PROTOCOL NUMBER: **CRLX301-101**

TITLE: ***Phase 1/2a Dose-Escalation Study of CRLX301 in Patients with Advanced Solid Tumor Malignancies***

STUDY PHASE: **Phase 1 and Phase 2a**

INVESTIGATIONAL PRODUCT: **CRLX301**

SPONSOR: **CERULEAN PHARMA AUSTRALIA PTY LTD**

[redacted]

CERULEAN PHARMA INC (parent company)

[redacted]

STUDY DIRECTOR: [redacted]
Senior VP and Chief Medical Officer, Cerulean Pharma Inc.

SAFETY MEDICAL MONITOR: [redacted]
Novotech, Sydney, Australia

PROTOCOL REVISION: **AMENDMENT 9**

VERSION DATE: **16-December-2016**

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(see confidentiality statement page 3)

SPONSOR PROTOCOL SIGNATURE PAGE

This Amendment 9 of the protocol number CRLX301-101 has been prepared and reviewed by the Sponsor for distribution to designated clinical sites, associated Ethics Committees / Institutional Review Boards, designated contractors, regulatory agencies, and with permission by the Sponsor. This version of the protocol and shall supersede the previous version of the specified protocol.

	22-Dec-16
Sponsor Signature	*Date*

[redacted]
Senior VP and Chief Medical Officer Cerulean Pharma Inc.

CONFIDENTIALITY STATEMENT

This document contains confidential information that is proprietary to Cerulean Pharma Australia PTY LTD and Cerulean Pharma Inc. (Cerulean). You may only disclose the contents to study personnel under your supervision who need to know the contents for the purpose of conducting a clinical study, in addition to your Ethics Committee (EC) or Institutional Review Board (IRB) or other Committees for evaluation of the investigational drug as appropriate under the following condition: the contents of this document must remain confidential and may not be disclosed to any other person or entity without prior written permission from Cerulean. This will not apply to disclosure that is required by governmental regulations or laws; however, you must promptly notify Cerulean of any such disclosure. Any supplemental information that may be added or appended to this document is also confidential and proprietary to Cerulean and must be treated in the same manner.

INVESTIGATOR ACKNOWLEDGEMENT

I have received and read the Investigator's Brochure for CRLX301 and this protocol number CRLX301-101, including all appendices, and agree to make all reasonable efforts to adhere to the protocol. I agree to conduct the study in compliance with all applicable Health Authority regulations (including 21 CFR Parts 312, 50 and 54), ICH Good Clinical Practice (GCP), and any locally applicable regulations. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

I agree that, prior to the commencement of this study, I must obtain all required Institutional approvals including Independent Ethics Committee/ Institutional Review Board associated with the clinical facility where the study will be conducted for this protocol and the informed consent document.

I will provide all study personnel under my supervision with copies of this protocol, the CRLX301 Investigator's Brochure, and access to all study-related information provided by the Sponsor and designated CRA. I will discuss this study-related information with my staff to ensure that they are fully informed about the investigational product and the protocol.

I agree to provide all patients with a signed and dated copy of the informed consent document, as required by FDA regulations and ICH GCP. I further agree to report to Cerulean any adverse events in accordance with the terms of this protocol, as per the applicable regulations from US FDA regulation 21 CFR 312.64 and from TGA in Australia where applicable.

Principal Investigator Printed Name	Site Number
Principal Investigator Signature	Date

SAFETY REPORTING AND CONTACT IN CASE OF EMERGENCY

CONTACT PAGE VERSION DATED: 16 December 2016 (Version 7)

Reporting Serious Adverse Event

Any death or serious adverse event (SAE)* occurring in a patient while receiving study drug (investigational medicinal product) or within 30 days of receiving study drug, even though the event may not appear to be study-drug related, **must be promptly reported** (within 24 hours) to the **24-Hour Emergency and SAE Submission Line.** Ensure that the event is identified on the reporting form as "serious" (see definitions below).

SAE IMMEDIATE NOTIFICATION METHODS		
24-Hour Emergency and SAE Submission Line	**SAE REPORT FORM SUBMISSION email or fax**	Submit paper SAE Form to email: [redacted] OR [redacted]

Contact for Urgent Medical or Eligibility Questions

For urgent medical study questions or patient eligibility questions, contact by telephone or email the **Study Safety Medical Monitor** and/or the alternative contacts. Responses will be provided within 24 hours.

EMERGENCY CONTACT INFORMATION		
Role in Study	**Contact Name**	**Email Address / Telephone**
Study Designated Safety Medical Monitor **All Sites/Regions**	[redacted]	[redacted]
Study Designated Project Manager	**See Investigator Site File**	**See Investigator Site File**
Cerulean Sponsor Study Medical Director **(Also safety contact back-up for US sites)**	[redacted]	[redacted]
Cerulean Sponsor Study Back-up Medical Director	[redacted]	[redacted]

DEFINITIONS FOR SAFETY REPORTING

SERIOUS ADVERSE EVENT CRITERIA*
A serious adverse event is any untoward medical occurrence that at any dose results in any of the following outcomes, regardless of relationship to study drug (see Section 8.4: Recording Adverse Events): • Death • Life-threatening • Inpatient hospitalization or prolongation of existing hospitalization • A persistent or significant disability/incapacity • A congenital anomaly/birth defect An important medical event that may jeopardize the patient and may require medical or surgical intervention to prevent any of the outcomes listed above should be reported following the SAE procedures.
SERIOUS UNEXPECTED SUSPECTED ADVERSE REACTIONS CRITERIA**
An unexpected adverse reaction is any untoward and unintended responses to an investigational product related to any dose administered, of which the nature, or severity, is not consistent with the available applicable product information. All **suspected adverse reactions** which occur during the study and that are **both unexpected and serious** (SUSARs) must be submitted to the Study Safety Medical Monitor via the expedited reporting procedures above.

PROTOCOL SYNOPSIS

Name of sponsor/company: CERULEAN PHARMA AUSTRALIA PTY LTD / CERULEAN PHARMA INC (parent company)

Name of investigational product: CRLX301

Title of study: Phase 1/2a Dose-Escalation Study of CRLX301 in Patients with Advanced Solid Tumor Malignancies

Study Number: CRLX301-101

Number of study center(s): approximately **7**

Study duration: approximately 3 years • Date first patient enrolled: December 2014 • Estimated date last patient completed: January 2018	**Phase of development:** Phase 1 includes: Schedule 1 (Q3W) and Schedule 2 (QW, no break or QW, 3 week on/1 week off, depending on enrollment cohort) dose escalation to establish maximally tolerated dose (MTD) / Recommended Phase 2 dose (RP2D) Phase 2a includes: Q3W and QW Stage 1 MTD/RP2D expansion and Stage 2 expansion

Objectives:

Study objectives are as follows:

Primary Study Objectives

Phase 1:

- To determine MTD / RP2D of CRLX301 when administered by intravenous (IV) infusion on Schedule 1 (Q3W: 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

Phase 2a:

- To further establish the safety and tolerability of the CRLX301 MTD / RP2D

Secondary Study Objectives

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

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Exploratory Study Objectives

- To evaluate the pharmacodynamic activity of CRLX301 in the blood and tumor biopsy specimens when available from patients
- To explore possible correlations between clinical response and/or toxicities with 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

Methodology:

Phase 1: Schedule 1 (Q3W) is an, open-label, 1+5 followed by classic 3+3 dose-escalation study with enrollment to continue until determination of the MTD/RP2D. Schedule 2 (QW, no break or QW, 3 week on/1 week off, depending on enrollment cohort*) is an open-label 3+3 dose escalation study with enrollment to continue until determination of the MTD /RP2D.

