STATISTICAL ANALYSIS PLAN

PHASE 1/2A DOSE-ESCALATION STUDY OF CRLX301 IN PATIENTS WITH ADVANCED SOLID TUMOR MALIGNANCIES

Protocol No.: CRLX301-101

Product Code: CRLX301

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SAP APPROVAL

By my signature, I confirm that this SAP has been approved for use on the CRLX301-101 study:

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List of Abbreviations

Abbreviation	Description
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
CI	Confidence Interval
CRPS	Castration Resistant Prostate Cancer
CSR	Clinical Study Report
CT	Computed Tomography
CTCS	Circulating Tumor Cells
DBP	Diastolic Blood Pressure
DLT	Dose Limiting Toxicity
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
ECRF	Electronic Case Report Form
ICH GCP	International Conference on Harmonization of Good Clinical Practice Guidelines
INR	International Normalized Ratio
IV	Intravenous
LDH	Lactate Dehydrogenase
MEDDRA	Medical Dictionary for Regulatory Activities
MPS	Mononuclear Phagocyte System
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
MUGA	Multiple Gated Acquisition
PD	Pharmacodynamic
PK	Pharmacokinetic
PSA	Prostate-Specific Antigen
PT	Preferred Term
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
QW	Weekly Dosing
Q3W	Dosing Every 3 Weeks
RBC	Red Blood Cells
RECIST	Response Evaluation Criteria In Solid Tumors
RP2D	Recommended Phase 2 Dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Standard Deviation
S.I.	International System of Units
SOC	System Organ Class
SOP	Standard Operating Procedure
SRC	Safety Review Committee
TEAE	Treatment Emergent Adverse Event
WBC	White Blood Cells
WHO-DD	World Health Organization Drug Dictionary

1.Introduction

The following Statistical Analysis Plan (SAP) provides the outline for the statistical analysis of the data from the CRLX301-101 study (protocol amendment version 9 dated 16 December 2016).

The study was prematurely terminated, therefore all the analyses that were planned in the protocol will not be performed. The purpose of this SAP is to describe the analyses that will be included in the abbreviated clinical study report (CSR).

2.Project Overview

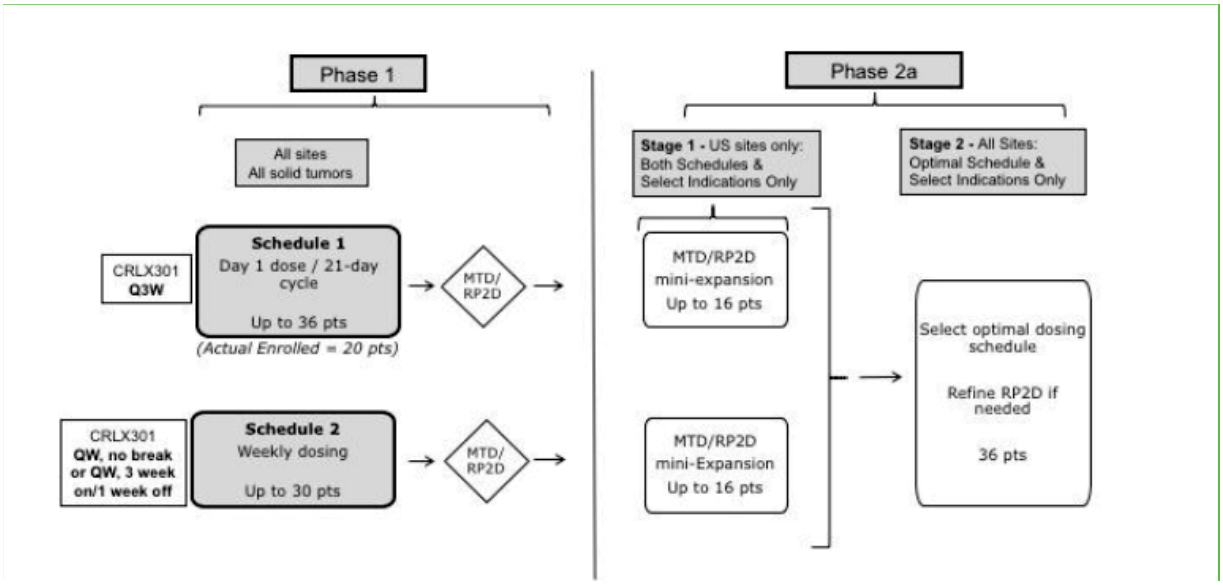
2.1.Description of the Study Design

This is a phase 1/2a, open-label, dose-escalation study of CRLX301 in patients with advanced solid tumor malignancies that will be conducted in two phases.

Up to 134 patients will be enrolled into the study: Up to 66 patients into Phase 1 and up to 68 patients into Phase 2a. The exact number of patients will depend on the actual number of cohorts that are enrolled, and the actual number of patients enrolled into each cohort.

The following schematic provides and overview of the study design.

Study Schematic



2.1.1.Phase 1 Dose Escalation Study

Phase 1 of the study is an open-label, dose-escalation study examining two separate dosing schedules to determine the maximum tolerated dose (MTD)/recommended Phase 2 dose (RP2D) of CRLX301 when administered by intravenous (IV) infusion.

The MTD is defined as the highest dose level at which fewer than two of six patients in a Phase 1 dose escalation cohort experiences a dose limiting toxicity (DLT) during the first three weeks of treatment. A DLT is defined as any adverse event (AE) that is possibly, probably, or related to CRLX301 that results in an unacceptable toxicity (refer to Section 3.1.3 of the Protocol) and occurs at any point during the first three weeks of treatment post-initiation of the study drug infusion.

The RP2D is defined as the dose which will be assigned in Phase 2a as advised by the Safety Review Committee (SRC) based on adverse events (AEs), anti-tumor activity of CRLX301 and available pharmacokinetic (PK) and pharmacodynamic (PD) data. The RP2D may be the same as the MTD dose level or it may be lower. The RP2D may not exceed the MTD.

Schedule 1 (dosing every three weeks [Q3W] dosing schedule) was initiated first and Amendment 6 incorporated Schedule 2 (weekly dosing [QW], no break dosing schedule). Amendment 9 altered Schedule 2 to a once weekly, three week on/one week off schedule for Cohorts 3 and 4, with the dosing schedule for additional cohorts to be determined by the SRC.

