of tarloxotinib in this population, including to determine whether there is an association between plasma exposure to tarloxotinib and effects on cardiac repolarization. Safety was assessed by repeated clinical evaluations including adverse events (AEs), suspected adverse reactions, unexpected events, serious AEs (SAEs), serious unexpected suspected adverse reactions, vital signs, physical examination, ECGs, clinical laboratory tests (serum chemistry, hematology, and urinalysis).

6.3.2.1 Adverse Events

Investigators collected information related to AEs throughout this clinical trial. All AEs occurring in all subjects were collected following exposure to study treatment (treatment emergent) until approximately 30 days after the last study treatment.

6.3.2.2 Vital Signs

Vital signs were obtained at each visit and prior to and following the start of each tarloxotinib infusion. Vital signs measured include: blood pressure (systolic and diastolic; mmHg); heart rate (beats per minute); body temperature (°C); respiration rate (breaths per minute); and weight (kg).

6.3.2.3 Physical Examinations

Complete physical examinations, including a review of all body systems, was performed at the Screening, Day 1 of all cycles, and the end of treatment (EOT) visits as shown in Table 2. Clinically significant findings observed during physical examination were reported as medical history (pre-treatment) or AEs (post-treatment).

6.3.2.4 Electrocardiograms

All 12-lead ECG tracings were performed once at the following visits: Screening, EOT, and Safety Follow-up. During Cycle 1, ECGs were performed at five time points (preinfusion, end of infusion [EOI], 1 hour after EOI, 2 hours after EOI, 3 hours after EOI, 4 hours after EOI), and hourly thereafter as needed. After Cycle 1, all treatment visits have ECGs performed at a minimum of three time points (preinfusion, 2 hours after EOI, 4 hours after EOI) and hourly thereafter as needed, as shown in Table 2.

6.3.3 Pharmacokinetic Measurements

Blood samples for tarloxotinib and tarloxotinib-E plasma concentrations were collected prior to and following tarloxotinib infusion on Cycle 1 Day 1 and Cycle 2 Day 1. Serum potassium samples were also collected after the infusion. All blood samples may be collected within the 5 or 10 minutes (see Table 2) prior to or following the protocol-specified time point.

Plasma samples were collected for evaluation of the pharmacokinetics of tarloxotinib and tarloxotinib-E in tumor tissue. Plasma sample were collected at approximately at pre-infusion, EOI, 3 hours after EOI, and 7 hours after EOT (Cycle 1 Day 1 only) for measurement of tarloxotinib and tarloxotinib-E concentrations at each Cycle 1 Day 1 and Cycle 2 Day 1 visits as indicated in Table 2. An optional tumor biopsy may have been conducted at Cycle 1 Day 15.

6.3.4 Tumor Tissue

All subjects had tumor tissue collected at baseline. Tumor samples obtained during screening may have also been used to determine levels of the reductase, six transmembrane epithelial antigen of the prostate, family member 4 (STEAP4). In addition to the above-mentioned tumor sample, an optional tumor tissue sample for measurement of the active metabolite (tarloxotinib-E) and tarloxotinib may have been collected from consenting subjects on Cycle 1 Day 15 after infusion along with a blood sample for PK. If the biopsy (and associated PK sample) was not able to be performed on the Cycle 1 Day 15 visit, it should have been collected within the 24 hours after the tarloxotinib infusion or after another infusion day.

6.3.5 Biomarker Analysis

Blood samples were collected for biomarker assessment (e.g., circulating tumor deoxyribonucleic acid [ctDNA]) at the Cycle 1 Day 1, Cycle 2 Day 2, and End of Treatment visits. Biomarker assessment may include ctDNA mutation analysis and evaluation of the concordance of EGFR and HER2 mutation identification between blood and tumor tissue.

Table 2 Study RAIN-701 Protocol Schedule Events (Protocol [Amendment 3] 24 October 2020)

Schedule of Events	SCR	Cycle 1 (Day)				Cycle 2 (Day)				Cycles 3+ (Day)				OBX	EOT[1]	FUP
		1	8	15	22	1	8	15	22	1	8	15	22			
Informed Consent	X															
Eligibility	X															
Medical/Disease History/ Smoking History	X															
Demographics	X															
Physical Examination	X	X				X				X					X	X
ECOG	X	X														
Weight	X	X				X				X					X	X
Vital Signs	X														X	X
Pre-infusion		X	X	X	X	X	X	X	X	X	X	X	X			
EOI		X	X	X	X	X	X	X	X	X	X	X	X			
30, 60, and 90 min after EOI[2]		X	X	X	X	X	X	X	X	X	X	X	X			
Electrocardiogram (12-lead)[3]	X														X	X
Pre-infusion		X	X	X	X	X	X	X	X	X	X	X	X			
EOI		X	X	X	X	X										
1 h after EOI[2]		X	X	X	X	X										
2 h after EOI[2]		X	X	X	X	X	X	X	X	X	X	X	X			
3 h after EOI[2]		X	X	X	X	X										
4 h after EOI[2]		X	X	X	X	X	X	X	X	X	X	X	X			
hourly thereafter as needed[2]		X	X	X	X	X	X	X	X	X	X	X	X			
Hematology Panel	X	X				X				X					X	X
Serum Chemistry Panel	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X

[1] Day 1 of Cycles 2+ and EOT Visit are Day 28 of the prior cycle
[2] For subjects with Grade 3 QTcF prolongation (≥ 501 msec or 60 msec increase compared to pre-infusion), repeat ECG every 15 to 30 minutes until resolved to Grade 2 (481 to 500 msec) or lower (≤ 499 msec) and then obtain ECGs every hour. If QTcF prolongation is ≥ Grade 3, an ECG may need to be repeated more frequently during a subject's visit as indicated in Table 6 , depending on the degree of the prolongation and per institutional standards.
[3] For subjects with ≥ Grade 3 (≥ 500 msec) QTcF prolongation with current or prior infusion

Schedule of Events	SCR	Cycle 1 (Day)				Cycle 2 (Day)				Cycles 3+ (Day)				OBX	EOT[1]	FUP
		1	8	15	22	1	8	15	22	1	8	15	22			
Serum Potassium																
EOI		X				X										
3 h after EOI[2]		X				X										
Urinalysis	X	X	X	X	X	X				X						X
Pregnancy Test[4]	X	X				X				X					X	
PK Samples																
Pre-infusion[6]		X				X										
EOI[6]		X				X										
3 h after EOI[6]		X				X										
7 h after EOI[6]		X[7]														
at optional tumor biopsy														X[5]		
Biomarker Sample		X				X								X[5]	X	
Potassium Supplementation[8]		X	X	X	X	X	X	X	X	X	X	X	X			
Tarloxotinib Infusion		X	X	X	X	X	X	X	X	X	X	X	X			
Tumor Tissue	X															
Optional Tumor Biopsy				X5										X[5]	X[9]	
Tumor Assessment	X	← Every 8 weeks (± 5 days) from Cycle 1 Day 1→														
Concomitant Medications	X	← Every Visit →												X	X	
Adverse Events Assessment		← Every Visit →												X	X	X

Abbreviations: CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; EOI = end of infusion; EOT = End-of-Treatment Visit; FUP = Follow-up Visit; MRI = magnetic resonance imaging; OBX = optional biopsy; PET = positron emissions tomography; PK = pharmacokinetic; QTcF = corrected QT interval as calculated according to Fridericia's formula; SCR = Screening Period

[4] Serum pregnancy at baseline, then urine dipstick, for women of childbearing potential.
[5] Collect blood (plasma samples for PK and biomarker including ctDNA) at time of biopsy
[6] Can be made ±5 minutes of scheduled event.
[7] In a subset of subjects.
[8] If applicable, see Section 6.2.2.
[9] Collect blood (plasma sample for biomarker) at time of biopsy

7 SAMPLE SIZE AND POWER

The primary objective of this study is to determine if tarloxotinib provides a clinically significant tumor response to subjects in each cohort, investigated by assessing if the true ORR is at least above some desirable target level following therapy with tarloxotinib.

According to the protocol, a Simon's 2-stage minimax design (Simon 1989) was used for all cohorts. The null hypothesis that the true response rate is 15% was tested against a one-sided alternative. In the first stage, 21 subjects were accrued. If there were 3 or fewer responses among these 21 subjects, the cohort was stopped for futility. Otherwise, 22 additional subjects may be accrued for a total of 43 subjects in each cohort. The null hypothesis will be rejected if 11 or more responses are observed in 43 subjects. This design yields a type I error rate of 0.0454 and power of 0.8014 when the true response rate is 31%. The probability of early termination at the end of the first stage is 0.61 if the true response rate is 15%.

8 ANALYSIS SETS

8.1 Intent-To-Treat Analysis Set

The Intent-To-Treat (ITT) Analysis Set will include all enrolled subjects regardless of Treatment Period eligibility or completion. The ITT Analysis Set will be the basis for demographics and baseline characteristics. Since enrolled subjects are subjects who received at least one dose of tarloxotinib, the ITT Analysis Set is functionally the same as the Primary Analysis Set.

8.2 Primary Analysis Set

The Primary Analysis Set (PAS), referred to as the Safety Population in the protocol, is defined as all subjects who subjects who received at least 1 dose of tarloxotinib. The Primary Analysis Set will be the analysis population for the safety and efficacy analyses.

9 GENERAL CONSIDERATIONS

9.1 Presentation of Summary Statistics

For most summary statistics, data will be analyzed and displayed in tabular format. Continuous and categorical data will be summarized by cohort and overall.

Continuous variables will be summarized using a 6-point descriptive summary (n, mean, standard deviation [SD], median, minimum, and maximum) unless otherwise specified. The same number of decimal places as in the observed value will be presented when reporting minimum and maximum; 1 additional decimal place than in the observed value will be presented when reporting mean, median, 95% confidence interval (CI); 2 additional decimal places than in the observed value will be presented when reporting stable disease (SD).

All categorical/qualitative data will be presented using the frequency of events and percentages. All percentages will be presented to 1 decimal place, unless otherwise specified. Percentages equal to 100 will be presented as 100% and percentages will not be presented for zero frequencies. For summaries of AEs and CMs, the percentages will be based on the number of subjects who received study drug.