- For Schedule 1 only, patients were accrued in a step-wise manner into two initial cohorts of only 1 patient each. Since the patient in the first cohort of 7.5 mg/m^2 did not experience a dose limiting toxicity (DLT) in Cycle 1, the protocol allowed proceeding to the next cohort level of 15 mg/m^2. Starting at cohort 3 for Schedule 1 at 30 mg/m^2, a minimum of 3 patients will be enrolled in all subsequent cohorts.
- For Schedule 2, a minimum of 3 patients will be enrolled for all planned cohorts. If a patient in any Phase 1 escalation cohort experiences a DLT during the first 3 weeks for either schedule, then the cohort will be expanded to sequentially enroll additional patients up to a total of 6 who complete 3 weeks of treatment as per assigned Schedule.
- A DLT is a treatment-emergent adverse event (TEAE) attributed to be at least possibly related to the investigational product in the first 3 weeks post-initiation of study drug infusion in either schedule and that meets the criteria for DLT as defined in the protocol. Enrollment in a Phase 1 dose cohort will be halted immediately when ≥2 patients within the same cohort experience a DLT during the first 3 weeks. The study Safety Review Committee (SRC) will review, at a minimum, the safety data at the end of Cycle 1 (3 weeks) for Schedule 1, or Week 3 for Schedule 2, for all cohorts to confirm DLTs and to determine if dose escalation should occur and at what dose level.

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The MTD is defined as the highest dose level at which fewer than 2 out of 6 patients experiences a DLT during Cycle 1 or the first 3 weeks.

***NOTE:** As of Amendment 9, for patients still receiving treatment in Schedule 2 Cohort 3 (45mg/m^2), and for patients enrolled in Schedule 2 Cohort 4 (54mg/m^2), dosing will be on a once weekly, 3 week on/1 week off schedule. The dosing schedule for additional Schedule 2 cohorts will be determined by the SRC. A single MTD/RP2D will be determined for Schedule 2. See Section 1.8.3:Rationale for Evaluation of QW, 3 week on/1 week off for Schedule 2.

Phase 2a: Stage 1 of Phase 2a will initiate when either dosing schedule determines the MTD/RP2D. For Stage 1, up to 16 patients will be enrolled into an expansion cohort for each dosing schedule at RP2D to further explore the safety and PK profile of CRLX301. Stage 2 of Phase 2a will initiate when Stage 1 expansion is complete for both dosing schedules. For Stage 2, the preferred dosing schedule (i.e., either Schedule 1 or 2) will be used for enrollment into additional RP2D expansion cohort of up to 36 patients.

Number of patients enrolled: Up to 134

Phase 1: Up to 66 evaluable patients are anticipated to be enrolled in the Phase 1 dose escalation cohorts (up to 36 patients in Schedule 1 (Q3W); up to 30 patients in Schedule 2 (QW, no break or QW, 3 week on/1 week off)). The exact number of patients is dependent on the actual patients per cohort and number of cohorts investigated in each dosing schedule. Patients who do not complete a minimum of 3 weeks of treatment and do not experience a DLT will be replaced.

Phase 2a: Up to 68 patients will be enrolled in Phase 2a RP2D expansion cohort(s) (up to 32 patients for Stage 1 and up to 36 patients for Stage 2).

Diagnosis and main criteria for inclusion:

Patients must meet the following criteria for inclusion:

1. Male or female adult patients ≥18 years of age
2. Diagnosis of histologically or cytologically confirmed, advanced solid tumor malignancy:
    a. For Phase 1: that is refractory to standard therapy and/or for whom no further standard therapy is available, especially for those for whom taxane chemotherapy may be a reasonable therapeutic choice, in the opinion of the Investigator.
    b. For Phase 2a: advanced/metastatic tumors considered responsive to taxanes
    c. For prostate cancer patients in Phase 2a: that is castration resistant prostate

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cancer (CRPC*) and has not been previously treated with taxanes (taxane-naïve [unless approved by Sponsor]) but has been treated with abiraterone and/or enzalutamide. ***NOTE:** CRPC is defined as:

i. **Castration:** Undergone surgical castration, or medical castration with testosterone < 50ng/dL

ii. **Resistant**: Disease progression while castrate with radiographic progression defined by Prostate Cancer Working Group 2 (PCWG2) criteria, **OR** disease progression defined as rise in PSA in subjects with baseline PSA of at least 2 ng/mL, **OR** disease progression as per RECIST1.1.

3. For patients enrolled in Phase 2a only: at least one measurable target lesion as defined by RECIST 1.1 criteria for solid tumors, except for patients with advanced prostate cancer (in which case as per the PCWG2 criteria). Tumors within a previously irradiated field should be designated as “non-target” unless progression is documented or a biopsy is obtained to confirm persistence at least 90 days following completion of radiation therapy.
4. If Patient has received:
    a. approved chemotherapy or small molecule targeted therapy; it has been ≥2 weeks since last dose before CRLX301 first dose (hereafter referred to as "first dose")
    b. investigational therapy; it has been ≥30 days before first dose
    c. local palliative radiation; it has been ≥14 days prior to first dose
    d. radiation or invasive surgery requiring general anesthesia; it has been ≥30 days prior to first dose
    e. chemotherapy with nitrosoureas or mitomycin C; it has been ≥45 days before first dose
5. ECOG Performance Status of 0 or 1
6. Life expectancy in opinion of Investigator of >12 weeks