Schedule 1 is an open-label, 1+5 (Cohorts 1 and 2) followed by classic 3+3 (all remaining cohorts) dose-escalation design and Schedule 2 will follow the classical 3+3 design for all cohorts. Patients will be sequentially enrolled into cohorts and study assessment will performed in accordance with the Schedule of Procedures (refer to the Protocol). Cohorts will continue enrolling until the planned number of patients are enrolled, or until the DLT criteria are met, in which case the cohort will be expanded to the maximum planned number of patients.

Patients will remain on study treatment until they experience progression of disease (unless there is evidence of clinical benefit and the investigator believes it is in the patient's best interest to continue the study drug treatment), unacceptable toxicity, or any other specified reason for discontinuation (refer to Section 6.1 of the Protocol).

The following tables give an overview of the planned dose levels and patient numbers for the two schedules.

Table 1: Schedule 1 Q3W Provisional Dose Escalation Scheme

Cohort	Dose Level	Number of Patients initially plus additional expansion if DLTs	Actual Enrollment as of Amendment 7
1	7.5 mg/m^2	1 to 6	1
2	15 mg/m^2	1 to 6	1
3*	30* mg/m^2	3 to 6	3
4*	45* mg/m^2	3 to 6	0*
5	60 mg/m^2	3 to 6	3
6	75 mg/m^2	3 to 6	6
7	90 mg/m^2	3 to 6	6
8	105 mg/m^2	3 to 6	Cohorts will not be open as MTD/RP2D selected as 75mg/m^2
9	120 mg/m^2	3 to 6	
10 and Additional Cohorts	135 mg/m^2 Increase dose levels by 15 mg/m^2 for additional cohorts (i.e. 150 mg/m^2, etc.)	3 to 6	

*SRC is allowed to dose escalate from 30 mg/m^2 to as high as 60 mg/m^2. No other planned dose level cohorts may be skipped during Phase 1.

Table 2: Schedule 2 QW Provisional Dose Escalation Scheme

Cohort	Proposed Dose Level*	Number of Patients initially plus additional expansion if DLTs
-1	20 mg/m^2 Only if starting dose level not tolerated	3 to 6
1	25 mg/m^2	3 to 6
2	35 mg/m^2	3 to 6
3**	45 mg/m^2	3 to 6
4**	54 mg/m^2	3 to 6
Additional Cohorts**	Increase dose levels by 5 mg/m^2 or otherwise recommended by SRC based on available safety and PK data (dose increment to the next higher dose level will not exceed 20%)	3 to 6

*SRC is allowed to dose escalate by as much as 40% (total over 3 weeks) for doses below 50mg/m^2 and by 20% (total over 3 weeks) for dose levels above 50mg/m^2.
** As of Amendment 9, for patients still receiving treatment in Schedule 2 Cohort 3, and for patients enrolled in Schedule 2 Cohort 4, dosing will be on a weekly, 3 week on/1 week off schedule. The dosing schedule for additional Schedule 2 cohorts will be determined by the SRC.

2.1.2.Phase 2a Expansion Study

Phase 2a will be an open-label RP2D expansion study.

Up to an additional 68 patients with advanced, histologically confirmed solid tumor malignancies will be enrolled in the Phase 2a expansion cohorts inclusive of Stage 1 (up to 32 patients) and Stage 2 (up to 36 patients). Enrollment will be limited to up to five specific tumor types.

Patients will be followed for safety, tumor response, and progression free survival while on the study per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 guidelines or with methodologies consistent with the specific tumor type. Treatment guidelines for the RP2D expansion cohorts will be the same as those for the Phase 1 dose expansion cohorts.

Phase 2a Stage 1 Expansion

Once either of the dosing schedules confirms the MTD from Phase 1 and the sponsor confirms that all required pharmacodynamic assays are ready, Phase 2a Stage 1 will initiate. This will be an expansion of up to 16 patients for each dose schedule at the RP2D. Up to five specific tumor types will be selected and only patients with the selected tumor types may enroll into Phase 2a Stage 1. At the time of Amendment 8, taxane naïve (unless approved by Sponsor) castration resistant prostate cancer (CRPC) has been selected as one of the indications for Ph2a Stage 1. Enrollment cap will be contingent upon enrolling at least six patients of the same indication (e.g. CRPC who are taxane naïve) and observation rates of anti-tumor activity. All sites will be notified of the select tumor type(s) in advance of initiating Stage 1. Due to shipping and processing requirements for circulating tumor cells (CTCs) and mononuclear phagocyte system (MPS) function (both of which require freshly collected whole blood samples) only US sites will enroll patients in Stage 1.

Phase 2a Stage 2 Expansion

Once both dosing schedules complete Phase 2a Stage 1, an optimal dosing schedule will be selected based on available safety and efficacy signals, PK and available PD data from both

schedules. Further refinement of the RP2D may also be explored. Phase 2a Stage 2 expansion will enroll up to 36 additional patients using one selected dosing schedule and RP2D. Up to five specific tumor types only will be allowed to enroll into Phase 2a Stage 2. Sites in both Australia and US will enroll into Stage 2. All sites will be notified of the select tumor types in advance of initiating Stage 2.

2.2.Objectives

2.2.1.Primary Objective

The primary objective for Phase 1 is to determine the MTD/RP2D of CRLX301 when administered by IV infusion on Schedule 1 (Dosing Day 1 of a 21-day cycle) or Schedule 2 (QW: weekly dosing, no break or QW, 3 week on/1 week off dosing) in patients with advanced solid tumor malignancies.

The primary objective for Phase 2a is to further establish the safety and tolerability of the CRLX301 MTD / RP2D.

2.2.2.Secondary Objectives

The secondary objectives of the study are:

- To evaluate the PK profile of CRLX301 (both the total drug and released docetaxel) in plasma for both dosing schedules
- To explore preliminary signals of efficacy for CRLX301

2.2.3.Exploratory Objectives

The exploratory objectives of the trial are:

- To evaluate the pharmacodynamic activity of CRLX301 in blood and tumor biopsy specimens when available from patients
- To explore possible correlations between clinical response, toxicities and biomarkers
- To explore the PK profile of CRLX301 (both the total drug and released docetaxel) in urine for both dosing schedules
- To explore potential factors affecting potential inter- and intra-patient PK variability and the preliminary relationship between response and the exposure to total and unconjugated docetaxel in plasma and urine.

2.3.Sample Size

No formal sample size calculations were performed.

In total, up to 134 patients (Phase 1: 66 patients and Phase 2a: 68 patients) were planned to be enrolled into the study. The exact number of patients will depend on the actual number of cohorts that are enrolled, and the actual number of patients enrolled into each cohort.