The statistical test for efficacy endpoints will not be performed.

Results of statistical analyses will be reported using summary tables, listings, and figures (TLFs). The ICH of Technical Requirements for Pharmaceuticals for Human Use numbering convention will be used for all TLFs.

All analyses and summaries will be produced using SAS® version 9.4 or higher.

9.2 Definitions and Derived Variables

9.2.1 Screened and Enrolled Subjects

9.2.1.1 Screened Subjects

Subjects who signed an informed consent form are considered Screened Subjects

9.2.1.2 Enrolled Subjects

Subjects who received at least one dose of tarloxotinib, are considered Enrolled Subjects.

9.2.2 Study Day

Study Day, which follows the CDISC Study Data Tabulation Model standard, is defined as (Assessment date - date of first study drug dosing + 1 day), where the assessment date is on or

after the date of first study drug dosing; (Assessment date - date of first study drug dosing), where the assessment date is before the date of first study drug dosing.

9.2.3 End of Study Treatment Definition

A subject is considered to have completed study treatment if the subject has completed the End of Treatment Visit.

9.2.4 End of Study Definition

A subject is considered to have completed the study if the subject has completed final safety follow-up visit. The end of the study is defined as the date of the last follow up visit of the last subject in the study.

9.2.5 Date Last Known Alive

If a subject died, the date last known alive is the subject's date of death. Otherwise, the date last known alive is the date of last contact with the subject in the study (e.g., the most recent date of any in-clinic visit, date of telephone contact, date of withdrawal of consent, date of study completion date, etc.).

9.2.6 Age

Age (years) will be calculated as the number of years between date of birth and date of the earliest informed consent, rounded down to the largest to a whole number less than or equal to the age at measurement.

9.2.7 Body Mass Index

Body mass index (kg/m^2) is derived as weight (kg) / [height (m) × height (m)].

9.2.8 Baseline Values

Baseline values are defined as the last, non-missing assessment prior to the first dose of study drug.

9.2.9 Sum of Target Lesions

The sum of target lesions is defined as the sum of the longest diameters for non-nodal lesions and the short axis for lymph nodes.

9.2.10 Evaluable Subjects

A subject is classified as response evaluable if they have at least one response assessment or if they discontinue from treatment due to death prior to obtaining at least one response assessment. Subjects discontinuing treatment for disease progression must have a disease assessment performed documenting the progression

9.2.10.1 Responder

All enrolled subjects who receive study treatment, have a baseline tumor assessment with documentation of measurable disease, have at least 1 on-study tumor assessment, whether or not this occurs at the specified imaging interval, will be considered evaluable for response. Subjects will be considered responders if they have a confirmed objective response of CR or PR according to RECIST v1.1 recorded from baseline until disease progression or death due to any cause.

9.2.11 RECIST Response Assessment

Table 3 Response Evaluation Criteria in Solid Tumours Guidelines

Response assessment	RECIST guideline, version 1.1
Target lesions	
Complete Response	Disappearance of all target lesions and reduction in the short axis measurement of all pathologic lymph nodes to ≤10 mm
Partial Response	≥30% decrease in the sum of the longest diameter of the target lesions compared with baseline
Progressive Disease	≥20% increase of at least 5 mm in the sum of the longest diameter of the target lesions compared with the smallest sum of the longest diameter recorded **OR** The appearance of new lesions, including those detected by fludeoxyglucose PET
Stable Disease	Neither partial response nor progressive disease
Non-target lesions	
Complete Response	Disappearance of all non-target lesions and normalization of tumor marker levels
Incomplete Response; Stable Disease	Persistence of 1 or more non-target lesions and/or the maintenance of tumor marker levels above normal limits
Progressive Disease	The appearance of 1 or more new lesions or unequivocal progression If subject has measurable disease, an increase in the overall level or substantial worsening in non-target lesions, such that tumor burden has increased, even if there is stable disease or partial response in target lesions

	If no measurable disease, an increase in the overall tumor burden comparable in magnitude with the increase that would be required to declare progressive disease in measurable disease (eg, an increase in pleural effusions from trace to large, or an increase in lymphangitic disease from localized to widespread)

9.2.11.1 Overall Response Rate

The overall response rate in each cohort will be estimated as the number of subjects with a confirmed objective response (CR or PR) divided by the number of enrolled subjects (defined in Section 9.2.10) in each respective cohort.

9.2.11.2 Best Overall Response Rate

Best overall response rate is calculated the same as the ORR (Section 9.2.11.1), but subjects are summarized at their best response level. Best to worst response is as follows: CR, PR, SD, and then PD.

9.2.12 Duration of Response

DOR as measured from the date of first objective response (CR or PR) to date of disease progression or death is documented. DOR data will be censored according to Table 4 for subjects who are alive with no objective documentation of (radiographic) disease progression by the data cut-date.

Table 4 Censoring Rules for Progression-Free Survival

Situation	Date of Censoring
No baseline radiologic assessment	Date of first study drug dose
No post-baseline radiologic assessment (and no death prior to first scheduled radiologic assessment)	Date of first study drug dose.
No progression or death on study	Date of last radiologic assessment
Documented progression or death after 2 or more consecutive missing radiologic assessments	Date of last radiologic assessment
New anticancer therapy started prior to progression	Date of last radiologic assessment prior to new anticancer therapy

9.2.13 Disease Control Rate

Disease control rate is defined as the number of subjects who have CR, PR, or SD for at least 2 cycles (8 weeks) according to the RECIST v1.1 recorded in the period between first study drug dose and disease progression or death to any cause. The DCR on each cohort will be estimated

by dividing the number of subjects with CR, PR, or SD for at least 2 cycles (8 weeks) by the number of subjects enrolled in each cohort.

9.2.14 Progression-Free Survival

Progression-free survival is defined as the time from the date of first tarloxotinib dose to the date of the first objective documentation of radiographic disease progression or death due to any cause, whichever occurs first. PFS data will be censored according to Table 4 for subjects who are alive with no objective documentation of (radiographic) disease progression by the data cut-date.

9.2.15 Overall Survival

Overall survival as measured from the date of first tarloxotinib dose to the date of death by any cause. In the absence of confirmation of death, survival time will be censored to last date the subject is known to be alive.

9.2.16 Study Drug Exposure Variables

9.2.16.1 Total Tarloxotinib Dose (mg) Taken

Total tarloxotinib dosage (mg) is defined as the cumulative dosage of tarloxotinib actually received over the Treatment Period, calculated as follows:

$$Total\ Tarloxotinib\ Dose = \sum_{i=1}^{k} (Actual\ Tarloxotinib\ Dose)_i$$

where

Σ represents the summation operator and the value in parentheses is summed over the sequence $i = 1$ to k, where k = number of tarloxotinib infusions subject received.

9.2.16.2 Actual Number of Infusions Administered

The number of infusions a subject received. Interrupted infusions also count as one infusion.

9.2.16.3 Actual Number of Cycles Administered

The number of cycles a subject initiated. This includes receiving infusions at each scheduled visit of the cycle (Day 1, Day 8, Day 15, and Day 22).

9.2.16.4 Actual Dose Intensity

Actual dose intensity (mg/day) is calculated as total cumulative dose received divided by actual number of infusions administered.

9.2.16.5 Treatment Duration

Treatment duration (days) is defined as (Last Dose Date – First Dose Date + 1 day). Treatment duration indexed by the 28-day cycles is defined as ([Last Dose Date – First Dose Date + 1 day]/28 days), rounded to one decimal place.

9.2.17 Prior, Concomitant and Post treatment Medications

All medication verbatim terms reported on the electronic case report form (eCRFs) will be mapped according to the World Health Organization (WHO) Drug Dictionary (WHO DD March 2020 B3). The medications will be mapped to Anatomical/Therapeutic/Chemical (ATC) class and preferred names.

A prior medication is considered to be any medication that is taken within a year prior to the first study drug dosing.

A concomitant medication is considered to be any medication that is continued from Screening and continued after the first study drug dosing (i.e., a prior medication can also be a CM if it continued after the first dose of study drug) or any medication with start dates or stop dates within the Treatment Period. Specifically, CMs are medications: that are continued from Screening and continued after the first study drug dosing, or with start dates or stop dates within the first dose date through last dose date + 24 hours, missing CM end date, or ongoing) with the study drug administration.

Post medications is considered to be any medication taken after the last study drug dose date + 24 hours, missing CM end date, or ongoing.

9.2.18 Adverse Events

All AE verbatim terms reported on the eCRFs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA® version 22.0). AE severity will be graded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE

2017) version 5. MedDRA will be used to map the AE verbatim to lowest level term, preferred term, and system organ class for summary purposes.

Table 5 Severity Grading Guideline for Adverse Events

Grade	Description
1	Mild; Asymptomatic or mild symptoms; Clinical or diagnostic observations only; Intervention not indicated
2	Moderate; Minimal, local or noninvasive intervention indicated; Limiting age-appropriate instrumental activities of daily living*
3	Severe or medically significant but not immediately life-threatening; Hospitalization or prolongation of hospitalization indicated; Disabling; Limiting self-care activities of daily living†
4	Life-threatening consequences; Urgent intervention indicated
5	Death related to adverse event

9.2.18.1 Treatment-Emergent Adverse Events

Treatment-emergent adverse events are defined as any AEs, regardless of relationship to study drug, that have an onset or worsening in severity on or after the first dose of study drug until 30 days after the final dose of study drug (safety follow-up visit).

Related TEAEs are those reported by investigators as related to the study drug.

9.2.18.2 Serious Adverse Events

Serious AEs are defined according to the NCI CTCAE v5.0, as described in Protocol Section 8.2.2 Adverse Event Severity.

9.2.18.3 Severe Adverse Events

Severe AEs are defined as events with a severity of Grade 3 or higher.

* Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
† Self-care activities of daily living refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden

9.2.18.4 Serious Unexpected Suspected Adverse Reaction

A serious AE deemed related to the study drug (adverse reaction) is considered "unexpected" if it is not listed in the Investigator's Brochure (i.e., ECG QT prolonged, Hypertension, Rash [rash, infusion site rash and rash erythematous]) or is not listed at the specificity or severity that has been observed.