7. Patients with acceptable pre-study hematology and biochemistry labs ≤3 days prior to first dose defined as:
    a. absolute neutrophil count (ANC) ≥1500 cells/µL (1.5 x10^9/L), without growth factor support
    b. platelet count ≥100,000 cells/µL (100 x10^9/L), without growth factor support
    c. hemoglobin ≥10 g/dL (100 g/L) for males, and ≥9 g/dL (90 g/L) for females
    d. total bilirubin within normal limits (WNL)
    e. AST/ALT ≤1.5 x upper limit of normal (ULN)
    f. serum creatinine ≤1.5 ULN or 24-hour clearance ≥40 mL/min
    g. PT/PTT ≤1.2 x ULN
8. Contraception requirements:
    a. Women of child-bearing potential, defined as women physiologically capable of becoming pregnant, must use highly effective methods of contraception during study treatment and for 30 days after the last dose of study treatment. Highly effective methods of contraception include:
        i. Total abstinence (when this is the preferred and usual lifestyle of the subject). Withdrawal and periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) are not acceptable methods of contraception.
        ii. Female sterilization (defined as having had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy, or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
        iii. Male sterilization for at least 6 months prior to screening. The vasectomized male partner should be the sole partner for that subject.
        iv. Use of oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception. In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment.
    b. Male subjects must use condoms during the study treatment period and for 120 days following the last dose of study drug.
9. Negative urine pregnancy test ≤3 days prior to first dose (women of childbearing potential only)

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10. Ability to understand and willingness to sign a written informed consent form
11. Able to comply with study visit schedule and assessments

Patients will be excluded for the following:

1. Uncontrolled grade 2 or greater toxicity except alopecia related to any prior treatment (i.e. chemotherapy, targeted therapy, radiation or surgery) within 7 days prior to C1D1 unless approved by the Medical Monitor
2. Prolongation of QT/QTc interval (QTc interval >450 msec. for males and >470 msec. for females) using the Fredericia method of QTc analysis. If single reading is above these minimum ranges, then repeat test in triplicate and evaluate eligibility based on average value
3. Women who are pregnant or nursing
4. Any known HIV infection or AIDS or any concurrent infection requiring IV antibiotics
5. Any chronic or concurrent acute liver disease, including viral hepatitis
6. Primary brain malignant tumors
7. Known metastases to the brain:
    a. CNS confirmed by CT requiring treatment or radiation therapy, or that have
    b. not been confirmed stable on imaging for ≥30 days prior to first dose
8. Uncontrolled hypertension >150 (systolic) and >100 (diastolic) mmHg
9. Concurrent participation in any other investigational study, unless non-interventional study and approved by Sponsor
10. Concurrent treatment with the following medication, unless approved by Sponsor:
    a. Anticoagulant
    b. Tubulin binding agents (e.g. colchicine)
    c. Strong CYP3A4 inhibitors (Appendix C)
11. History of stroke, deep venous thrombosis (DVT), transient ischemic attack (TIA), or myocardial infarction, within 6 months prior to first dose

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12. History of other cancer type, except for cutaneous basal cell or squamous cell carcinoma, or cervical in situ or very low/low risk prostate cancer within the last 2 years prior to first dose
13. Uncontrolled concurrent disease or illness including but not limited to:
    a. symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia
    b. unstable or untreated cardiac conditions or ejection fraction of <50% as determined by echocardiogram (ECHO) or multiple gated acquisition scan (MUGA); **NOTE:** ECHO or MUGA required at screening only in subjects with known history of cardiac insufficiency **and** symptomatic within 3 months prior to screening.
    c. diabetes mellitus
    d. coagulation disorder
    e. psychiatric illness that would limit compliance with study requirements, as determined by the Investigator
14. History of severe hypersensitivity reaction to taxanes
15. For Phase 2a Stage 2: treatment with a taxane within 6 months of first dose; **NOTE:** advanced prostate cancer patients must be taxane-naïve
16. Peripheral neuropathy defined as one or more of the following unless approved by the Sponsor:
    a. Active peripheral neuropathy within 30 days prior to first dose defined as:
        i. Motor neuropathy of any grade (e.g., distal extremity weakness, loss of deep tendon reflex)
        ii. ≥Grade 2 neurosensory symptoms (e.g., pain, numbness, paresthesia, dysesthesia, etc.)
    b. History of ≥ Grade 3 neurologic reactions to prior chemotherapy; in particular, any neurological reactions that required a dose reduction or discontinuation from prior taxane therapy.
17. Other severe, acute, or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or study drug administration or that may interfere with the interpretation of study results and,

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in the judgment of the investigator, would make the patient inappropriate for the study.
Investigational product, dosage and mode of administration: CRLX301 patients will receive an intravenous infusion of CRLX301 on either Dosing Schedule 1: Day 1 of a 21-day cycle (Q3W) or Dosing Schedule 2: weekly dosing (QW, no break or QW, 3 week on/1 week off dosing, depending on enrollment Cohort), and will continue the treatment schedule until progression of disease or unacceptable toxicity (see Section 6.1: Reasons for Discontinuation from Treatment). In Phase 1, the initial dose per patient will be determined by their enrollment Cohort and assigned dosing schedule according to the protocol dosing scheme. Phase 2a patients will all be dosed at the MTD/RP2D for either dosing schedule in Stage 1 and at the preferred dosing schedule at RP2D for Stage 2.
Duration of Treatment: 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 other specified reason for discontinuation (Section 6.1: Reasons for Discontinuation from Treatment).
Reference therapy, dosage and mode of administration: All patients will receive CRLX301 via an intravenous infusion over approximately 120 minutes.
Criteria for evaluation: **Dose Limiting Toxicities**: 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: Definition of Dose-Limiting Toxicity) and occurs at any point during Cycle 1 or the first 3 weeks post-initiation of study drug infusion. The event must be assessed by the Investigator and Safety Medical Monitor and/or Study Director, and be determined to be unrelated to disease progression, intercurrent illness, or concomitant medications. All DLTs will be graded according to the current version of the National Cancer Institute's (NCI) Common Terminology Criteria for Adverse Events (CTCAE 4.03). **Safety:** Safety variables will include AEs, clinical laboratory parameters, vital signs, and ECG parameters. For each safety parameter, the last assessment made before the first dose of the investigational product for each period will be used as the baseline for all analyses of that safety parameter.

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Pharmacokinetic evaluation:

Schedule 1 (Q3W):

Plasma and urine samples for (PK) evaluation will be collected from Phase 1 and Phase 2a Stage 1 patients during Cycle 1 and from available patients in Cycle 3 and Cycle 6 as per the schedule defined in Section 5.13: Pharmacokinetic Sample Collection.

If Schedule 1 is selected for Phase 2a Stage 2 expansion, patients will have plasma samples collected using the same schedule defined in Phase 1 until up to 10 patients have undergone PK collection at RP2D during both Cycle 1 and a repeat dose in either Cycle 3 and/or Cycle 6.

Schedule 2 (QW, no break or QW, 3 week on/1 week off):

Plasma and urine samples for PK evaluation will be collected from Phase 1 and Phase 2a Stage 1 patients during Week 1 and from available patients in Weeks 2 through 8 as per the schedule defined in Section 5.13: Pharmacokinetic Sample Collection.