2.4.Assignment of Subjects to Treatment Groups

This is an open-label, non-randomised study and no attempts will be made to mask the treatment that patients will receive. Patients will be enrolled sequentially and will be aware of the cohort into which they are enrolled.

For Phase 1, the patient dosing schedule, cohort and corresponding dose level assignment will be provided in writing from the Sponsor to the Investigator when the patient's study identification number is assigned. Protocol Amendment 9 (11th of November 2016), altered the dosing frequency of Schedule 2, but data for all patients that were ongoing or yet to be enrolled

when the amendment became effective will be analysed based on the specific dosing schedule that the patient was enrolled to at the start of the study.

For Phase 2a, all patients will be assigned to the CRLX301 dose level that is determined to be the RP2D (75 mg/m^2 is the confirmed MTD). The patient dosing schedule will be provided in writing from the Sponsor to the Investigator when the patient's study identification number is assigned.

3.Statistical Considerations

Data will be handled and processed per the sponsor representative's (Novotech) Standard Operating Procedures (SOPs), which are written based on the principles of Good Clinical Practice (GCP).

3.1.General Considerations

All data collected during the study (data originating from the electronic case report forms [eCRFs] or electronic transfers [i.e., safety laboratory, PK concentrations, etc.]) will be presented in the data listings. Event-based listings will be sorted by study phase, schedule/cohort, subject number and event identifier (i.e., AE number). Assessment-based listings will be sorted by study phase, schedule/cohort, subject number, parameter name (alphabetically unless specifically stated otherwise), visit and time point (if applicable).

All summary tables will present the results by study phase, schedule/dose level and overall schedule, as applicable.

Unless otherwise stated, the following methods will be applied:

- Continuous variables: Descriptive statistics will include the number of non-missing values (n), arithmetic mean, standard deviation (SD), median, minimum and maximum values.

  The minimum and maximum values will be displayed to the same decimal precision as the source data, the arithmetic mean and median values will be displayed to one more decimal than the source data, and the SD values will be displayed to two more decimals than the source data for the specific variable.

  The appropriate precision for derived variables will be determined based on the precision of the data on which the derivations are based, and statistics will be presented in accordance with the abovementioned rules.

- Categorical variables: Descriptive statistics will include counts and percentages per category. The denominator in all percentage calculations will be the number of patients in the relevant analysis population with non-missing data, unless specifically stated otherwise. Two-sided 95% Clopper-Pearson confidence intervals (CIs) will be presented where appropriate.

  Percentages and CIs will be rounded to one decimal place. Percentages will not be displayed for zero counts.

- Repeat/unscheduled assessments: Only values collected at scheduled study visits/time points will be presented in summary tables. If a repeat assessment was performed, the result from the original assessment will be presented as the result at the specific visit/time point. All collected data will be included in the data listings.

- Assessment windows: All assessments will be included in the data listings and no visit windows will be applied to exclude assessments that were performed outside of the protocol specified procedure windows.

- Result display convention: Results will be centre-aligned in all summary tables and listings. Subject identifiers, visit and parameter labels may be left-aligned if required.

- Date and time display conventions: The following display conventions will be applied in all outputs where dates and/or times are displayed:
    - Date only: YYYY-MM-DD
    - Date and time: YYYY-MM-DD/HH:MM

If only partial information is available, unknown components of the date or time will be presented as 'NK' (not known), i.e., '2016-NK-NK'. Times will be reported in military time.

3.2.Key Definitions

The following definitions will be used:

- Baseline: The baseline value is defined as the last available valid, non-missing observation for each patient prior to first study drug infusion. Repeat and unscheduled assessments will be included in the derivation of the baseline values.
- Change from Baseline: The change from baseline value is defined as the difference between the result collected/derived at a post-baseline visit/time point and the baseline value.

  The change from baseline value at each post-baseline visit/time point will be calculated for all continuous parameters using the following formula:

  Change from Baseline Value = Result at Visit/Time Point – Baseline Value

  The change from baseline value will only be calculated if the specific post-baseline visit/time point result and the baseline value for the parameter are both available, and will be treated as missing otherwise. In the data listings, the change values will be set to 'N/A' (not applicable) for pre-baseline assessments.
- Study day: The study day of an event is defined as the relative day of the event starting with the date of the first study drug infusion (reference date) as Day 1 (there will be no Day 0).

  The study day of events occurring before the first study drug infusion will be calculated as:

  Study Day = (Date of Event - Date of First Study Drug Infusion)

  For events occurring on or after Day 1, study day will be calculated as:

  Study Day = (Date of Event - Date of First Study Drug Infusion) + 1

  Study days will only be calculated for events with complete dates, and will be undefined for events that are 'Ongoing' at the end of the study.

  Relative days compared to an alternative reference point will be calculated similarly, but the alternative starting reference start date will be used instead of the date of the first study drug infusion.

3.3.Handling of Data Following Protocol Amendment 9

Protocol Amendment 9 resulted in the introduction of a new QW dosing schedule that became effective on the 11th of November 2016. All data for patients that were already enrolled at the time of the amendment (Cohorts 3 and 4) will be analysed under the dosing schedule that the patients were originally enrolled to. Patients who were enrolled after the amendment became effective will be analysed under the new QW dosing schedule.

3.4.Hypothesis Testing

No formal hypothesis testing will be performed and only descriptive summaries will be presented.

3.5.Multiple Comparisons and Multiplicity Adjustments.

Not applicable for this study.

3.6.Handling of Missing Data

All data will be analysed as collected and missing values will not be imputed or replaced.

3.7.Coding of Events and Medications

Adverse event verbatim terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 20.0. Terms will be coded to the full MedDRA hierarchy, but the system organ class (SOC) and preferred terms (PT) will be of primary interest for the analysis.

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO-DD, SEP-2016). Medications will be mapped to the full WHO-DD Anatomical Therapeutic Chemical (ATC) class hierarchy, but the ATC Level 3 terms and PTs will be of primary interest in this analysis.