9.3 Analysis Windows

Clinical visits may occur outside protocol-specified windows. Therefore, instead of relying solely on visit labels in the clinical database, analysis visits and their windows are defined using Study Day (See Section 9.2.2). For the purposes of data analysis and summary, assessments and/or measurements will be flagged based on the collection date/time that is closest to the protocol-scheduled time point (or target Study Day). Analysis visit windows are presented in by type of assessments and/or measurements.

Table 6 Visit Analysis Windows (Clinic visits only)

Protocol Specified Visit	Target Study Day	Start (days)	Stop (days)
Screening	**-114**	low	-1
Cycle 1 Day 1	**1**	1	4
Cycle 1 Day 8	**8**	5	11
Cycle 1 Day 15	**15**	12	18
Cycle 1 Day 22	**22**	19	25
Cycle 2 Day 1	**29**	26	32
Cycle 2 Day 8	**36**	33	39
Cycle 2 Day 15	**43**	40	46
Cycle 2 Day 22	**50**	47	53
Cycle 3 Day 1	**57**	54	60
Cycle 3 Day 8	**64**	61	67
Cycle 3 Day 15	**71**	68	74
Cycle 3 Day 22	**78**	75	81
Cycle 4 Day 1	**85**	82	88
Cycle 4 Day 8	**92**	89	95
Cycle 4 Day 15	**99**	96	102
Cycle 4 Day 22	**106**	103	109
Cycle 5 Day 1	**113**	110	116
Cycle 5 Day 8	**120**	117	123
Cycle 5 Day 15	**127**	124	130
Cycle 5 Day 22	**134**	131	137

Protocol Specified Visit	Target Study Day	Start (days)	Stop (days)
Cycle 6 Day 1	**141**	138	144
Cycle 6 Day 8	**148**	145	151
Cycle 6 Day 15	**155**	152	158
Cycle 6 Day 22	**162**	159	165
Cycle 7 Day 1	**169**	166	172
Cycle 7 Day 8	**176**	173	179
Cycle 7 Day 15	**183**	180	186
Cycle 7 Day 22	**190**	187	193
Cycle 8 Day 1	**197**	194	200
Cycle 8 Day 8	**204**	201	207
Cycle 8 Day 15	**211**	208	214
Cycle 8 Day 22	**218**	215	221
Cycle 9 Day 1	**225**	222	228
Cycle 9 Day 8	**232**	229	235
Cycle 9 Day 15	**239**	236	242
Cycle 9 Day 22	**246**	243	249
Cycle 10 Day 1	**253**	250	256
Cycle 10 Day 8	**260**	257	263
Cycle 10 Day 15	**267**	264	270
Cycle 10 Day 22	**274**	271	277
End of Treatment	**Treatment End Date**	Study Day <= (ADSL.TRTEDT - ADSL.TRTSDT + 1)	
Follow-up	**Treatment End Date + 30 Days (± 7 days)**	Study Day > (ADSL.TRTEDT - ADSL.TRTSDT + 1)	high

10 STATISTICAL AND ANALYSIS ISSUES

10.1 Adjustments for Covariates

No adjustments for covariates will be performed in the study.

10.2 Handling Dropouts or Missing Data

Missing data will not be imputed. Every effort will be made by the Sponsor to ensure completeness of data collection.

10.2.1 Handling of Laboratory Data

A retest value will be used if the first test is invalidated, e.g., specimen hemolyzed.

10.2.2 Handling of Safety Data

10.2.2.1 Adverse Events

If the time of onset (before or after intake of study drug) cannot be determined whether an AE is treatment-emergent because of a partial onset date, the event will be counted as a TEAE.

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

- Day and month are missing and the year is equal to or after the year of the first date of study drug dosing;
- Month is missing and the year is after the year of the first date of study drug dosing;
- Day is missing and the year is equal to the year of the first date of study drug dosing and the month is equal to or after the month of the first date of study drug dosing; or
- Year is missing.

If severity or relationship of an AE to study drug is not recorded, the severity or relationship will be imputed as “severe” or relationship as “possibly related,” for analysis purposes.

10.2.2.2 Concomitant Medications

If start date of a medication is missing, the medication will be considered to have started prior to the study. Such a medication may also be considered concomitant, depending on the stop date or lack thereof. If the stop date of a concomitant medication is missing, then the medication will be treated as ongoing. If the start date of a medication is missing, the stop date will be used to determine whether or not it is concomitant. Medications with other incomplete start dates or end dates will be imputed as follows:

Incomplete medication start date/time:
- If only have a YEAR, impute as Jan. 1.
- Else if only have YEAR and MONTH, impute as Day 1 of month.
- Otherwise missing, no imputation.

Incomplete medication end date/time:
- If only have a YEAR, impute as December 31.
- Else if only have YEAR and MONTH, then impute to last day of the month.
- Otherwise missing, no imputation.

10.3 Multicenter Considerations

This trial will be conducted at 14 study centers in the United States, Canada, and other regions. Data from all study centers will be pooled for efficacy and safety analyses. Because the number of subjects at each center is likely to be small, no analyses will be performed by center. Subjects from all centers will be pooled for all analyses.

10.4 Multiple Comparisons, Multiplicity

Efficacy variables will be assessed without adjustment for multiple comparisons.

10.5 Active-Control Studies

There is no comparator in this study as all subjects are treated with tarloxotinib.

10.6 Examination of Subgroups

Efficacy variables will be assessed without examination of subgroups.

11 STUDY SUBJECTS

11.1 Subject Enrollment and Disposition

11.1.1 Enrolled Subjects

An accounting of the study subjects will be tabulated. Subjects not completing the study will be listed along with the reason for their premature discontinuation. Reasons for premature discontinuation will be summarized.

Enrolled (Section 9.2.1) subjects will be summarized by cohort and overall.

Treatment Periods

- Number of subjects enrolled (ITT)
  - Number (%) of subjects who discontinued from the study treatment
    - The primary reason for withdrawal from the study treatment
  - Number (%) of subjects who completed the study
  - Number (%) of subjects who discontinued from the study
    - The primary reason for withdrawal from the study

The percentages will be based on the total subjects who are enrolled (ITT).

A listing of disposition will be provided for all enrolled subjects.

11.2 Protocol Deviations

Protocol deviations will be neither listed nor summarized because RAIN-701 was discontinued and this SAP will support an abbreviated clinical study report, which does not include protocol deviations per FDA guidance (Food and Drug Administration, 1999).

11.3 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized and listed for all treated subjects (ITT). Demographic characteristics will include age, sex, race, and ethnicity. A subject listing of demographics will be provided.

11.3.1 Key Baseline Demographics

The following parameters from each of the individual baseline and historical summaries will be summarized in a single summary:

- Age
- Age group, n (%)
- Sex, n (%)
- Race, n (%)
- Ethnicity, n (%)
- Smoking status, n (%)
- Baseline weight (kg)
- ECOG performance status, n(%)
- Mutation status, n (%)
- Stage at time of disease, n (%)
- Stage at time of study entry, n (%)

11.4 Medical History

Medical history and current medical conditions will be mapped to preferred terms and system organ classes using the MedDRA® Dictionary (version 23.0) Medical history will be summarized by system organ class (SOC) and preferred term (PT) by cohort and overall for ITT subjects. A subject listing of general medical history will include start date/end date, verbatim medical history term, SOC, PT, and ongoing status (Yes, No). Additional subject listings of prior radiation therapy and prior surgeries will contain the start date and end date (if available) and

type of procedure. The subject listing of prior systemic therapies will include at a start date, end date, medication, reason the therapy ended, and best overall response.

12 STUDY DRUG AND OTHER MEDICATIONS

12.1 Exposure to Study Drug and Study Treatment Compliance

Summaries of study drug exposure and compliance will be summarized overall and by cohort. The source for study drug dosing and compliance is drug exposure.

The summaries will include total number of cycles initiated, the median (range) of cycles administered, and dose intensity (see definitions in Section 9.2.11) by cohort and overall. The denominators for percentages will be the number of subjects who received the study treatment.

12.2 Prior and Concomitant Medications

Prior and concomitant medications (see definition in Section 9.2.10), will be summarized using WHO DD ATC class and preferred name. The summary results will be presented by cohort. Prior medications will be summarized by cohort. Concomitant medications will be summarized by cohort and overall.

These summaries will present the number and percentage of subjects using each medication. Subjects may have more than one medication within an ATC class and preferred name. At each summary level subjects are counted once if they reported one or more medications at that level. Each summary will be ordered by descending frequency of incidence of ATC class and preferred name within each ATC class.

All medications will be provided in a subject listing with flags indicating study drug dose level. The variables include, but not limited to: Start date/end date/ongoing, medication name, ATC class and preferred name, indication, dose, unit, form, frequency, and route.

13 EFFICACY ANALYSES

13.1 Primary Analysis

The primary analysis was planned after all subjects stop tarloxotinib treatment until documented disease progression or unacceptable toxicity. The primary analysis will not be performed because RAIN-701 was discontinued and this SAP supports an abbreviated clinical study report. Additionally, efficacy analyses are unlikely to be significant because the sample size is small and the analyses will be underpowered. In place of formal primary analyses, selected efficacy endpoints will be summarized descriptively.

13.2 Primary Efficacy

The primary objective of this study is to evaluate the ORR of tarloxotinib as defined as a CR or PR according to RECIST v1.1 recorded from baseline until disease progression or death due to any cause.

The numbers and percentages of subjects meeting each response will be summarized, and the ORR will be summarized by cohort along with the corresponding 2-sided 95% CI calculated using the binomial exact method. All treatment responses and all tumor assessments will be listed.

The maximum percent reduction from baseline in the sum of target lesions will be displayed as a waterfall plot. The waterfall plot will have a y-axis that will be the maximum percent change from baseline in the sum of target lesions, and the x-axis will be each cohort and overall.

The best overall response (Section 13.3) will be reported similarly.