If Schedule 2 is selected for Phase 2a Stage 2 expansion, patients will have plasma samples collected using the same schedule defined in Phase 1 until up to 10 patients have undergone PK collection at RP2D during both Week 1 and a repeat dose during Week 4 or Week 7 if the QW, no break dosing schedule is selected or during both Week 1 and a repeat dose during Week 3 or Week 7 if the QW, 3 week on/1 week off dosing schedule is selected.

Disease status: Disease status will be evaluated at screening and every 8-9 weeks for both dosing schedules while on study treatment (until disease progression) by CT scan, or by alternative methodologies consistent with tumor type and reviewed by Medical Monitor. See **Follow Up** for required tumor evaluations in patients who discontinue from study treatment for reasons other than progression.

Tumor marker disease evaluation: Tumor marker data to evaluate disease status are collected only if appropriate for tumor-type and if feasible per Investigator discretion.

Efficacy: Tumor response evaluations will be performed by either following RECIST guidelines, version 1.1 or alternative methodologies consistent with tumor type (e.g., PCWG2 criteria for prostate cancer). Tumor assessments by imaging methodology should be completed every 9 weeks for Schedule 1 and for QW, no break cohorts in Schedule 2. As of Amendment 9, tumor assessments by imaging methodology should be completed every 8 weeks for QW, 3 week on/1 week off cohorts in Schedule 2. At investigator discretion, imaging should be repeated 3-4 weeks after a partial or complete response is observed. PSA assessment for Phase 2a prostate cancer patients should be done every 3-4 weeks. See **Follow Up** for required tumor evaluations in patients who discontinue from study treatment for reasons other than progression.

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Additional blood collection for biomarker research: Additional blood samples will be collected from all Phase 2a patients for additional biomarker research. Additionally, remaining plasma from PK samples from all patients who agree will be used for additional research for the same purposes.

Additional blood collection for pharmacodynamic research: In Phase 2a Stage 1 only, blood samples will be collected for isolation of circulating tumor cells (CTCs) and for mononuclear phagocytic system (MPS) function testing. CTC isolation will explore the utility of comparing the integrity of microtubule skeleton in CTCs from pre- and post-treatment patient samples as a potential read-out of CRLX301 PD activity. MPS function test will explore potential drug clearance in addition to renal and hepatic clearance of the study drug.

Optional tumor tissue collection for research: Archived tumor tissue and pre- and post-dose tumor biopsy will be collected, as available, from all patients who consent to these optional collections. The tissue will be used for additional research to include exploration of markers for efficacy (e.g. proliferation, apoptosis, and cell cycle) and CRLX301 localization; it may also include genetic testing related to the cancer diagnosis for research purposes only, no other genetic testing will be performed.

Discontinuation: Eligible patients who are enrolled into the study will be discontinued from study treatment if any of the following occur:

- Documented radiographic or clinical 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 treatment despite disease progression
- Grade 4 hypersensitivity/infusion related reaction (may also be discontinued for Grade 3; see Table 7)
- AE with clinically unacceptable toxicities (unless there is evidence of sustained therapeutic benefit and the investigator believes it is in the patient's best interest to continue the treatment despite the toxicity) including:
  - unresolved related AE $\geq$Grade 2 that causes a delay of >21 days to initiation of next dose of CRLX301 (both dosing schedules)
  - bilirubin >1.2 ULN, or AST and/or ALT >1.5 × ULN concomitant with alkaline phosphatase >2.5 × ULN; if either of these are unresolved for >21 days from planned next dose
  - any other clinically unacceptable toxicity (in agreement with the study Medical Monitor)
- Withdrawal of consent

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- Subject non-compliance with study schedule
- Protocol violation (including lack of compliance or excessive deviations with study schedule) in agreement with the Sponsor/Medical Monitor and/or Study Director
- Lost to follow-up (after repeated attempts for >30 days have been made to contact the patient including letters sent by registered mail)
- Request for discontinuation by a regulatory agency (i.e. FDA)
- Investigator decision (in consultation with the Safety Medical Monitor and/or Medical Director and the patient) if there are changes in the patient's medical condition and/or intercurrent illness that render the patient unacceptable for further treatment. The reason for removal must be documented in the eCRF.

Follow-up: Once study treatment is discontinued, all patients who are alive and not lost to follow-up are to be closely followed for evidence of delayed effects of study drug for 30 days from the last dose of study drug.

For patients who are discontinued from study treatment for reasons other than disease progression, they will continue to have tumor evaluation with methodologies consistent with tumor type until another anti-cancer treatment is started, progression of disease, death, loss to follow up or withdrawal of consent, whichever comes first. Therefore, continued evaluations may be possible for some patients after the 30-day post dose visit.

Statistical Methods

Phase 1:

The primary endpoint is the frequency of DLTs for each dosing schedule as a function of CRLX301 dose.

Phase 2a:

The primary endpoints are:

- Safety and tolerability, evaluated by the following parameters:
  - Type, frequency and severity of AE(s)
  - Laboratory parameters (hematology and chemistry, especially those associated with bone marrow and hepatic function)
  - Vital signs
  - Physical examination
  - 12-lead ECG

The secondary endpoints are:

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- PK parameters in plasma: area under the concentration versus time curve (AUC), maximum concentration (Cmax), half-life ($t_{1/2}$), volume of distribution (Vd), clearance (CL) for both total and released docetaxel after single dose and multiple doses when available for each dosing schedule.
- Efficacy measures: best overall response, duration of overall response, duration of stable disease, objective response rate, disease control rate, and progression free survival as per RECIST version 1.1 or methodologies consistent with specific tumor type

Patients who receive any amount of study drug, including those who withdraw prematurely from the study, will be included within four analysis populations as specified below:

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

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

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.

MTD and/or RP2D Efficacy Evaluable Populations: 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 1 follow-up tumor assessment via imaging or methodologies consistent with specific tumor type.

Schedules 1 and 2 will be analyzed separately. As appropriate analysis for each cohort in Phase 1 and for each of the MTD expansion cohorts will be reported separately. For Schedule 2, a single MTD/RP2D will be determined, but other analyses will be reported separately for QW, no break cohorts and QW, 3 week on/1 week off cohorts.

Descriptive statistics including, mean, median, standard deviation (SD), minimum, and maximum values will be presented as appropriate for all cohorts treated. PK parameters for individual patients will be calculated, summary (mean +/- SD, min, max, geometric mean and geometric coefficient of variation) of PK parameters for each dose cohort and cycle will be calculated and statistical analyses will be computed to evaluate differences between dose cohorts and cycles. Tumor response rates will be summarized with their 95% Pearson-Clopper confidence intervals. Time to event endpoints will be analyzed by survival analysis methods.