3.8.Treatment Group and Visit Display Conventions

The following treatment labels will be used in all outputs in the order presented below:

- Phase 1 Schedule 1:
    - Q3W CRLX301 7.5 mg/m^2
    - Q3W CRLX301 15 mg/m^2
    - Q3W CRLX301 30 mg/m^2
    - Q3W CRLX301 60 mg/m^2
    - Q3W CRLX301 75 mg/m^2
    - Q3W CRLX301 90 mg/m^2
    - Q3W CRLX301 All Patients
- Phase 1 Schedule 2:
    - QW CRLX301 25 mg/m^2
    - QW CRLX301 35 mg/m^2
    - QW CRLX301 45 mg/m^2
    - QW CRLX301 54 mg/m^2
    - QW (3 Weeks On/1 Week Off) CRLX301 45 mg/m^2
    - QW (3 Weeks On/1 Week Off) CRLX301 54 mg/m^2
    - QW CRLX301 All Patients
- Phase 2a:
    - Q3W CRLX301 75 mg/m^2
    - QW (3 Weeks On/1 Week Off) CRLX301 75 mg/m^2

Visit labels will be used as reported in the clinical database.

4.Analysis Populations

The protocol defines four analysis populations but due to the premature termination of the study all data displays will be based on the Safety Population.

Data for Screen Failures will not be presented in any of the summary tables or data listings.

4.1.Population Descriptions

4.1.1.Safety Analysis Population

The Safety Population will consist of all patients who received any amount of investigational product.

Patients will be analysed based on the actual treatment received.

4.1.2.Pharmacokinetic Analysis Population

The PK Analysis Population will consist of all patients who received at least part of one dose of CRLX301, have at least one PK sample collected on Cycle 1 Day 1 or Week 1 Day 1 of the study, and have evaluable PK parameters.

4.1.3.MTD and/or RP2D Population

The MTD and/or RP2D population will include all patients treated at the MTD and/or RP2D for each dosing schedule from both Phase 1 and Phase 2a of the study.

4.1.4.MTD and/or RP2D Efficacy Evaluable Population

The MTD and/or RP2D evaluable population will include all patients treated at the MTD/RP2D for each dosing schedule, who have had tumor assessment at baseline and undergone at least one follow-up tumor assessment via imaging or methodologies consistent with specific tumor type.

5.Patient Disposition and Analysis Populations

5.1.Patient Disposition

Patient disposition will be summarised using counts and percentages and will be based on the safety population. The number and percentage of enrolled patients, patients withdrawing from the study treatment as well as the primary reason for treatment termination will be presented.

All disposition information collected on the Treatment Termination eCRF page will be listed together with the date that the patient provided informed consent (from the Add Patient eCRF page) and the dates and times of the first and last study drug infusions (from the Treatment(s) eCRF pages).

All follow-up status information collected on the Follow-up Status eCRF page will be listed together with the date of the last study drug infusion.

A listing will be produced for patients that died during or after study participation. The listing will include the date and cause of death (as reported on the Treatment Termination or Follow-up Status eCRF pages), the dates of the first and last study drug infusions as well as the relative study day of death compared to the first and last study drug infusions (refer to Section 3.2). In addition, as separate listing will be produced for patients that died within 30 days of their last study drug infusion.

5.2.Analysis Populations

The number of patients included in of each of the defined analysis populations will be summarised using counts and percentages and will be based on the safety population.

In addition, the inclusion/exclusion of each patient into/from each of the defined analysis populations will be listed.

6.Protocol Deviations

All reported protocol deviations/violations will be listed.

7.Demographic and Baseline Information

Demographic and other baseline characteristics information collected during the screening period will be analysed based on the safety population.

Continuous variables will be summarised as described in Section 3.1 and categorical variables will be summarised using counts and percentages. Endpoints will be summarised by study phase, dosing schedule (where applicable) and dose level, and for all patients overall within the dosing schedules.

7.1.Demographics and Baseline Data

Demographic and baseline characteristics data, including age, gender, ethnicity, race, height (cm), weight (kg), body mass index (BMI) (kg/m^2), body surface area (BSA) (m^2), childbearing potential (Yes/No) and the Eastern Cooperative Oncology Group (ECOG) status at baseline will be summarised. The summary table will also include the primary site of the disease at study entry.

Body mass index (kg/m^2) will be calculated as:

$$BMI\ (kg/m^2) = Weight\ (kg) / (Height\ (cm) * 100)^2$$

Demography and baseline body measurement data (as collected on the Add Patient and Vital Signs eCRF pages or derived) will be listed in a single listing. The remaining baseline characteristics will be listed in the Baseline Patient Characteristics listing.

7.2.Oncology History

All information collected on the Oncology History eCRF page will be listed.

7.3.Medical History

All information collected on the Medical History eCRF page will be listed.

7.4.Prior Anti-Neoplastic Treatment

All information collected on the Prior Anti-Neoplastic Surgery, Prior Anti-Neoplastic Therapy Medication and Prior Anti-Neoplastic Radiotherapy eCRF pages will be listed. Separate listings will be created for each type of treatment.

7.5.Echocardiogram (ECHO) and Multiple Gated Acquisition (MUGA) Scan Results

All information collected on the MUGAECHO eCRF page will be listed.

7.6.Head Computed Tomography (CT)/ Magnetic Resonance Imaging (MRI) Scan Results

All information related to the head CT or MRI scan collected on the Pre-Study ECOG SCAN eCRF page will be listed.

7.7.Pregnancy Test Results

All information related to childbearing potential and pregnancy test results collected on the LAB TEST eCRF pages will be listed. This listing will include all pregnancy test results collected during the study.

7.8.Patient Eligibility

All information collected on the Inclusion Exclusion Criteria eCRF page will be listed.

7.9.Assignment to Treatment

All information collected on the Randomization eCRF page will be listed. The date of informed consent and the date and time of the first study drug infusion will also be included on the listing.

8.Study Drug Administration and Extent of Exposure

Study drug administration and exposure outputs will be based on the safety population.

The total number of treatment cycles/weeks will be calculated as the number of cycles/weeks during which a patient received any part of a study drug infusion.

The total dose of study drug administered (mg) will be calculated as the sum of the total doses of study drug administered at each treatment visit during the study.

The duration of exposure (days) will be calculated as the difference between the date of the first and last study drug infusions + 1 day.

The total number of treatment cycles/weeks will be summarize using counts and percentages. The total dose of study drug administered and duration of exposure values will be summarized as continuous variables as described in Section 3.1,

All study drug administration information collected on the Treatment(s) eCRF page will be listed. Exposure information (number of treatment cycles, total dose administered and the duration of exposure) will be listed separately.

9.Efficacy

The planned exploratory analyses of efficacy are based on the evaluation of the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 findings or by alternative response evaluations for specific tumor types. Tumor measurement and evaluations were performed at the time points specified in the Schedule of Procedures (refer to the Protocol). Results were reported on the Tumor Measurement and Staging eCRF page. In addition, bone scan, prostate-specific antigen (PSA) (as appropriate for the specific disease) and tumor marker data were collected.