13.3 Secondary Efficacy

The secondary efficacy objective is to evaluate further measures of antitumor activity of tarloxotinib including:

- Best overall response (Reporting as described in Section 13.2),
- Duration of response (Section 13.3.1),
- Disease control rate (Section 13.2),

- Progression-free survival (Section 13.3.2), and
- Overall survival (Section 13.3.2)

The additional secondary objectives of exploratory biomarkers of hypoxia in tumor tissue and plasma exposure to tarloxotinib and effects on cardiac repolarization will not have analyses or descriptive summarization of these endpoints due to the limited data basis.

13.3.1 Duration of Response

DOR will be summarized using descriptive statistics (Section 9.1) for each cohort and overall. The DOR data will be listed for each subject.

13.3.2 Survival Reporting

The PFS and OS will be summarized using the Kaplan-Meier method and displayed graphically by cohort and overall: Median event times and the corresponding 2-sided 95% CI will be provided. The number and % of subjects with disease progression or death will be provided. The number and % of subjects censored as well as reasons for censoring will be provided. A listing of survival data will be provided.

13.4 Exploratory Objectives

The exploratory objectives are:

- To evaluate the concordance of EGFR mutation, HER2 mutation, and NRG1, EGFR, HER2, and HER4 fusion detection between tissue and plasma using ctDNA
- To evaluate exploratory biomarkers of hypoxia in tumor tissue including 6 transmembrane epithelial antigen of the STEAP4 expression and ERBB family and cancer cell signaling pharmacodynamic markers
- To evaluate the pharmacokinetics of tarloxotinib and tarloxotinib-E in tumor tissue

Analysis and descriptive summary of these exploratory endpoints are outside the scope of this SAP.

13.5 Subgroup Analyses

No examination of subgroups is planned.

14 SAFETY ANALYSES

One of the study objectives is to assess the safety of tarloxotinib. Safety will be assessed by repeated clinical evaluations including adverse events (AEs), serious AEs (SAEs), suspected serious unexpected suspected adverse reactions, vital signs, physical examination, electrocardiograms (ECGs), clinical laboratory tests (serum chemistry, hematology, and urinalysis). All analyses of the safety data will be performed using the primary analysis set. All descriptive statistics (described in Section 9.1) will be presented by cohort and overall.

14.1 Adverse Events

Safety will be assessed by repeated clinical evaluations including adverse events (AEs), serious AEs (SAEs), serious unexpected suspected adverse reactions (SUSARs), and deaths.

Safety data will be summarized descriptively. AEs will be summarized by severity, seriousness, and relationship to study drug. All AEs including the AE verbatim term and the associated AE MedDRA preferred term will be provided in the subject data listings. Incidence of treatment-emergent AEs will be summarized descriptively by cohort and total.

TEAEs are defined in Section 9.2.18.1. All reported AEs (including non-TEAEs) will be listed. Separate listings will be provided for suspected adverse reactions, unexpected events, SAEs, and serious unexpected suspected adverse reactions. All TEAE summary tables will present the number and percentages of subjects reporting TEAEs, unless otherwise specified. A summaries of TEAEs by severity, seriousness, and relation to study drug will be tabulated.

14.1.1 Overall Summary of TEAEs

Overall summary of TEAEs will be presented by cohort and overall. Subjects will be counted only once at the highest severity when summarizing TEAE by severity. The overall summary will include the following:

- Number (%) of subjects with any TEAEs
- Number (%) of subjects with any TEAEs by severity
- Number (%) of subjects with any serious TEAEs
- Number (%) of subjects with any related TEAEs
- Number (%) of subjects with any serious unexpected suspected adverse reactions

- Number (%) of subjects with any TEAEs leading to study drug discontinuation
- Number (%) of subjects with any AEs leading to death

14.1.2 Summary of TEAEs by System Organ Class and Preferred Term

AEs will be summarized by MedDRA SOC and PT. Subjects can experience more than one AE per SOC and PT. At each level of subject summarization (SOC or PT or severity), subjects will be counted once if they reported at least one AE at that level (SOC or PT or severity). Each summary will be ordered by SOC alphabetically and by PT in descending order of the total incidence within each SOC. Summary tables will be created for each of the following types of AEs:

- TEAEs
- Severe (≥ Grade 3) TEAEs
- Related TEAEs
- TEAEs leading to study drug discontinuation
- Serious TEAEs
- Serious unexpected suspected adverse reactions
- TEAEs leading to death

14.1.3 Summary of TEAEs by Preferred Term

AEs will be summarized by MedDRA preferred term (PT). Subjects can experience more than one AE per PT. At each preferred term, subjects will be counted once if they reported at least one AE at that level (PT). Each summary will be ordered by PT in descending order of the incidence. Summary tables will be created for each of the following types of AEs:

- TEAEs
- Severe (≥ Grade 3) TEAEs
- Related TEAEs
- TEAEs leading to study drug discontinuation
- Serious TEAEs
- Serious unexpected suspected adverse reactions
- TEAEs leading to death

14.2 Clinical Laboratory Evaluation

Results for clinical laboratory parameters (serum chemistry and hematology), vital signs, ECGs, and physical examinations will be summarized by cohort and combined and by study visits. Descriptive summary statistics in observed values as well as changes from baseline will be

presented. In addition, thresholds of marked laboratory abnormalities based on NCI CTCAE v5.0 will be summarized by worst grade shift from baseline (see Appendix B).

Table 7 shows clinical laboratory assessments (hematology, chemistry, and urinalysis) that were performed performed. Chemistry and hematology laboratory parameters will be summarized by cohort and scheduled visit. Urinalysis assessments will be listed but not summarized due to their qualitative nature.

Table 7 Clinical Laboratory Parameters

Chemistry		Hematology	Urinalysis
Sodium	Creatinine	Hematocrit	Specific gravity
Potassium	Total Bilirubin	Hemoglobin	Protein
Chloride	AST/SGOT	WBC count	Glucose
Bicarbonate	ALT/SGPT	Neutrophils	Ketones
Calcium	~~ALP~~‡	Lymphocytes	Urobilinogen
Magnesium	Albumin	Monocytes	Occult blood
Phosphorous	Total protein	Eosinophils	~~Microscopic sediment evaluation~~‡
Glucose		Basophils	
Blood urea nitrogen		Platelet count	WOCBP only: β-HCG§

ALT = alanine aminotransferase; ALP = alkaline phosphatase; AST = aspartate aminotransferase; HCG = β-human chorionic gonadotropin pregnancy; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; WBC = white blood count; WOCBP = women of child-bearing potential

Numeric results will be summarized using (6-point) descriptive statistics at baseline and at each scheduled post-baseline time point, unless otherwise specified. Changes from baseline will also be summarized by scheduled time point, where available. Selected laboratory results will be listed with CTCAE reference ranges.

14.3 Vital Signs

Descriptive statistics for pulse rate, respiratory rate, temperature, weight, and blood pressure (systolic and diastolic) including baseline values and change from baseline values, will be summarized by cohort and scheduled time point. All vital signs parameters will be listed.

‡ Alkaline phosphatase and microscopic sediment evaluation will neither be listed nor summarized due to lack of data
§ β-HCG pregnancy test may be collected as a serum, urine, or urine dipstick assessment

14.4 12-Lead Electrocardiogram

Electrocardiogram (ECG) data, such as clinical interpretation of ECGs, heart rate (HR) values, and interval assessments of QRS duration, PR interval, QT interval, and the Fridericia's corrected value of the interval between the Q and T waves on the ECG tracing (QTcF) will be listed. Descriptive statistics for observed values and change from baseline at each scheduled time point will be presented for these 12-lead ECG interval and HR assessments will be presented as actual values and as changes from the baseline values by 6-point descriptive summary statistics (n, mean, SD, median, minimum, and maximum). The numbers and percentages of subjects who meet categorical analyses such as the following criteria at each scheduled ECG time point will be presented.

- Absolute QTcF interval:
    - QTcF interval < 450
    - QTcF interval 451 to 480 msec
    - QTcF interval 481 to 500 msec
    - QTcF interval ≥ 501 msec
- Change from predose baseline in QTcF interval:
    - ≤ 30 msec
    - 31 to 60 msec
    - 60 msec

The numbers and percentages of subjects meeting each criterion will be summarized for each ECG time point, as well as for each subject overall at any time.

Abnormal ECG findings not present at the pre-dose baseline will be summarized as the number of subjects with each finding at 1 or more ECG times. Descriptive waveform morphology changes will be provided.

15 CHANGES RELATIVE TO THE PROTOCOL-SPECIFIED ANALYSIS

Protocol Section 9.2.3 states "Deviations will be defined prior to database lock. Handling of major deviations in statistical analyses will be defined in the SAP" and further defines a Per-Protocol analysis set excludes subjects with certain, pre-specified deviations. RAIN-701 was terminated and the analysis will support an abbreviated clinical study report, which does not include protocol deviations per FDA guidance for industry, Submission of Abbreviated Reports and Synopses in Support of Marketing Applications. Analysis will be performed on the safety population which includes all subjects who received at least 1 dose of tarloxotinib. Analysis of a Per Protocol (PP) population where subjects with major protocol deviations are removed is not necessary for the aCSR. The abbreviated CSR will provide a comprehensive safety analysis for all subjects receiving at least 1 dose of tarloxotinib. Additionally, the primary efficacy analysis of ORR will include all treated subjects. Efficacy analyses are not interpretable as RAIN-701 was terminated and did not enroll the intended sample size to support statistical analyses.

Protocol Section 7 states, "In accordance with RECIST v1.1, response (PR and CR) must be confirmed by a second tumor assessment at least 8 weeks after the initial observed response." SAP Section 6.3.1 text instead states that the confirmation assessment must be at least 4 weeks after the initial observed response, which is aligned with the true RECIST v1.1 criteria. The efficacy endpoint (Section 9.2.13) still follows the protocol text in defining the disease control for at least 8 weeks (2 cycles).

Protocol Table 12 states "Microscopic sediment evaluation, as clinically indicated" as a urinalysis assessment, but these microscopic sediment urinalysis assessments were not collected. Similarly, Protocol Table 12 lists ALP as a serum chemistry assessment, but it was not collected.

Units and reference ranges of the local laboratory assessments were not collected. The Sponsor has assigned units and lab normal ranges for each parameter (e.g., lower limit of normal, upper limit of normal) based on available information and Harrison's Principles of Internal Medicine (Appendix A).