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No formal sample size calculation is proposed as this study is not powered to demonstrate statistical significance. A detailed description of analysis methods will be prepared by the Sponsor designated study biostatistician in the study Statistical Analysis Plan.

SCHEDULE OF PROCEDURES – SCHEDULE 1 (Q3W / DAY 1 DOSING OF A 21-DAY CYCLE)

Procedures	Pre-Study	Cycle 1, 3, 6[1]							Cycle 2, 4, 5, 7[1] through discontinuation				EOS	Follow Up[28]
Study Day	–30 to 0	1		2	3	8	15	22[2]	1	8	15	22[2]	30d (+10d) post last dose	(if applies) Every 8-9 weeks post last tumor evaluation
		Pre-dose	0-6 h	24 h	48 h	168 h	336 h	504 h	0 h	168 h	336 h	504 h		
Informed Consent / HIPPA	X													
Medical history	X													
Concomitant medications	X	X		X	X	X	X	X	X[2]	X	X	X	X	
ECOG	X												X	
Physical examination[3]	X	X						X	X[2]			X	X	
Height, weight and BSA[4]	X	X[4]							X[4]					
Vital signs[5]	X	X[5]	X[5]			X		X	X[2,5]	X		X	X	
ECHO or MUGA (perform if needed)[6]	X													
ECG	X	X[7]	X[7]						X[8]				X	
CT brain scan (pre-screen if needed)	X[9]													
Hematology[10, 11]	X	X[10]				X	X	X	X[2, 11]	X[11]	X[11]	X[11]	X	
Chemistry[10, 11]	X	X[10]				X	X	X	X[2, 11]	X[11]	X[11]	X[11]	X	
Coagulation[10]	X	X[12]	Prior to post-dose biopsy as applicable (only from patients who undergo)											
Urinalysis with microscopy[10, 11]	X	X[10]				X		X	X[2, 11]	X[11]		X[11]	X	
Pregnancy test[13]	X[13]	X[13]											X[13]	
PK blood: Ph 1; Ph 2a Stg 1 & subset Stg 2 only[14]		X	X	X	X	X	X[15]	X						
PK urine :Ph 1 and Ph 2a Stg 1 only[16]		X	X			X								
Blood sample for biomarker: Ph 2a only[17]		X[17]		X[17]									X	
CTC: Ph 2a Stg 1 only[18]		X[18]	X[18]	X[18]		X[18]			X[18]	X[18]			X	
MPS function: Ph 2a Stg 1 only[19]		X[19]												
Tumor measurement and staging	X[20]						X[20]				X[20]		X[21]	X[28]
PSA for prostate patients only in Phase 2a[22]	X[22]							X[22]				X[22]	X[22]	X[28]
Tumor biopsy[23]	X	Collect post-dose biopsy any time after 3rd dose completed (C3D1) if applicable												
Tumor marker Data[24]	X[24]	Collected based on tumor type and institution guidelines/Standard of Care												
Premedication[25]	X[25]	X[25]					X[25]		X[25]		X[25]			
CRLX301 infusion[26]			X						X					
Assessment for adverse events		X	X	X		X	X	X	X	X	X	X	X	

Archived Tumor Tissue[27]	X													

1. Clinic visit window rules: For C1 and C2 no visit windows. For C3 through C7 allowable window for Day 1 visit only is ±1 day; for C4 and C5 allowable window for D8 and D15 clinic visits is ±1 day; as of C7D8 and for all subsequent visits, allowable window is ±2 days.
2. D22 is the equivalent of pre-dose D1 in the subsequent cycle.
3. Complete PE of body systems must be performed by the Investigator during pre-study and EOS (includes weight). Limited PE is performed pre-dose on C1D1 and at the end of each cycle (D22).
4. Height required at pre-study only; repeat weight measurement C1D1 to calculate BSA not necessary if pre-study assessment was ≤3 days prior to C1D1. Record weight measurement at each subsequent cycle pre-dose and recalculate BSA only if body weight changes by more than 10% and change is attributed to dry weight.
5. Refer to Section 5.7 for vital sign collection time points. Collect VS C1D1 pre-dose, during infusion at 30 min and 60 min, and end of infusion; post infusion at +60 min, +3 hr, and +6 hr (-1 hr); VS for all subsequent cycles D1 at pre-dose, +60 min. post-infusion, D8, D22, and EOS visit. Temperature (T) only at pre-dose, +6 hr (-1 hr) post infusion and at EOS visit. As of Cycle 7 collect vital signs pre-dose and at EOS day of visit only.
6. ECHO or MUGA performed pre-study only for patients with a known history of cardiac insufficiency and symptomatic in the last 3 months, and only if prior ECHO or MUGA **not** available within 30 days of first dose.
7. ECG required pre-dose and at +1hr (+30min) after end of infusion.
8. ECG required in C2 only pre-dose and at +1hr (+30min) after end of infusion.
9. CT brain scan required to confirm known brain metastases have been stable for ≥ 30 days prior to C1D1. If a patient is asymptomatic at pre-study with no history of brain metastases, additional brain scanning for eligibility is not required.
10. Chemistry, hematology, urinalysis and coagulation panels are referenced in Section 5.11. Assessment do not need to be repeated on C1D1 if assessment was ≤3 days prior to C1D1. As of Cycle 2 it is permissible to perform pre-dose hematology, chemistry and urinalysis within 24 hours of dosing.
11. As of Cycle 8 perform hematology, chemistry, urinalysis at the beginning of the cycle only on Day 1 pre-dose. The Day 8 (all three assessments) and Day 15 (hematology and chemistry only) time points are only performed in Cycles 1-7.
12. Coagulation within 3 days of first dose only for C1. Not performed in C3 or C6; also performed prior to post-dose biopsy in patients who consent to biopsy
13. Pregnancy test is performed only at pre-study, prior to C1D1 dosing if needed and at EOS: repeat urine pregnancy test on C1D1 not necessary if pre-study assessment was ≤3 days prior to C1D1. Test should be repeated as needed for women of child-bearing potential if suspicion of pregnancy. Positive urine pregnancy tests should be confirmed with a serum pregnancy test.
14. For Phase 1, Phase 2a Stage 1 and for up to 10 patients in Phase 2a Stage 2 plasma PK will be collected in C1, C3 and C6: On D1 pre-dose; after initiation of infusion at 30 min (during infusion) and 60 min (during infusion); at end of infusion; and after end of infusion at +30 min, +60 min, +3 hr, and +6 hr (-1 hr). Collect on D2; D3; D8, and D15 (C1 only). Collect pre-dose on D1 in C2, C4 & C7. Refer to Section 5.13 for complete details on PK time points and allowable windows.
15. D15 plasma PK collection in C1 only.
16. For Phase 1 and for Phase 2a Stage 1 urine PK will be collected on D1 in C1, C3 and C6. Collect a 15 mL spot urine sample pre-dose; then collect all urine from start of infusion (0 h) through 6 h post-infusion. On D8 collect a15 mL spot urine sample.