The full planned efficacy analyses will however not be performed for the abbreviated CSR and this SAP will only focus on the analysis of the best overall response rates.

The efficacy analysis will be based on the safety population.

9.1.Best Overall Response

The best overall response is the best response (based on the RECIST v1.1 guidelines) recorded from the start of the treatment until disease progression/recurrence (taking the smallest measurements recorded since the treatment started as a reference for progressive disease).

9.1.1.Biostatistical Methods

The best overall response will be summarized by counts and percentages. In addition, two-sided 95% Clopper-Pearson CIs will be presented for the response rates within each RECIST response category.

Tumor measurement data (including the RECIST evaluations) will be listed separately for target and non-target tumors and new lesion data. A separate listing will be produced for the overall tumor response at each evaluation, and the best overall response will be flagged.

9.2.Other Efficacy Data

Bone scan and PSA (Tumor assessment using PCWG2 eCRF) and tumor marker (Tumor Markers eCRF) data will be listed separately (if data is available in the clinical database).

10.Safety

Statistical methods for the safety analyses will be descriptive in nature and no formal statistical comparisons will be made. Endpoints will be summarised by study phase, dosing schedule (where applicable) and dose level, and for all patients overall within the dosing schedules per the methods described in Section 3.1.

Safety variables will include AEs, clinical laboratory parameters, vital signs, electrocardiogram (ECG) parameters, and the use of concomitant medications.

Safety endpoints will be analysed based on the safety population.

10.1.Adverse Events

An AE is defined as any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, experienced by a patient during the clinical study or the specified safety follow-up period, regardless of relationship to study drug. Pre-existing conditions are not seen as AEs unless the condition worsens during the trial.

Treatment-emergent adverse events (TEAEs) are defined as AEs that commenced on or after the first study drug infusion. Events that started more than 30 days after the last study drug infusion will not be considered to be treatment-emergent.

Serious AEs (SAEs) are defined as AEs where the events are reported as ‘Serious’ (with a corresponding reason(s) indicating why the event is deemed to be serious).

Severe AEs are defined as AEs where the event severity rating is reported as ‘Severe’, ‘Life-Threatening or Disabling’ or ‘Death’.

Treatment-related AEs are defined as AEs where the relationship to study drug is reported as ‘Possibly Related’, ‘Probably Related’, ‘Related’ or is missing.

Adverse events leading to the premature discontinuation of study medication are defined as AEs the action taken was reported as ‘Study medication permanently discontinued’ on the Adverse Events eCRF page.

A DLT is defined as any AE possibly, probably, or definitely related to CRLX301 that meets the per protocol criteria for DLT (see Section 3.1.3 of the Protocol) and occurs at any point during Cycle 1 or the first 3 weeks post initiation of study drug infusion.

10.1.1.Biostatistical Methods

Adverse events will be summarised by study phase, dosing schedule/cohort.

All tables will present the number of patients who experienced an AE (count and percentage) and the actual number of AEs (counts only), within each specific category. Patients who experienced multiple AEs will only be counted once in each relevant category (SOC and PT),

but all events will be included in the event counts. System organ class terms will be sorted alphabetically, and PTs will be sorted alphabetically within SOCs. In addition to the summaries by the coded terms, the number of patients who experienced at least one TEAE during specific phase will be presented.

Tables will only include TEAEs.

The overall summary of TEAEs table will present the total number of patients who experienced a TEAE and the total number of TEAEs within each of the following categories:

- At least one TEAE
- At least one serious TEAE
- At least one DLT
- At least one severe TEAE
- At least one treatment-related TEAE
- At least one TEAE leading to the premature discontinuation of study medication.

The summary of TEAEs table will include the number of patients who experienced at least one TEAE and the corresponding number of events, and furthermore summarize the TEAE data by SOC and preferred term within SOCs.

The summary of SAEs table will include the number of patients who experienced at least one SAE and the corresponding number of SAEs, and furthermore summarize the SAE data by SOC and preferred term within SOCs.

The summary of DLTs table will include the number of patients who experienced at least one DLT and the corresponding number of DLTs, and furthermore summarize the DLT data by SOC and preferred term within SOCs.

The summary of Grade 3/4 (severity rating) treatment-related TEAEs table will include the number of patients who experienced at least one treatment-related severe or life-threatening or disabling TEAE and the corresponding number of TEAEs, and furthermore summarize the TEAE data by SOC and preferred term within SOCs.

The summary of TEAEs by worst severity tables will include the number of patients who experienced at least one TEAE, the number of patients who experienced at least one TEAE within each severity rating (‘Mild’, ‘Moderate’, ‘Severe’, ‘Life-threatening or Disabling’, ‘Death’) and the corresponding number of events within each rating. In addition, the TEAE data will be summarized by SOC, preferred term within SOC, and the severity rating within SOC/PT. Patients who experienced multiple AEs under a specific PT will only be counted once under the worst reported severity rating, but all events under the rating will be included in the event counts. System organ class terms will be sorted alphabetically, PTs will be sorted alphabetically within SOCs and severity ratings will be sorted in increasing order of severity within SOC/PT.

The summary of treatment-related TEAEs by worst severity rating tables will be similar to the corresponding TEAE tables, but will be based on the subset of patients who experienced treatment-related TEAEs.

The summary of TEAEs by strongest relationship to study drug (causality) tables will include the number of patients who experienced at least one TEAE, the number of patients who experienced at least one TEAE within each relationship category (‘Unrelated’, ‘Unlikely’ ‘Possibly’, ‘Probably’, ‘Related’) and the corresponding number of events within each category. In addition, the TEAE data will be summarized by SOC, preferred term within SOC, and relationship category within SOC/PT. Patients who experienced multiple AEs under a specific PT will only be counted once under the strongest reported relationship category, but all events under the category will be included in the event counts. System organ class terms will be

sorted alphabetically, PTs will be sorted alphabetically within SOCs and relationship categories will be sorted in increasing order of causality within SOC/PT.

The summary of treatment-related TEAEs by strongest relationship to study drug tables will be similar to the corresponding TEAE tables, but will be based on the subset of patients who experienced treatment-related TEAEs.

All information that was collected on the Adverse Events eCRF as well as the coded MedDRA terms will be included in the listings. Furthermore, the relative event start and stop days (refer to Section 3.1) will be presented where complete event start and stop dates are available.