Adverse events were coded with MedDRA version 22.0 and medical history events were coded with MedDRA version 23.0.

16 References

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17 Appendix A: Local Laboratory Units and Reference Ranges by Site and Parameter

When a reference range is followed by an asterisk, it is sourced from Harrison's Principles of Internal Medicine, 19th edition.

Table 8 Site 101 Units and Reference Ranges by Parameter

SITE NUMBER	PANEL	PARAMETER	SEX	AGE	UNITS	REFERENCE LOW	REFERENCE HIGH
101	Chemistry	Albumin			g/dL	3.5	5
101	Chemistry	ALP			/L	45	117
101	Chemistry	ALT/SGPT			/L	15	41
101	Chemistry	AST/SGOT			/L	3	34
101	Chemistry	Bicarbonate			mmol/L	18	23
101	Chemistry	Blood urea nitrogen	M		mg/dL	9	20
101	Chemistry	Blood urea nitrogen	F		mg/dL	7	17
101	Chemistry	Calcium			mmol/L	1.12	1.32
101	Chemistry	Chloride			mmol/L	98	107
101	Chemistry	Creatinine	M		mg/dL	0.66	1.5
101	Chemistry	Creatinine	F		mg/dL	0.52	1.04
101	Chemistry	Glucose			mg/dL	65	140
101	Chemistry	Magnesium			mg/dL	1.6	2.3
101	Chemistry	Phosphorous			mg/dL	2.5	4.5
101	Chemistry	Potassium			mmol/L	3.5	5.1
101	Chemistry	Sodium			mmol/L	137	145
101	Chemistry	Total Bilirubin			mg/dL	0.2	1.3
101	Chemistry	Total protein			g/dL	6.3	8.2
101	Hematology	Basophils			k/uL	0	0.2
101	Hematology	Eosinophils			k/uL	0	0.7
101	Hematology	Hematocrit	M		%	37.5	49.5
101	Hematology	Hematocrit	F		%	34.5	44
101	Hematology	Hemoglobin	M		g/dL	12.5	16.5
101	Hematology	Hemoglobin	F		g/dL	11	14.5
101	Hematology	Lymphocytes			k/uL	0.6	4.9
101	Hematology	Monocytes			k/uL	0.1	1.3
101	Hematology	Neutrophils			k/uL	1.7	8.1
101	Hematology	Platelet count			k/uL	145	400

SITE NUMBER	PANEL	PARAMETER	SEX	AGE	UNITS	REFERENCE LOW	REFERENCE HIGH
101	Hematology	WBC count			k/uL	4	10.8
101	Urinalysis	Glucose				Normal	
101	Urinalysis	Ketones				Negative	
101	Urinalysis	Occult blood				Negative	
101	Urinalysis	Protein				Negative	
101	Urinalysis	Specific gravity				1.003	1.03
101	Urinalysis	Urobilinogen			mg/dL	< 2.0	

Table 9 Site 102 Units and Reference Ranges by Parameter

SITE NUMBER	PANEL	PARAMETER	SEX	AGE	UNITS	REFERENCE LOW	REFERENCE HIGH
102	Chemistry	Albumin			g/dL	3.5*	5.5*
102	Chemistry	ALP					
102	Chemistry	ALT/SGPT			U/L	7*	41*
102	Chemistry	AST/SGOT			U/L	12*	38*
102	Chemistry	Bicarbonate			meq/L	22*	30*
102	Chemistry	Blood urea nitrogen			mg/dL	7*	20*
102	Chemistry	Calcium			mg/dL	8.7*	10.2*
102	Chemistry	Chloride			meq/L	102*	109*
102	Chemistry	Creatinine	F		mg/dL	0.5*	0.9*
102	Chemistry	Creatinine	M		mg/dL	0.6*	1.2*
102	Chemistry	Glucose			mg/dL	65*	95*
102	Chemistry	Magnesium			mg/dL	1.5*	2.3*
102	Chemistry	Phosphorous			mg/dL	2.7	4.5
102	Chemistry	Potassium			meq/L	3.5*	5*
102	Chemistry	Sodium			meq/L	136*	146*
102	Chemistry	Total Bilirubin			mg/dL	0.1	1.3
102	Chemistry	Total protein			g/dL	6.7*	8.6*
102	Hematology	Basophils			10^9/L	0	0.2
102	Hematology	Eosinophils			10^9/L	0	0.4
102	Hematology	Hematocrit	M		%	39.2	50.2
102	Hematology	Hematocrit	F		%	35.7	46.7
102	Hematology	Hemoglobin	M		g/dL	14.3	18.1
102	Hematology	Hemoglobin	F		g/dL	12.1	16.3
102	Hematology	Lymphocytes			10^9/L	1	4.8
102	Hematology	Monocytes			10^9/L	0.2	0.9

SITE NUMBER	PANEL	PARAMETER	SEX	AGE	UNITS	REFERENCE LOW	REFERENCE HIGH
102	Hematology	Neutrophils			10^9/L	1.8	6.6
102	Hematology	Platelet count			10^9/L	150	400
102	Hematology	WBC count			10^9/L	4	11.1
102	Urinalysis	Glucose				NEGATIVE	
102	Urinalysis	Ketones				NEGATIVE	
102	Urinalysis	Occult blood				NEGATIVE	
102	Urinalysis	Protein				NEGATIVE	
102	Urinalysis	Specific gravity				1.001	1.035
102	Urinalysis	Urobilinogen			mg/dL	< 2.0	

Table 10 Site 103 Units and Reference Ranges by Parameter

SITE NUMBER	PANEL	PARAMETER	SEX	AGE	UNITS	REFERENCE LOW	REFERENCE HIGH
103	Chemistry	Albumin			g/dL	3.4	5
103	Chemistry	ALP			IU/L	38	126
103	Chemistry	ALT/SGPT	M		IU/L	17	63
103	Chemistry	ALT/SGPT	F		IU/L	14	54
103	Chemistry	AST/SGOT			IU/L	15	41
103	Chemistry	Bicarbonate			mmol/L	21	31
103	Chemistry	Blood urea nitrogen			mg/dL	8	26
103	Chemistry	Calcium			mg/dL	8.4	10.2
103	Chemistry	Chloride			mmol/L	98	107
103	Chemistry	Creatinine			mg/dL	0.5	1.4
103	Chemistry	Glucose			mg/dL	65*	95*
103	Chemistry	Magnesium			mg/dL	1.6	2.3
103	Chemistry	Phosphorous			mg/dL	2.5	4.6
103	Chemistry	Potassium			mmol/L	3.5	5
103	Chemistry	Sodium			mmol/L	136	146
103	Chemistry	Total Bilirubin			mg/dL	0.3	1.5
103	Chemistry	Total protein			g/dL	6.3	7.7
103	Hematology	Basophils			10^9/L	0	0.06
103	Hematology	Eosinophils			10^9/L	0	0.4
103	Hematology	Hematocrit	M		%	38	48.8
103	Hematology	Hematocrit	F		%	34.1	43.3
103	Hematology	Hemoglobin	M		g/dL	12.9	16.9
103	Hematology	Hemoglobin	F		g/dL	11.6	14.6

SITE NUMBER	PANEL	PARAMETER	SEX	AGE	UNITS	REFERENCE LOW	REFERENCE HIGH
103	Hematology	Lymphocytes			10^9/L	0.8	3.65
103	Hematology	Monocytes			10^9/L	0.3	0.9
103	Hematology	Neutrophils			× 109/L	1.42*	6.34*
103	Hematology	Platelet count			× 109/L	165*	415*
103	Hematology	WBC count			10^9/L	3.8	10.6
103	Urinalysis	Glucose				Negative	
103	Urinalysis	Ketones				Negative	
103	Urinalysis	Occult blood				Negative	
103	Urinalysis	Protein				Negative	
103	Urinalysis	Specific gravity				1.001	1.035
103	Urinalysis	Urobilinogen				Normal	

Table 11 Site 104 Units and Reference Ranges by Parameter

SITE NUMBER	PANEL	PARAMETER	SEX	AGE	UNITS	REFERENCE LOW	REFERENCE HIGH
104	Chemistry	Albumin	M		g/dL	3.7	5.3
104	Chemistry	Albumin	F		g/dL	4.2	5.5
104	Chemistry	ALP			U/L	34	104
104	Chemistry	ALT/SGPT			U/L	7	52
104	Chemistry	AST/SGOT			U/L	13	39
104	Chemistry	Bicarbonate			mmol/L	21	31
104	Chemistry	Blood urea nitrogen			mg/dL	7	25
104	Chemistry	Calcium			mg/dL	8.6	10.3
104	Chemistry	Chloride			mmol/L	98	107
104	Chemistry	Creatinine	M		mg/dL	0.7	1.3
104	Chemistry	Creatinine	F		mg/dL	0.6	1.2
104	Chemistry	Glucose		low - 50	mg/dL	70	115
104	Chemistry	Glucose		51 - high	mg/dL	85	125
104	Chemistry	Magnesium			mg/dL	1.9	2.7
104	Chemistry	Phosphorous			mg/dL	2.5	5
104	Chemistry	Potassium			mmol/L	3.5	5.1
104	Chemistry	Sodium			mmol/L	136	145
104	Chemistry	Total Bilirubin			mg/dL	0	1.4
104	Chemistry	Total protein			g/dL	6	8.3

SITE NUMBER	PANEL	PARAMETER	SEX	AGE	UNITS	REFERENCE LOW	REFERENCE HIGH
104	Hematology	Basophils			THOUS/MCL	0	0.2
104	Hematology	Eosinophils			THOUS/MCL	0	0.5
104	Hematology	Hematocrit			%	39.5	50
104	Hematology	Hemoglobin			g/dL	13.5	16.9
104	Hematology	Lymphocytes			THOUS/MCL	0.9	3.3
104	Hematology	Monocytes			THOUS/MCL	0	0.8
104	Hematology	Neutrophils			THOUS/MCL	2	8.1
104	Hematology	Platelet count			THOUS/MCL	150	400
104	Hematology	WBC count			THOUS/MCL	4	10.5
104	Urinalysis	Glucose			mg/dL	Negative	
104	Urinalysis	Ketones			mg/dL	Negative	
104	Urinalysis	Occult blood			/HPF	2	
104	Urinalysis	Protein			mg/dL	Negative	
104	Urinalysis	Specific gravity				1.003	1.03
104	Urinalysis	Urobilinogen			mg/dL	< 2	