17. Blood sample for biomarkers in Phase 2a Stage 1 and Stage 2 only. Collect only in C1 and C3: D1 pre-dose and D2.
18. CTCs in Phase 2a Stage 1 only. Collect only in C1: D1 pre-dose, 4hrs (-1hr) after end of infusion, 24hrs (+/- 4hrs) after end of infusion (D2) and on D8; and in C2: D1 pre-dose, 4hrs (-1hr) after end of infusion and on D8.
19. MPS function in Phase 2a Stage 1 only. Collect pre-dose in Cycles 1 and 3 only.
20. Perform the tumor measurement at the end of every third cycle or every 9 weeks (Cycle 3, 6, 9, etc.) within a week prior to D22 (as of D15 +6 days) until the patient discontinues study drug treatment due to disease progression. If a complete or partial response per RECIST1.1 criteria or with methodologies consistent with tumor type is reported, then repeat evaluation 3-4 weeks later for confirmation, at discretion of investigator. If stable response per RECIST1.1 criteria or with methodologies consistent with tumor type is reported, then continue repeat evaluation at end of every third cycle (every 9 weeks). See Section 5.15.3 for alternative methodologies. Patients in Phase 1 with non-measurable disease will require Investigator and Medical Monitor review to determine proper disease staging, if any is required. Bone scans will also be required at each tumor evaluation for CRPC patients enrolled into Phase 2a.
21. Tumor measurement and staging not required at EOS if previous evaluation was less than 22 days prior.
22. For prostate cancer patients in Phase 2a only: collect PSA pre-study; pre-dose at the start of every cycle starting at Cycle 2; at EOS only if it has been > 14 days since the last PSA measurement; and during Follow-Up if applicable at the same time tumor evaluation is performed
23. Collect tumor biopsy only if accessible and feasible to collect and with consent of patient; collect pre-study prior to first dose. Collect post-dose any time after 3rd dose completed (C3D1).
24. Tumor marker data will be collected per Institution guidelines only if appropriate for evaluation of disease for the specific tumor-type and if feasible; repeat as per standard of care.
25. During screening, patients will be provided with Day (-1) oral premedication. Patients will be instructed on when (the night prior to the first CRLX301 infusion) and how to take these medications by the study staff. On D15 of each cycle, oral premedication will be provided to each patient for the subsequent cycle. Refer to Section 5.10.2 for complete details on premedication. **NOTE:** Site staff will call each patient within 72 hours prior to D(-1) to remind patient to take premedication.
26. **NOTE:** Prior to initiation of CRLX301 infusion, site will confirm whether patient took premedication regimen the prior evening (D(-1)). If patient did not take premedication, CRLX301 infusion will be initiated at discretion of investigator. Each CRLX301 infusion should start as slow as possible with no more than 15mL infused over the first 15 minutes. Provided the patient does not experience any infusion related symptoms during these 15 minutes, the rate of infusion can be gradually increased to complete the infusion in approximately 120 minutes (inclusive of 50mL flush). Refer to the Pharmacy Manual and Section 5.10.3.1 for complete administration instructions.
    NOTE: If hypersensitivity event occurs, **collect blood sample for tryptase evaluation within 3 hours of event**. If patient is to be retreated collect blood sample for tryptase prior to each subsequent infusion. See Table on Clinical Laboratory Test Parameters and Timing
27. Archived tumor tissue confirmed if available and patient has consented. Preparation of slides and shipment to central lab will not be triggered until sponsor advises sites in writing.
28. Patients who are discontinued from study treatment for reasons other than disease progression will continue to have tumor evaluation by RECIST1.1 or with methodologies consistent with tumor type every 8-9 weeks per investigator discretion until another anti-cancer treatment is started, progression of disease, death, loss to follow up or withdrawal of consent, whichever comes first. Therefore, continued scans may be possible for some patients after the EOS. Prostate cancer patients in Phase 2a only will also have PSA collected at the same time tumor evaluation is repeated.

SCHEDULE OF PROCEDURES – SCHEDULE 2 (QW: WEEKLY DOSING, NO BREAK / DAY 1 OF EACH WEEK)

Procedures	**Pre-Study**	**Week of Treatment**					**Treatment post W7[1]**				**Follow Up[27] (if applies)** Every 8-9 weeks post last tumor evaluation
Study Week		**1, 4, 7[1]**			**2, 3, 5, 6[1]**		**QW**	**Q2W**	**Q3W**	**EOS**	
Day of Week		**D1**		**D2**	**D1**		**D1[1]**	**D1[1]**	**D1[1]**	**30 (+10) days post last dose**	
Time point	**-30 to 0 day**	**Pre-dose**	**0 - +6h**	**24h**	**Pre-dose**	**0 - +6h**	**e.g. W8, W11, etc.**	**e.g. W9, W12, etc.**	**e.g. W10, W13, etc.**		
Informed Consent / HIPPA	X										
Medical history	X										
Concomitant medications	X	X		X	X		X	X	X	X	
ECOG	X									X	
Physical examination	X[2]	X[3]							X[3]	X[2]	
Height, weight & BSA[4]	X	X			X		X	X	X		
Vital signs[5]	X	X[5]	X[5,]		X[5]	X[5]	X[6]	X[6]	X[6]	X[5]	
ECHO or MUGA (perform if needed)[7]	X										
ECG	X	X	X[8]							X	
CT brain scan (pre-screen if needed)[9]	X										
Hematology[10]	X	X			X		X	X	X	X	
Chemistry[10]	X	X			X		X	X	X	X	
Coagulation[10]	X	X[11]	Perform coagulation prior to post-dose biopsy as applicable (after third dose)								
Urinalysis w/ microscopy[10]	X	X			X		X	X	X	X	
Pregnancy test[12]	X[12]	X[12]								X[12]	
PK blood: Ph 1, Ph 2a Stg 1 & subset Stg 2 only[13]		X	X[13]	X	X[13]						
PK urine: Ph1 & Ph2a Stg 1 only		X[14]	X[14]		X[15]		X[15]				
Blood sample for biomarker –Ph2a only[16]		X[16]		X[16]						X	
CTC – Ph2a Stg 1 only[17]		X[17]	X[17]	X[17]	X[17]	X[17]				X	
MPS function – Ph2a Stg 1 only		X[18]									
Tumor measurement and staging [19]	X							X		X[20]	X[27]
PSA for prostate patients only in Phase 2a[21]	X[21]	X[21]			X[21]				X[21]	X[21]	X[27]
Tumor biopsy[22]	X	Collect post-dose biopsy if applicable any time after the third (W3) dose is completed									
Tumor marker Data[23]	X	Collect data as available based on tumor type and institution guidelines/ Standard of Care									
Archived Tumor Tissue[24]	X										
Premedication[25]	X[25]	X[25]			X[25]		X[25]	X[25]	X[25]		
CRLX301 infusion[26]			X			X	X	X	X		