In addition, DLTs, SAEs, AEs that lead to premature discontinuation of study medication and AEs of Special Interest will be listed separately.

10.2.Safety Laboratory Assessments

Blood and urine samples will be collected at the time points specified in the Schedule of Procedures (refer to the Protocol) to conduct hematology, chemistry, coagulation and urinalysis (including microscopy) analyses.

The following tests will be performed within each of the specified test panels:

- Hematology: White blood cell (WBC) count (with automated differential for absolute neutrophils, lymphocytes, monocytes, eosinophils, and basophils), red blood cell (RBC) count, haemoglobin, haematocrit, platelet count, and reticulocyte count.
- Chemistry: Sodium, potassium, calcium, chloride, glucose, blood urea nitrogen (BUN) or urea, creatinine, total protein, alkaline phosphatase, albumin, total bilirubin, direct and indirect bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), inorganic phosphorus, uric acid, cholesterol, triglyceride levels, and tryptase (only required if patient experience an infusion related reaction).
- Coagulation: Prothrombin time (PT), partial thromboplastin time (PTT), and international normalized ratio (INR).
- Urinalysis: Specific gravity, pH, protein, glucose, ketones, bilirubin, microscopy (red blood cells/high-power field, white blood cells/high-power field, and casts/low-power field), and blood.

The results for each laboratory parameter within the hematology, chemistry and coagulation test panels will be reported on the respective eCRF pages. The results will include the actual measurement/concentration, the unit of measure (if applicable), the lower and upper limits of the normal range for each specific test (if applicable), as well as a flag indicating whether the result is clinically significant or not (‘Yes’/’No’).

The urinalysis test results (‘Negative’, ‘Positive’) are reported on the Urinalysis eCRF page. For specific gravity and pH only, the results will include the actual measurement/concentration, the unit of measure (if applicable), the lower and upper limits of the normal range for each test (if applicable), as well as a flag indicating whether the result is clinically significant or not (‘Yes’/’No’).

10.2.1.Biostatistical Methods

All laboratory data collected at scheduled and unscheduled visits will be included in the listings, but only results collected as scheduled visits will be included in the summary tables.

Results for individual parameters may be reported in different units depending on the analyzing laboratory. If required, the results (and the corresponding normal range cut-off values) for individual parameters may be converted to S.I. units to summarize the data.

For the all parameters where a unit value has been reported, the parameter names that will be used in the outputs will comprise of the test name and the unit of measure, for example, 'Albumin (g/L)'. For the urinalysis parameters, the parameter name will be the reported test name only. Parameters will be sorted alphabetically within tables and listings.

For all parameters where a normal range limit value was reported, the normal range will be derived based on the available lower and upper limit values and any reported mathematical symbols. If both a lower and upper limit value is available, the normal range will be presented as '(Lower, Upper)'. If only one of the limit values exist, 'N/A' will be used to replace the 'missing' limit value (for example, '(N/A, Upper)'), unless a direction has been specified, in which case the normal range will be displayed as '(< or > Limit)'.

The reported results for each parameter with a defined normal range will be classified ('Low', 'Normal', 'High') in relation to the defined normal range limits. If a result is equal to the normal range cut-off value, the result will be considered 'Normal'.

The change from baseline values at each post-baseline visit will be calculated for all parameters with continuous results (except for specific gravity and pH).

The decimal precision to which the summaries for each parameter will presented will be based on the maximum number of decimals to which the reported result or the normal range limits are presented to in the raw data. The results and normal ranges will be displayed to the same decimal precision in the listings.

If a result for a parameter that is normally considered continuous is reported as a range (i.e., the result for basophils is reported as '<0.01' for a single time point), the result may be converted to a numeric value that is smaller than the reported result to contribute to the derivations and the summary statistics. Any conversion rules that are applied will be highlighted in the footnotes of the affected tables and listings. The original reported result value will however be included in the listing.

The summary of hematology, chemistry and coagulation results tables will present summary statistics for each laboratory parameter within the specific test panel. For each parameter, summaries will be presented for the baseline and each scheduled post-baseline visit. In addition, summaries will be presented for the change from baseline values at each scheduled post-baseline visit.

The summary of urinalysis table will present counts and percentages for the reported results at baseline and each post-baseline visit within each test parameter. Result categories will be order alphabetically, or in ascending order.

The summary of hematology, chemistry and coagulation result classifications tables will present summaries (counts and percentages) for the baseline and each scheduled post-baseline visit for each of the defined categories ('Low', 'Normal', 'High') within each parameter with a defined normal range, within the specific test panel.

The listings of haematology, chemistry and coagulation results will include all the information (fields) that was collected on the respective eCRF pages including the derived results classifications. In addition, the observations that were used as the baseline records (values) for each parameter will be flagged, and the change from baseline values at each post-baseline visit will be presented.

The listing of urinalysis data will include all the information (fields) that was collected on the Urinalysis eCRF page. In addition, the observation that was used as the baseline record (value) for each parameter will be flagged.

Separate listing that include only the subset of patients that had at least one abnormal result will also be created for each test panel. For the abnormal hematology, chemistry and coagulation results listings, all the results for every parameter where at least one 'Low' or 'High' classification was observed will be included. For the abnormal urinalysis results listing, all the results for every parameter where at least one result was reported as 'Positive' (or 'Low' or 'High' for specific gravity and pH) will be included.

10.3.Vital Signs Measurements

The following vital signs measurements were taken at the time points specified in the Schedule of Procedures (refer to the Protocol):

- Heart Rate (beats/min)
- Systolic blood pressure (SBP) (mmHg)
- Diastolic blood pressure (DBP) (mmHg)
- Respiratory rate (breaths/min)
- Temperature (C)
- Height (cm)
- Weight (kg)
- BSA (m^2)
- BMI (kg/m^2)

The results for each parameter were reported on the Vital Signs eCRF page.

10.3.1.Biostatistical Methods

All vital signs data collected at scheduled and unscheduled visits will be included in the listings, but only results collected as scheduled visits will be included in the summary tables.

The parameter names that will be used in the outputs will comprise of the test name and the unit of measure, for example, 'Systolic Blood Pressure (mmHg)'. Parameters will be sorted in the order that the measurements were collected in on the Vital Signs eCRF page within the tables and listings.

The change from baseline to the pre-dose assessment at each post-baseline visit will be calculated for all parameters. In addition, the change from the pre-infusion value to each post-infusion time point (i.e., 30 minutes after infusion) will be calculated for heart rate, SBP, DBP, and respiratory rate where vital signs were collected during and after the infusion period.