Table 12 Site 105 Units and Reference Ranges by Parameter

SITE NUMBER	PANEL	PARAMETER	SEX	AGE	UNITS	REFERENCE LOW	REFERENCE HIGH
105	Chemistry	Sodium			mEq/L	135	145
105	Chemistry	Potassium			mEq/L	3.6	5.2
105	Chemistry	Chloride			mEq/L	98	108
105	Chemistry	Bicarbonate			mEq/L	22	32
105	Chemistry	Calcium			mg/dL	8.9	10.2
105	Chemistry	Phosphorous			mg/dL	2.5	4.5
105	Chemistry	Magnesium			mg/dL	1.8	2.4
105	Chemistry	Blood urea nitrogen			mg/dL	8	21
105	Chemistry	Albumin			g/dL	3.5	5.2
105	Chemistry	ALP			U/L		

SITE NUMBER	PANEL	PARAMETER	SEX	AGE	UNITS	REFERENCE LOW	REFERENCE HIGH
105	Chemistry	ALT/SGPT	M	0 -< 50	U/L	10	64
105	Chemistry	ALT/SGPT	M	50 - high	U/L	10	48
105	Chemistry	ALT/SGPT	F		U/L	7	33
105	Chemistry	AST/SGOT			U/L	9	38
105	Chemistry	Creatinine	M		mg/dL	0.51	1.18
105	Chemistry	Creatinine	F		mg/dL	0.38	1.02
105	Chemistry	Glucose			mg/dL	62	125
105	Chemistry	Total Bilirubin			mg/dL	0.2	1.3
105	Chemistry	Total protein			g/dL	6	8.2
105	Hematology	Hematocrit	M		%	38	50
105	Hematology	Hematocrit	F		%	36	45
105	Hematology	Hemoglobin	M		g/dL	13	18
105	Hematology	Hemoglobin	F		g/dL	11.5	15.5
105	Hematology	Neutrophils			thou/uL	1.8	7
105	Hematology	Lymphocytes			thou/uL	1	4.8
105	Hematology	Monocytes			thou/uL	0	0.8
105	Hematology	Eosinophils			thou/uL	0	0.5
105	Hematology	Basophils			thou/uL	1.8	7
105	Hematology	Platelet count			thou/uL	150	400
105	Hematology	WBC count			x10^3/uL	20	1000
105	Urinalysis	Glucose				Negative	
105	Urinalysis	Ketones				Negative*	
105	Urinalysis	Occult blood				1.005	1.03
105	Urinalysis	Protein				negative	
105	Urinalysis	Specific gravity					
105	Urinalysis	Urobilinogen				negative	

Table 13 Site 107 Units and Reference Ranges by Parameter

SITE NUMBER	PANEL	PARAMETER	SEX	AGE	UNITS	REFERENCE LOW	REFERENCE HIGH
107	Chemistry	Albumin			g/L	38	50
107	Chemistry	ALP			U/L	40	150
107	Chemistry	ALT/SGPT			U/L	7	40
107	Chemistry	AST/SGOT			U/L	5	34
107	Chemistry	Bicarbonate			mmol/L	23	29

SITE NUMBER	PANEL	PARAMETER	SEX	AGE	UNITS	REFERENCE LOW	REFERENCE HIGH
107	Chemistry	Blood urea nitrogen			mmol/L	2.5*	7.1*
107	Chemistry	Calcium			mmol/L	2.2	2.62
107	Chemistry	Chloride			mmol/L	100	110
107	Chemistry	Creatinine	M		µmol/L	64	110
107	Chemistry	Creatinine	F		µmol/L	50	98
107	Chemistry	Glucose			mmol/L	3.8	7
107	Chemistry	Magnesium			mmol/L	0.7	1.1
107	Chemistry	Phosphorous			mmol/L	0.81*	1.4*
107	Chemistry	Potassium			mmol/L	3.2	5
107	Chemistry	Sodium			mmol/L	135	145
107	Chemistry	Total Bilirubin			µmol/L	low	< 23
107	Chemistry	Total protein			g/L	65	80
107	Hematology	Hematocrit			L/L	0.42	0.54
107	Hematology	Hematocrit			L/L	0.33	0.47
107	Hematology	Hemoglobin	M		g/L	140	180
107	Hematology	Hemoglobin	F		g/L	120	160
107	Hematology	Neutrophils			10^9/L	2	7.5
107	Hematology	Lymphocytes			10^9/L	1.5	4
107	Hematology	Monocytes			10^9/L	0.2	0.8
107	Hematology	Eosinophils			10^9/L	0.04	0.4
107	Hematology	Basophils			10^9/L	0	0.2
107	Hematology	Platelet count			10^9/L	150	400
107	Hematology	WBC count			10^9/L	4	11
107	Urinalysis	Glucose				Negative	
107	Urinalysis	Ketones				Negative	
107	Urinalysis	Occult blood				Negative	Trace
107	Urinalysis	Protein				Negative	Trace
107	Urinalysis	Specific gravity				1.005	1.03
107	Urinalysis	Urobilinogen			umol/L	low	< 17

Table 14 Site 110 Units and Reference Ranges by Parameter

SITE NUMBER	PANEL	PARAMETER	SEX	AGE	UNITS	REFERENCE LOW	REFERENCE HIGH
110	Chemistry	Albumin			g/L	39	50
110	Chemistry	ALP	M		U/L	42	110
110	Chemistry	ALP	F		U/L	32	93

SITE NUMBER	PANEL	PARAMETER	SEX	AGE	UNITS	REFERENCE LOW	REFERENCE HIGH
110	Chemistry	ALP	F		U/L	47	124
110	Chemistry	ALT/SGPT	M		U/L	8	58
110	Chemistry	ALT/SGPT	F	16 - 50	U/L	7	36
110	Chemistry	ALT/SGPT	F	51 - high	U/L	8	45
110	Chemistry	AST/SGOT	M		U/L	15	38
110	Chemistry	AST/SGOT	F	16 - 50	U/L	14	30
110	Chemistry	AST/SGOT	F	51 - high	U/L	15	37
110	Chemistry	Bicarbonate			mmol/L	21	31
110	Chemistry	Blood urea nitrogen	M	16 - 30	mmol/L	2.5	6.3
110	Chemistry	Blood urea nitrogen	M	31 - 40	mmol/L	3.1	8
110	Chemistry	Blood urea nitrogen	M	41 - 50	mmol/L	3.6	7.8
110	Chemistry	Blood urea nitrogen	M	50 - high	mmol/L	3	8.8
110	Chemistry	Blood urea nitrogen	F	16 - 40	mmol/L	2.5	6.4
110	Chemistry	Blood urea nitrogen	F	41 - 50	mmol/L	2.8	6.7
110	Chemistry	Blood urea nitrogen	F	50 - high	mmol/L	2.9	8
110	Chemistry	Calcium		16 -< 59	mmol/L	2.11	2.55
110	Chemistry	Calcium		59 - high	mmol/L	2.24	2.63
110	Chemistry	Chloride			mmol/L	100	109
110	Chemistry	Creatinine	M		umol/L	67	109
110	Chemistry	Creatinine	F		umol/L	49	882
110	Chemistry	Glucose			mmol/L	3.6*	5.3*
110	Chemistry	Magnesium			mmol/L	0.66	1.07
110	Chemistry	Phosphorous			mmol/L	0.88	1.45
110	Chemistry	Potassium			mmol/L	3.6	5
110	Chemistry	Sodium			mmol/L	136	148
110	Chemistry	Total Bilirubin			umol/L	4	23
110	Chemistry	Total protein			g/L	67	87
110	Hematology	Hematocrit	M			0.395	0.488
110	Hematology	Hematocrit	F			0.347	0.449

SITE NUMBER	PANEL	PARAMETER	SEX	AGE	UNITS	REFERENCE LOW	REFERENCE HIGH
110	Hematology	Hemoglobin	M		g/dL	13.3	17.1
110	Hematology	Hemoglobin	F		g/dL	11.5	14.8
110	Hematology	Neutrophils			x10^9/L	2.01	7.42
110	Hematology	Lymphocytes			x10^9/L	1.06	3.61
110	Hematology	Monocytes			x10^9/L	0.26	0.85
110	Hematology	Eosinophils			x10^9/L	0.02	0.45
110	Hematology	Basophils			x10^9/L	0.02	0.09
110	Hematology	Platelet count			x10^9/L	167	396
110	Hematology	WBC count			x10^9/L	3.89	9.93
110	Urinalysis	Glucose			mg/dL	Negative	
110	Urinalysis	Ketones			mg/dL	Negative	
110	Urinalysis	Occult blood				Negative	
110	Urinalysis	Protein			mg/dL	Negative	
110	Urinalysis	Specific gravity				1.005	1.03
110	Urinalysis	Urobilinogen			E.U./dL	0.2	1

Table 15 Site 111 Units and Reference Ranges by Parameter

SITE NUMBER	PANEL	PARAMETER	SEX	AGE	UNITS	REFERENCE LOW	REFERENCE HIGH
111	Chemistry	Albumin			g/dL	3.4	5
111	Chemistry	ALP			U/L	46	116
111	Chemistry	ALT/SGPT			U/L	12	78
111	Chemistry	AST/SGOT			U/L	15	37
111	Chemistry	Bicarbonate			mEq/L	21	32
111	Chemistry	Blood urea nitrogen			mg/dL	7	18
111	Chemistry	Calcium			mg/dL	8.5	10.4
111	Chemistry	Chloride			mEq/L	98	107
111	Chemistry	Creatinine			mg/dL	0.51	1.17
111	Chemistry	Glucose			mg/dL	70	110
111	Chemistry	Magnesium			mg/dL	1.8	2.4
111	Chemistry	Phosphorous			mg/dL	2.5	4.9
111	Chemistry	Potassium			mEq/L	3.5	5.1
111	Chemistry	Sodium			mEq/L	136	145
111	Chemistry	Total Bilirubin			mg/dL	0	1
111	Chemistry	Total protein			g/dL	6.4	8.2
111	Hematology	Hematocrit	M		%	38	50