Procedures	**Pre-Study**	**Week of Treatment**					**Treatment post W7[1]**				**Follow Up[27] (if applies)** Every 8-9 weeks post last tumor evaluation
Study Week		**1, 4, 7[1]**			**2, 3, 5, 6[1]**		**QW**	**Q2W**	**Q3W**	**EOS**	
Day of Week		**D1**		**D2**	**D1**		**D1[1]**	**D1[1]**	**D1[1]**	**30 (+10) days post last dose**	
Time point	**-30 to 0 day**	**Pre-dose**	**0 - +6h**	**24h**	**Pre-dose**	**0 - +6h**	**e.g. W8, W11, etc.**	**e.g. W9, W12, etc.**	**e.g. W10, W13, etc.**		
Assessment for AEs		X		X	X		X	X	X	X	

Abbreviations: BSA = body surface area, CT = computerized tomography, D = Day, Dx = Day 'x', ECG = electrocardiogram, EOS = End of Study, hr(s) = hour(s), min=minutes, PE = physical examination, PK = Pharmacokinetic, T = temperature, VS = vital sign(s), W = week(s)

1. Clinic visit window rules: For W1 through W8 no visit windows. As of W9 allowable window for dosing is +/- 1d.
2. Complete PE must be performed by the Investigator during pre-study and EOS (includes weight).
3. Limited PE is performed pre-dose on W1 and pre-dose every 3 weeks (W4, W7, etc.).
4. Height required at pre-study only; not necessary to repeat weight on D1W1 if per-study was ≤3 days prior to W1D1. Record weight measurement at each week pre-dose and recalculate BSA only if body weight changes by more than 10% and change is attributed to dry weight.
5. Refer to Section 5.7 for vital sign collection time points. In W1, W4 and W7: D1 pre-dose, during infusion at 30 min and 60 min; end of infusion; post infusion at +60 min, +3 hr and +6 hr (-1 hr). In W2-3 and W5-6: D1 pre-dose and at end of infusion. VS for all subsequent weeks D1 at pre-dose, and EOS visit. Temperature (T) is recorded: W1, W4, W7 pre-dose and 6hrs (-1 hr) after end of infusion; W2, W3, W5 & W6 record temperature pre-dose and at end of infusion; all subsequent weeks record T pre-dose; and EOS.
6. As of W8 and for EOS, collect vital signs and temperature pre-dose only (day of visit for EOS).
7. ECHO or MUGA performed pre-study only for patients with a known history of cardiac insufficiency and symptomatic in the last 3 months, and only if prior ECHO or MUGA **not** available within 30 days of first dose.
8. ECG required +1hr (+30min) after end of infusion.
9. CT brain scan required to confirm if brain metastases have been stable for ≥ 30 days prior to W1D1. If a patient is asymptomatic at pre-study with no history of brain metastases, additional brain scanning for eligibility is not required.
10. Chemistry, hematology, urinalysis and coagulation panels are referenced in Section 5.11. It is not necessary to repeat W1D1 assessment if pre-study assessment was ≤3 days prior to W1D1. All safety labs must be performed pre-dose for clinic days while on study treatment. As of W2: permissible to perform D1 chemistry, hematology and urinalysis within 24 hours of dosing.
11. Coagulation within 3 days of first dose only in W1. Not needed for other weeks unless post-dose biopsy performed.
12. Pregnancy test is performed only at pre-study, prior to W1D1 dosing if needed and at EOS: repeat pregnancy test on W1D1 not necessary if pre-study test was ≤3 days prior to W1D1. Test should be repeated as needed for women of child-bearing potential if suspicion of pregnancy. Positive urine pregnancy tests should be confirmed with a serum pregnancy test.
13. For Phase 1, Phase 2a Stage 1 and for up to 10 patients in Phase 2a Stage 2, plasma PK will be collected on the dosing day in weeks 1, 4 & 7: On D1 pre-dose; after initiation of infusion at 30 min (during infusion) and 60 min (during infusion); at end of infusion; and after end of infusion at +30 min, +60 min, +3 hr and +6 hr (-1 hr). Also collect on D2. In Weeks 2, 3, 5 & 6 a pre-dose sample will be collected Refer to Section 5.13 for complete details on PK time points.

14. For Phase 1 and for Phase 2a Stage 1 urine PK will be collected on the dosing day in weeks 1, 4 & 7. Collect a 15 mL spot urine pre-dose; then collect all urine from start of infusion (0 h) through 6 h post-infusion.
15. Collect 15 ml spot urine for PK during week 2, 5, and 8 only pre-dose.
16. Blood sample for biomarker in Phase 2a Stage 1 and Stage 2 only. During treatment collect only W1 and W4: D1 pre-dose and D2.
17. Blood for CTC in Phase 2a Stage 1 only. Collect blood for CTC only at Week 1 pre-dose, 4hrs (-1hr) after end of infusion, 24hrs (+/-4hrs) after end of infusion (Day 2); Week 2 pre-dose; Week 4 pre-dose and 4hrs (-1hr) after end of infusion; and Week 5 pre-dose.
18. Collect blood for MPS function test in phase 2a Stage 1 pre-dose only in Week 1 and 4.
19. Perform the tumor measurement every 9 weeks (+6 days) (W9, W18, etc) until the patient discontinues study drug treatment due to disease progression. If a complete or partial response per RECIST 1.1 criteria or with methodologies consistent with tumor type is reported, then repeat evaluation 3-4 weeks later for confirmation at discretion of investigator. If stable response per RECIST criteria or with methodologies consistent with tumor type is reported, then continue repeat evaluation every 9 weeks. See Section 5.15.3 for alternative methodologies. In Phase 1, patients with non-measurable disease will require Investigator and Medical Monitor review to determine proper disease staging, if any is required. Bone scans will be required at each tumor evaluation for CRPC patients enrolled into Phase 2a.
20. EOS tumor measurement and staging is not required if previous evaluation was less than 22 days prior.
21. For prostate cancer patients only in Phase 2a: collect PSA pre-study; pre-dose at the start of every third week starting at Week 4 (e.g. W4, W7, W10, etc.); at EOS only if it has been > 14 days since the last PSA measurement; and during Follow-Up if applicable at the same time tumor evaluation is performed.
22. Collect tumor biopsy only if accessible and feasible to collect and with consent of patient; collect biopsy pre-study prior to first dose. Collect post-dose biopsy any time after the third dose is completed.
23. Tumor marker data will be collected per Institution guidelines only if appropriate for evaluation of disease for the specific tumor-type and if feasible; repeat as per standard of care.
24. Archived tumor tissue confirmed if available and patient has consented. Preparation of slides and shipment to central lab will not be triggered until Sponsor advises sites in writing.
25. During screening, patients will be provided with Day(-1) oral premedication. Patients will be instructed on when (prior to the first CRLX301 infusion) and how to take these medications by the study staff. On D1 or D2 (as applicable of given week), oral premedication will be provided to each patient for the subsequent week's dosing event. Refer to Section 5.10.2 for complete details on premedication. **NOTE:** Site staff will call each patient within 72 hours prior to D(-1) to remind patient to take premedication.
26. **NOTE:** Prior to initiation of CRLX301 infusion, site will confirm that patient ingested premedication regimen the prior evening (D(-1)). If patient did not take premedication, CRLX301 infusion will be initiated at discretion of investigator. Each CRLX301 infusion should start as slow as possible with no more than 15mL infused over the first 15 minutes. Provided the patient does not experience any infusion related symptoms during these 15 minutes, the rate of infusion can be gradually increased to complete the infusion in approximately 120 minutes, inclusive of the 50mL flush. Refer to the Pharmacy Manual and Section 5.10.3.1 for complete administration instructions.
    NOTE: If hypersensitivity event occurs, **collect blood sample for tryptase evaluation within 3 hours of event**. If patient to be retreated, collect blood sample for tryptase prior to each subsequent infusion. See Table on Clinical Laboratory Test Parameters and Timing.