The decimal precision to which the summaries for each parameter will presented will be based on the maximum number of decimals to which the results were reported on the eCRF.

The summary of vital signs measurements table will present summary statistics for the results at the baseline and each scheduled post-baseline visit for each of the parameters (excluding height, weight, BSA and BMI). In addition, summaries will be presented for the change from baseline values at each scheduled post-baseline visit.

The summary of vital signs measurements collected during the infusion period table will present summary statistics for the results at the pre-infusion and each scheduled post-infusion time point for each of the parameters (excluding temperature, height, weight, BSA and BMI), at each visit. In addition, summaries will be presented for the change from the pre-infusion values at each scheduled post-infusion time points at the specific visit.

The summary of body measurements table will present summary statistics for the results at the baseline and each scheduled post-baseline visit for height, weight, BSA and BMI. In addition, summaries will be presented for the change from baseline values at each scheduled post-baseline visit.

The listings of vital signs measurements and body measurements will include all the information (fields) that was collected on the Vital Signs eCRF page. In addition, the observations that were used as the baseline record (value) for each parameter will be flagged, and the change from baseline values at each post-baseline visit will be presented.

The listing of vital signs measurements collected during the infusion period will include all the information (fields) that was collected on the Vital Signs eCRF page. In addition, the change from the pre-infusion values at each post-baseline visit will be presented.

10.4.Echocardiogram (ECG) Measurements

The following echocardiogram (ECG) measurements were taken at the time points specified in the Schedule of Procedures (refer to the Protocol):

- Heart Rate (beats/min)
- PR Interval (msec)
- QRS Duration (msec)
- QT Interval (msec)
- QTcF (msec)
- ECG Result (overall interpretation)

The results for each parameter were reported on the ECG eCRF page.

10.4.1.Biostatistical Methods

All ECG data collected at scheduled and unscheduled visits will be included in the listings, but only results collected as scheduled visits will be included in the summary tables.

The parameter names that will be used in the outputs will comprise of the test name and the unit of measure (where applicable), for example, ‘Heart Rate (mmHg)’. Parameters will be sorted in the order that the measurements were collected in on the ECG eCRF page within the tables and listings.

The decimal precision to which the summaries for each parameter will presented will be based on the maximum number of decimals to which the results were reported on the eCRF.

The summary of ECG measurements table will present summary statistics for the results at the baseline and each scheduled post-baseline visit/time point for each of the parameters (excluding the overall interpretation). In addition, summaries will be presented for the change from baseline values at each scheduled post-baseline visit/time point.

The summary of overall ECG interpretation results table will present counts and percentages for the reported results at baseline and each post-baseline visit/time point. Result categories will be order as ‘Normal’, ‘Abnormal NCS’ and ‘Abnormal CS’.

The listing of ECG measurements will include all the information (fields) that was collected on the ECG eCRF page apart from the overall interpretation results. In addition, the observations that were used as the baseline record (value) for each parameter will be flagged, and the change from baseline values at each post-baseline visit/time point will be presented.

The listing of overall ECG interpretation results will include all the information (fields) that was collected on the ECG eCRF page. In addition, the observations that were used as the baseline record (value) will be flagged.

10.5.Eastern Cooperative Oncology Group (ECOG) Performance Status

The ECOG performance status was assessed at the time points specified in the Schedule of Procedures (refer to the Protocol) and the findings were reported on the ECOG SCAN eCRF page.

10.5.1.Biostatistical Methods

All ECOG data collected at scheduled and unscheduled visits will be included in the listings, but only results collected as scheduled visits will be included in the summary tables.

The summary of ECOG performance status table will present counts and percentages for the reported results at baseline and each post-baseline visit.

The listing ECOG performance status results will include all the information (fields) that was collected on the ECOG SCAN eCRF page. In addition, the observations that were used as the baseline record (value) will be flagged.

10.6.Concomitant Medications

Prior medications are defined as any medication where the use was stopped prior to the first application of study drug.

Concomitant medications are defined as any medication (other than the study drug) that was used at least once after the first infusion of study drug. Medications that were stopped on the same date as the first study drug infusion will be analysed as concomitant medications. If a clear determination cannot be made (partial medication end dates) the medication will be classified as concomitant. Medications that were started after the End of Study visit will not be considered to be concomitant medications in the summary table.

Premedications are defined as medications that are administered as a precaution to minimize the risk and/or severity of infusion-related hypersensitivity reactions. Premedications will be medications where the indication was specified as ‘Premedication’ on the Concomitant Medication eCRF page.

10.6.1.Biostatistical Methods

Concomitant mediations will be summarised by ATC Level 3 terms and by PT within the ATC ter. Within each category, the number of patients who used the medication (count and percentage) will be presented. Patient who used the same medication on multiple occasions will only be counted once in the specific category (ATC or PT). Anatomical Therapeutic Chemical terms will be sorted alphabetically, and PTs will be sorted alphabetically within ATC term. In addition to the summaries by the coded terms, the number of patients who used at least one concomitant medication during the study will be presented.

All information that was collected on the Concomitant Medication eCRF as well as the coded WHO-DD terms will be included in the listings. Furthermore, the relative medication start and stop days (refer to Section 3.1) will be present where complete medication start and stop dates are available.

Prior medications (history of medication use) will be listed as part of the baseline characteristics. Concomitant medications and pre-medications will be listed separately.

11.Pharmacokinetic Concentrations

The derivation of PK parameters and a formal PK analysis does not fall within the scope of this SAP.

All information collected on the PK and Biomarker Samples eCRF page will be listed. If available, the actual concentration results from the PK laboratory will be included in the listings.

Separate listings will be produced for blood and urine PK data.

12.Changes to the Planned Analysis

Due to the early termination of the study and the decision that only an abbreviated CSR will be produced, the efficacy and PK analyses proposed in the study protocol will not be performed.

13.Interim and Final Analysis

13.1.Interim Analyses

No interim analyses are planned for the study.

13.2.Final Analysis (End of Study)

The final analysis will be conducted after all patients have completed the study, the clinical database has been locked, and the analysis populations have been approved.

The final analysis will be based on the final version of the SAP. Any deviations from the planned analysis will be documented in the CSR.