SITE NUMBER	PANEL	PARAMETER	SEX	AGE	UNITS	REFERENCE LOW	REFERENCE HIGH
111	Hematology	Hematocrit	F		%	34	45
111	Hematology	Hemoglobin	M		g/dL	13	17.5
111	Hematology	Hemoglobin	F		g/dL	11.6	15.4
111	Hematology	Neutrophils			K/uL	1.5	8
111	Hematology	Lymphocytes			K/uL	1	4
111	Hematology	Monocytes			K/uL	0.2	1
111	Hematology	Eosinophils			K/uL	0	0.6
111	Hematology	Basophils			K/uL	0	0.2
111	Hematology	Platelet count			K/uL	140	390
111	Hematology	WBC count			K/uL	3.5	10.5
111	Urinalysis	Glucose				NEGATIVE	
111	Urinalysis	Ketones				NEGATIVE	
111	Urinalysis	Occult blood				NEGATIVE	
111	Urinalysis	Protein			mg/dL	< 10	
111	Urinalysis	Specific gravity				1.005	1.035
111	Urinalysis	Urobilinogen			EU/dL	0.2	1

Table 16 Site 113 Units and Reference Ranges by Parameter

SITE NUMBER	PANEL	PARAMETER	SEX	AGE	UNITS	REFERENCE LOW	REFERENCE HIGH
113	Chemistry	Albumin		Apr-60	g/dL	3.4	4.2
113	Chemistry	Albumin		61 - 70	g/dL	2.5	5.5
113	Chemistry	Albumin		71 - 80	g/dL	3.6	4.8
113	Chemistry	Albumin		81 - 90	g/dL	3.5	4.8
113	Chemistry	Albumin		90 - high	g/dL	3.2	4.6
113	Chemistry	ALP			IU/L		
113	Chemistry	ALT/SGPT	M		IU/L	0	44
113	Chemistry	ALT/SGPT	F		IU/L	0	32
113	Chemistry	AST/SGOT			IU/L	0	40
113	Chemistry	Bicarbonate			mmol/L	20	29
113	Chemistry	Blood urea nitrogen		18 - 39	mg/dL	6	20
113	Chemistry	Blood urea nitrogen		40 - 59	mg/dL	6	24
113	Chemistry	Blood urea nitrogen		60 - 89	mg/dL	8	27

SITE NUMBER	PANEL	PARAMETER	SEX	AGE	UNITS	REFERENCE LOW	REFERENCE HIGH
113	Chemistry	Blood urea nitrogen		90 - high	mg/dL	10	36
113	Chemistry	Calcium			mg/dL	4.5	5.6
113	Chemistry	Chloride			mmol/L	97	106
113	Chemistry	Creatinine			mg/dL	0.76	1.27
113	Chemistry	Creatinine			mg/dL	0.57	1
113	Chemistry	Glucose			ng/mL	65	199
113	Chemistry	Magnesium			mg/dL	1.6	2.3
113	Chemistry	Phosphorous			mg/dL	2.5	4.5
113	Chemistry	Potassium			mmol/L	3.5	5.2
113	Chemistry	Sodium			mmol/L	134	144
113	Chemistry	Total Bilirubin			mg/dL	0	1.2
113	Chemistry	Total protein			g/dL	6	8.5
113	Hematology	Hematocrit			%	43.5	53.7
113	Hematology	Hemoglobin			g/dL	14.1	18.1
113	Hematology	Neutrophils			x10E3/uL	1.4	7
113	Hematology	Lymphocytes			x10E3/uL	0.7	3.1
113	Hematology	Monocytes			x10E3/uL	0.1	0.9
113	Hematology	Eosinophils			x10E3/uL	0	0.4
113	Hematology	Basophils			x10E3/uL	0	0.2
113	Hematology	Platelet count			x10E3/uL	150	450
113	Hematology	WBC count			x10E3/uL	3.4	10.8
113	Urinalysis	Glucose				Negative	
113	Urinalysis	Ketones				Negative	
113	Urinalysis	Occult blood				Negative	
113	Urinalysis	Protein				Negative	
113	Urinalysis	Specific gravity				1	1.035
113	Urinalysis	Urobilinogen				Normal	

Table 17 Site 116 Units and Reference Ranges by Parameter

SITE NUMBER	PANEL	PARAMETER	SEX	AGE	UNITS	REFERENCE LOW	REFERENCE HIGH
116	Chemistry	Albumin		20 - 60	g/L	35	52
116	Chemistry	Albumin		61 - 90	g/L	32	46
116	Chemistry	ALP			U/L	40	150
116	Chemistry	ALT/SGPT			U/L	< 56	

SITE NUMBER	PANEL	PARAMETER	SEX	AGE	UNITS	REFERENCE LOW	REFERENCE HIGH
116	Chemistry	AST/SGOT			U/L	5	34
116	Chemistry	Bicarbonate			mmol/L	22	29
116	Chemistry	Blood urea nitrogen	M		mmol/L	3.2	7.4
116	Chemistry	Blood urea nitrogen	F		mmol/L	2.5	6.7
116	Chemistry	Calcium			mmol/L	2.1	2.55
116	Chemistry	Chloride			mmol/L	98	107
116	Chemistry	Creatinine	M		umol/L	63.6	110.5
116	Chemistry	Creatinine	F		umol/L	50.4	98.1
116	Chemistry	Glucose			mmol/L	3.6*	5.3*
116	Chemistry	Magnesium			mmol/L	0.66	1.07
116	Chemistry	Phosphorous			mmol/L	0.74	1.52
116	Chemistry	Potassium			mmol/L	3.5	5.1
116	Chemistry	Sodium			mmol/L	136	145
116	Chemistry	Total Bilirubin			umol/L	5.1	20.5
116	Chemistry	Total protein			g/L	64	83
116	Hematology	Hematocrit		M	%	37	52
116	Hematology	Hematocrit		F	%	35	47
116	Hematology	Hemoglobin		M	g/dL	12.5	17.5
116	Hematology	Hemoglobin		F	g/dL	11.5	16
116	Hematology	Neutrophils			K/uL	1.7	88
116	Hematology	Lymphocytes			K/uL	1	4.5
116	Hematology	Monocytes			K/uL	0.2	1
116	Hematology	Eosinophils			K/uL	0	0.5
116	Hematology	Basophils			K/uL	0	0.2
116	Hematology	Platelet count			K/uL	150	400
116	Hematology	WBC count			× 109/L	3.54*	9.06*
116	Urinalysis	Glucose				Negative	
116	Urinalysis	Ketones				Negative	
116	Urinalysis	Occult blood				Negative	
116	Urinalysis	Protein				Negative	
116	Urinalysis	Specific gravity				1.001	1.035
116	Urinalysis	Urobilinogen					

Table 18 Site 117 Units and Reference Ranges by Parameter

SITE NUMBER	PANEL	PARAMETER	SEX	AGE	UNITS	REFERENCE LOW	REFERENCE HIGH
117	Chemistry	Albumin		18 - 59	g/dL	3.7	4.8
117	Chemistry	Albumin		60 - 89	g/dL	3.2	4.6
117	Chemistry	Albumin		90 - high	g/dL	2.9	4.5
117	Chemistry	ALP		15 - 20	IU/L	50	180
117	Chemistry	ALP		20 - high	IU/L	40	140
117	Chemistry	ALT/SGPT				7*	41*
117	Chemistry	AST/SGOT				12*	38*
117	Chemistry	Bicarbonate			meq/L	22*	30*
117	Chemistry	Blood urea nitrogen			mg/dL	10	25
117	Chemistry	Calcium			mg/dL	8.6	10.4
117	Chemistry	Chloride			mmol/L	98	111
117	Chemistry	Creatinine	M		mg/dL	< 1.28	
117	Chemistry	Creatinine	F		mg/dL	< 1.16	
117	Chemistry	Glucose			mg/dL	50	140
117	Chemistry	Magnesium			mg/dL	1.8	2.3
117	Chemistry	Phosphorous			mg/dL	2.5	4.5
117	Chemistry	Potassium			mmol/L	3.5	5
117	Chemistry	Sodium			mmol/L	135	145
117	Chemistry	Total Bilirubin			mg/dL	< 1.2	
117	Chemistry	Total protein			g/dL	6	8.3
117	Hematology	Hematocrit	M		%	41	53
117	Hematology	Hematocrit	F		%	36	46
117	Hematology	Hemoglobin	M		g/dL	13.5	17
117	Hematology	Hemoglobin	F		g/dL	12	15
117	Hematology	Neutrophils			K/uL	1.8	7.7
117	Hematology	Lymphocytes			K/uL	1.1	4
117	Hematology	Monocytes			K/uL	0	0.8
117	Hematology	Eosinophils			K/uL	0	0.7
117	Hematology	Basophils			K/uL	0	0.2
117	Hematology	Platelet count			K/uL	150	450
117	Hematology	WBC count			K/uL	3.8	10.6

SITE NUMBER	PANEL	PARAMETER	SEX	AGE	UNITS	REFERENCE LOW	REFERENCE HIGH
117	Urinalysis	Glucose				Negative	
117	Urinalysis	Ketones				Negative	
117	Urinalysis	Occult blood				Negative	
117	Urinalysis	Protein				Negative	
117	Urinalysis	Specific gravity				1.005	1.03
117	Urinalysis	Urobilinogen			U/dL	< 2.0	