14.Software

The following software will be used to perform the statistical analyses:

- SAS® Version 9.4 or higher (SAS Institute, Cary, North Carolina, USA)

15.Tables

No.	Title	Analysis Populations
Table 14.1.1	Patient Enrollment and Disposition	Safety
Table 14.1.2	Demographics	Safety
Table 14.2.1	Best Overall Tumor Response	Safety
Table 14.3.0	Study Drug Exposure	Safety
Table 14.3.1.1	Overall Summary of Treatment-Emergent Adverse Events	Safety
Table 14.3.1.2.1	Incidence of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	Safety
Table 14.3.1.2.2	Incidence of Serious Adverse Events by System Organ Class and Preferred Term	Safety
Table 14.3.1.2.3	Incidence Dose Limiting Toxicities by System Organ Class and Preferred Term	Safety
Table 14.3.1.3	Incidence of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst Severity Rating	Safety
Table 14.3.1.4	Incidence of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Strongest Relationship to Study Drug	Safety
Table 14.3.1.5.1	Incidence of Treatment-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	Safety
Table 14.3.1.5.2	Incidence of Treatment-Related Serious Adverse Events by System Organ Class and Preferred Term	Safety
Table 14.3.1.6	Incidence of Treatment-Related Treatment-Emergent CTCAE Grade 3/4 Adverse Events by Treatment, Preferred Term	Safety
Table 14.3.2.1.1	Hematology Results (Summary of Actual and Change from Baseline Values)	Safety
Table 14.3.2.1.2	Hematology Result Classifications	Safety
Table 14.3.2.2.1	Chemistry Results (Summary of Actual and Change from Baseline Values)	Safety
Table 14.3.2.2.2	Chemistry Result Classifications	Safety
Table 14.3.2.3.1	Coagulation Results (Summary of Actual and Change from Baseline Values)	Safety
Table 14.3.2.3.2	Coagulation Result Classifications	Safety
Table 14.3.2.4	Urinalysis Results	Safety
Table 14.3.3.1	Vital Signs Measurements (Summary of Actual and Change from Baseline Values)	Safety
Table 14.3.3.2	Vital Signs Measurements During Infusion Period (Summary of Actual and Change from Pre-Infusion Values)	Safety
Table 14.3.3.1	Body Measurements (Summary of Actual and Change from Baseline Values)	Safety
Table 14.3.4.1	12-Lead Electrocardiogram (ECG) Measurements (Summary of Actual and Change from Baseline Values)	Safety
Table 14.3.4.2	12-Lead Electrocardiogram (ECG) Overall Interpretation	Safety
Table 14.3.5	Eastern Cooperative Oncology Group (ECOG) Performance Status	Safety
Table 14.3.6	Concomitant Medications by Anatomical Therapeutic Chemical Class and Preferred Term	Safety

16.Listings

No.	Title	Analysis Populations
Listing 14.3.2.1	Deaths	Safety
Listing 14.3.2.2	Serious Adverse Events	Safety
Listing 14.3.2.3	Adverse Events Leading to Permanently Discontinuation of Study Medication	Safety
Listing 14.3.2.4	Dose-Limiting Toxicities	Safety
Listing 14.3.2.5	Deaths within 30 Days of Last Study Drug Infusion	Safety
Listing 16.1.7	Assignment to Treatment	Safety
Listing 16.2.1.1	Analysis Populations	Safety
Listing 16.2.1.2	Patient Disposition	Safety
Listing 16.2.1.3	Follow-Up Status	Safety
Listing 16.2.2	Protocol Deviations	Safety
Listing 16.2.4.1	Demographics and Baseline Data	Safety
Listing 16.2.4.2	Baseline Patient Characteristics	Safety
Listing 16.2.4.3	Oncology History	Safety
Listing 16.2.4.4	Medical History	Safety
Listing 16.2.4.5	Prior Anti-Neoplastic Surgery	Safety
Listing 16.2.4.6	Prior Anti-Neoplastic Therapy Medications	Safety
Listing 16.2.4.7	Prior Anti-Neoplastic Radiotherapy	Safety
Listing 16.2.4.8	Prior Medications	Safety
Listing 16.2.4.9	Echocardiogram (ECHO) and Multiple Gated Acquisition (MUGA) Scan Results	Safety
Listing 16.2.4.10	Head Computed Tomography (CT)/ Magnetic Resonance Imaging (MRI) Scan Results	Safety
Listing 16.2.4.11	Pregnancy Test Results	Safety
Listing 16.2.4.12	Patient Eligibility	Safety
Listing 16.2.5.1	Premedications	Safety
Listing 16.2.5.2	Study Drug Infusions	Safety
Listing 16.2.5.3	Study Drug Exposure	Safety
Listing 16.2.5.4	Blood Pharmacokinetic CRLX301 Concentrations	Safety
Listing 16.2.5.5	Urine Pharmacokinetic CRLX301 Concentrations	Safety
Listing 16.2.6.1.1	Target Tumor Assessments	Safety
Listing 16.2.6.1.2	Non-Target Tumor Assessments	Safety
Listing 16.2.6.1.3	New Lesion Assessments	Safety
Listing 16.2.6.2	Overall Tumor Response	Safety
Listing 16.2.6.3	Bone Scan Results	Safety
Listing 16.2.6.4	Prostate-Specific Antigen (PSA) Results	Safety
Listing 16.2.6.5	Tumor Markers	Safety
Listing 16.2.7.1	Adverse Events	Safety
Listing 16.2.7.2	Adverse Events of Special Interest	Safety
Listing 16.2.8.1	Hematology Results	Safety
Listing 16.2.8.2	Abnormal Hematology Results	Safety
Listing 16.2.8.3	Chemistry Results	Safety
Listing 16.2.8.4	Abnormal Chemistry Results	Safety
Listing 16.2.8.5	Coagulation Results	Safety
Listing 16.2.8.6	Abnormal Coagulation Results	Safety
Listing 16.2.8.7	Dipstick Urinalysis Results	Safety
Listing 16.2.8.8	Abnormal Dipstick Urinalysis Results	Safety
Listing 16.2.8.9	Urine Microscopy Results	Safety
Listing 16.2.9.1.1	Vital Signs Measurements	Safety

No.	Title	Analysis Populations
Listing 16.2.9.1.2	Vital Signs Measurements During Infusion Period	Safety
Listing 16.2.9.1.3	Body Measurements	Safety
Listing 16.2.9.2.1	12-Lead Electrocardiogram (ECG) Measurements	Safety
Listing 16.2.9.2.2	12-Lead Electrocardiogram (ECG) Overall Interpretation	Safety
Listing 16.2.9.3	Eastern Cooperative Oncology Group (ECOG) Performance Status	Safety
Listing 16.2.10	Concomitant Medications	Safety