Table 19 Site 122 Units and Reference Ranges by Parameter

SITE NUMBER	PANEL	PARAMETER	SEX	AGE	UNITS	REFERENCE LOW	REFERENCE HIGH
122	Chemistry	Albumin			g/dL	3.5	5.2
122	Chemistry	ALP	M		U/L	40	130
122	Chemistry	ALP	F		U/L	35	105
122	Chemistry	ALT/SGPT	M		U/L	low	41
122	Chemistry	ALT/SGPT	F		U/L	low	33
122	Chemistry	AST/SGOT	M		U/L	low	40
122	Chemistry	AST/SGOT	F		U/L	low	32
122	Chemistry	Bicarbonate			meq/L	22*	30*
122	Chemistry	Blood urea nitrogen		18 -< 60	mg/dL	6	20
122	Chemistry	Blood urea nitrogen		60 - 90	mg/dL	8	23
122	Chemistry	Blood urea nitrogen		> 90	mg/dL	8.6	10
122	Chemistry	Calcium		18 -< 60	mg/dL	8.6	10
122	Chemistry	Calcium		60 - 90	mg/dL	8.8	10.2
122	Chemistry	Calcium		> 90	mg/dL	8.2	9.6
122	Chemistry	Chloride			mmol/L	98	107
122	Chemistry	Creatinine	M		mg/dL	0.7	1.2
122	Chemistry	Creatinine	F		mg/dL	0.5	0.9
122	Chemistry	Glucose			mg/dL	74	109
122	Chemistry	Magnesium		20 -< 60	mg/dL	1.6	2.6
122	Chemistry	Magnesium		60 - 90	mg/dL	1.6	2.4
122	Chemistry	Phosphorous			mg/dL	2.5	4.5
122	Chemistry	Potassium			mmol/L	3.4	4.5
122	Chemistry	Sodium			mmol/L	136	145

SITE NUMBER	PANEL	PARAMETER	SEX	AGE	UNITS	REFERENCE LOW	REFERENCE HIGH
122	Chemistry	Total Bilirubin			mg/dL	low	1.2
122	Chemistry	Total protein			g/dL	6.4	8.3
122	Hematology	Hematocrit	M		%	40.1	51
122	Hematology	Hematocrit	F		%	34.1	44.9
122	Hematology	Hemoglobin	M		g/dL	13.7	17.5
122	Hematology	Hemoglobin	F		g/dL	11.2	15.7
122	Hematology	Neutrophils			k/uL	2.3	7.1
122	Hematology	Lymphocytes			k/uL	0.8	3.5
122	Hematology	Monocytes			k/uL	0.2	0.8
122	Hematology	Eosinophils			k/uL	0.1	0.4
122	Hematology	Basophils			k/uL	0	0.1
122	Hematology	Platelet count			k/uL	150	450
122	Hematology	WBC count			k/uL	4	10.5
122	Urinalysis	Glucose				Negative	
122	Urinalysis	Ketones				Negative	
122	Urinalysis	Occult blood				Negative	
122	Urinalysis	Protein				Negative	
122	Urinalysis	Specific gravity				1.001	1.03
122	Urinalysis	Urobilinogen				Normal	

18 Appendix B: Common Terminology Criteria for Adverse Events for Laboratory Parameters

Table 20 Common Terminology Criteria for Adverse Events v5.0, November 27, 2017

Panel	Parameter	CTCAE Term	Definition	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Chemistry	**Sodium**	**Hypernatremia**	A disorder characterized by laboratory test results that indicate an elevation in the concentration of sodium in the blood.	>ULN - 150 mmol/L	>150 - 155 mmol/L; intervention initiated	>155 - 160 mmol/L; hospitalization indicated	>160 mmol/L; life-threatening consequences	Death
Chemistry	**Sodium**	**Hyponatremia**	A disorder characterized by laboratory test results that indicate a low concentration of sodium in the blood.	<LLN - 130 mmol/L	125-129 mmol/L and asymptomatic	125-129 mmol/L symptomatic; 120-124 mmol/L regardless of symptoms	<120 mmol/L; life-threatening consequences	Death
Chemistry	**Potassium**	**Hyperkalemia**	A disorder characterized by laboratory test results that indicate an elevation in the concentration of potassium in the blood; associated with kidney failure or sometimes with the use of diuretic drugs	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L; intervention initiated	>6.0 - 7.0 mmol/L; hospitalization indicated	>7.0 mmol/L; life-threatening consequences	Death
Chemistry	**Potassium**	**Hypokalemia**	A disorder characterized by laboratory test results that indicate a low concentration of potassium in the blood.	<LLN - 3.0 mmol/L	Symptomatic with <LLN - 3.0 mmol/L; intervention indicated	<3.0 - 2.5 mmol/L; hospitalization indicated	<2.5 mmol/L; life-threatening consequences	Death
Chemistry	**Calcium**	**Hyper-calcemia**	A disorder characterized by laboratory test results that indicate an elevation in the concentration of calcium (corrected for albumin) in blood.	>ULN - 2.9 mmol/L	>2.9 - 3.1 mmol/L; symptomatic	>3.1 - 3.4 mmol/L; hospitalization indicated	>3.4 mmol/L; life-threatening consequences	Death
Chemistry	**Calcium**	**Hypocalcemia**	A disorder characterized by laboratory test results that indicate a low concentration of calcium (corrected for albumin) in the blood.	<LLN - 2.0 mmol/L	<2.0 - 1.75 mmol/L; symptomatic	<1.75 - 1.5 mmol/L; hospitalization indicated	<1.5 mmol/L; life-threatening consequences	Death

Panel	Parameter	CTCAE Term	Definition	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Chemistry	**Magnesium**	**Hypermagnesemia**	A disorder characterized by laboratory test results that indicate an elevation in the concentration of magnesium in the blood.	>ULN - 3.0 mg/dL; >ULN - 1.23 mmol/L		>3.0 - 8.0 mg/dL; >1.23 - 3.30 mmol/L	>8.0 mg/dL; >3.30 mmol/L; life-threatening consequences	Death
Chemistry	**Magnesium**	**Hypomagnesemia**	A disorder characterized by laboratory test results that indicate a low concentration of magnesium in the blood.	<LLN - 1.2 mg/dL; <LLN - 0.5 mmol/L	<1.2 - 0.9 mg/dL; <0.5 - 0.4 mmol/L	<0.9 - 0.7 mg/dL; <0.4 - 0.3 mmol/L	<0.7 mg/dL; <0.3 mmol/L; lifethreatening consequences	Death
Chemistry	**Glucose**	**Hypoglycemia**	A disorder characterized by laboratory test results that indicate a low concentration of glucose in the blood.	<LLN - 55 mg/dL; <LLN - 3.0 mmol/L	<55 - 40 mg/dL; <3.0 - 2.2 mmol/L	<40 - 30 mg/dL; <2.2 - 1.7 mmol/L	<30 mg/dL; <1.7 mmol/L; lifethreatening consequences; seizures	Death
Chemistry	**Creatinine**	**Creatinine increased**	A finding based on laboratory test results that indicate increased levels of creatinine in a biological specimen.	>ULN - 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 x baseline; >3.0 - 6.0 x ULN	>6.0 x ULN	
Chemistry	**Total Bilirubin**	**Blood bilirubin increased**	A finding based on laboratory test results that indicate an abnormally high level of bilirubin in the blood. Excess bilirubin is associated with jaundice.	>ULN - 1.5 x ULN if baseline was normal; > 1.0 - 1.5 x baseline if baseline was abnormal	>1.5 - 3.0 x ULN if baseline was normal; >1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 10.0 x ULN if baseline was normal; >3.0 - 10.0 x baseline if baseline was abnormal	>10.0 x ULN if baseline was normal; >10.0 x baseline if baseline was abnormal	
Chemistry	**AST/SGOT**	**Aspartate aminotransferase increased**	A finding based on laboratory test results that indicate an increase in the level of aspartate aminotransferase (AST or SGOT) in a blood specimen.	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	

Panel	Parameter	CTCAE Term	Definition	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Chemistry	**ALT/SGPT**	**Alanine aminotransferase increased**	A finding based on laboratory test results that indicate an increase in the level of alanine aminotransferase (ALT or SGPT) in the blood specimen.	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	
Chemistry	**ALP**	**Alkaline phosphatase increased**	A finding based on laboratory test results that indicate an increase in the level of alkaline phosphatase in a blood specimen.	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	
Chemistry	**Albumin**	**Hypoalbuminemia**	A disorder characterized by laboratory test results that indicate a low concentration of albumin in the blood.	<LLN - 3 g/dL; <LLN - 30 g/L	<3 - 2 g/dL; <30 - 20 g/L	<2 g/dL; <20 g/L	Life-threatening consequences; urgent intervention indicated	Death
Hematology	**Hemoglobin**	**Anemia**	A disorder characterized by a reduction in the amount of hemoglobin in 100 ml of blood. Signs and symptoms of anemia may include pallor of the skin and mucous membranes, shortness of breath, palpitations of the heart, soft systolic murmurs, lethargy, and fatigability.	<LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	<10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	<8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated	Life-threatening consequences; urgent intervention indicated	Death
Hematology	**Hemoglobin**	**Hemoglobin increased**	A finding based on laboratory test results that indicate increased levels of hemoglobin above normal.	Increase in >0 - 2 g/dL	Increase in >2 - 4 g/dL	Increase in >4 g/dL		
Hematology	**Neutrophils**	**Neutrophil count decreased**	A finding based on laboratory test results that indicate a decrease in number of neutrophils in a blood specimen.	<LLN - 1500/mm3; <LLN - 1.5x 10e9 /L	<1500 - 1000/mm3; <1.5 - 1.0x 10e9 /L	<1000 - 500/mm3; <1.0 - 0.5 x10e9 /L	<500/mm3; <0.5 x 10e9 /L	

Panel	Parameter	CTCAE Term	Definition	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Hematology	**Lymphocytes**	**Lymphocyte count decreased**	A finding based on laboratory test results that indicate a decrease in number of lymphocytes in a blood specimen.	<LLN - 800/mm3; <LLN - 0.8 x 10e9/L	<800 - 500/mm3; <0.8 - 0.5 x 10e9/L	<500 - 200/mm3; <0.5 - 0.2 x 10e9/L	<200/mm3; <0.2 x 10e9/L	
Hematology	**Eosinophils**	**Eosinophilia**	A disorder characterized by laboratory test results that indicate an increased number of eosinophils in the blood.	>ULN and >Baseline		Steroids initiated		
Hematology	**Platelet count**	**Platelet count decreased**	A finding based on laboratory test results that indicate a decrease in number of platelets in a blood specimen.	<LLN - 75.0 x 10e9/L	<75.0 - 50.0 x 10e9/L	<50.0 - 25.0 x 10e9/L	<25.0 x 10e9/L	