27. Patients who are discontinued from study treatment for reasons other than disease progression will continue to have tumor evaluation by RECIST 1.1 or with methodologies consistent with tumor type until another anti-cancer treatment is started, progression of disease, death, loss to follow up or withdrawal of consent, whichever comes first. Prostate cancer patients in Phase 2a only will also have PSA collected at the same time tumor evaluation is repeated.

SCHEDULE OF PROCEDURES – SCHEDULE 2 (QW, 3 WEEK ON/1 WEEK OFF)

Procedures	**Pre-Study**	**Week of Treatment (Week 1 to Week 8)**						**Treatment post W8[1]**			
Study Week		**1, 3, 7[1]**			**2, 5, 6[1]**		**4,8[1]**	**3 week on/1 week off**	**Q4W**	**EOS**	**Follow Up[27] (if applies)** Every 8-9 weeks post last tumor evaluation
Day of Week		**D1**		**D2**	**D1**		**D1**	**D1[1]**	**D1[1]**	**30 (+10) days post last dose**	
Time point	**-30 to 0 day**	**Pre-dose**	**0 - +6h**	**24h**	**Pre-dose**	**0 - +6h**		**e.g. W9, W10, W11, W13, W14, W15, etc.**	**e.g. W9, W13, etc.**		
Informed Consent / HIPPA	X										
Medical history	X										
Concomitant medications	X	X		X	X		X	X		X	
ECOG	X[2]									X	
Physical examination	X[2]	X[3]			X[3]				X	X[2]	
Height, weight & BSA[4]	X	X			X			X			
Vital signs[5]	X	X[5]	X[5,]		X[5]	X[5]	X[5]	X[6]		X[6]	
ECHO or MUGA (perform if needed)[7]	X										
ECG	X	X	X[8]							X	
CT brain scan (pre-screen if needed)[9]	X										
Hematology[10]	X	X			X		X	X		X	
Chemistry[10]	X	X			X		X	X		X	
Coagulation[10]	X	X[11]	Perform coagulation prior to post-dose biopsy as applicable (after third dose)								
Urinalysis w/ microscopy[10]	X	X			X		X	X		X	
Pregnancy test[12]	X[12]	X[12]								X[12]	
PK blood: Ph 1, Ph 2a Stg 1 & subset Stg 2 only[13]		X	X[13]	X	X[13]						
PK urine: Ph1 & Ph2a Stg 1 only		X[14]	X[14]		X[15]						
Blood sample for biomarker –Ph2a only[16]		X[16]		X[16]						X	

Procedures	**Pre-Study**	**Week of Treatment (Week 1 to Week 8)**						**Treatment post W8[1]**			
Study Week		**1, 3, 7[1]**			**2, 5, 6[1]**		**4,8[1]**	**3 week on/1 week off**	**Q4W**	**EOS**	**Follow Up[27] (if applies)** Every 8-9 weeks post last tumor evaluation
Day of Week		**D1**		**D2**	**D1**		**D1**	**D1[1]**	**D1[1]**	**30 (+10) days post last dose**	
Time point	**-30 to 0 day**	**Pre-dose**	**0 - +6h**	**24h**	**Pre-dose**	**0 - +6h**		**e.g. W9, W10, W11, W13, W14, W15, etc.**	**e.g. W9, W13, etc.**		
CTC – Ph2a Stg 1 only[17]		X[17]	X[17]	X[17]	X[17]					X	
MPS function – Ph2a Stg 1 only		X[18]									
Tumor measurement and staging [19]	X								X[19]	X[20]	X[27]
PSA for prostate patients only in Phase 2a[21]	X[21]				X[21]				X	X[21]	X[27]
Tumor biopsy[22]	X	Collect post-dose biopsy if applicable any time after the third (W3) dose is completed									
Tumor marker Data[23]	X	Collect data as available based on tumor type and institution guidelines/ Standard of Care									
Archived Tumor Tissue[24]	X										
Premedication[25]	X[25]	X[25]			X[25]			X[25]			
CRLX301 infusion[26]			X			X		X			
Assessment for AEs		X		X	X		X	X		X	

Abbreviations: BSA = body surface area, CT = computerized tomography, D = Day, Dx = Day 'x', ECG = electrocardiogram, EOS = End of Study, hr(s) = hour(s), min=minutes, PE = physical examination, PK = Pharmacokinetic, T = temperature, VS = vital sign(s), W = week(s)

1. Clinic visit window rules: For W1 through W8 no visit windows. There is no dosing on W4 and W8, but clinic visit required. As of W9 allowable window for dosing is +/- 1d. Clinic visits not required on non-dosing weeks as of W9.
2. Complete PE and ECOG must be performed by the Investigator during pre-study and EOS (includes weight).
3. Limited PE is performed pre-dose on W1 and pre-dose every 4 weeks (W5, W9, etc.).
4. Height required at pre-study only; not necessary to repeat weight on D1W1 if per-study was ≤3 days prior to W1D1. Record weight measurement at each week pre-dose and recalculate BSA only if body weight changes by more than 10% and change is attributed to dry weight.
5. Refer to Section 5.7 for vital sign collection time points. In W1, W3 and W7: D1 pre-dose, during infusion at 30 min and 60 min; end of infusion; post infusion at +60 min, +3 hr and +6 hr (-1 hr). In W2, W5 and W6: D1 pre-dose and at end of infusion. In W4 and W8: at clinic visit. Temperature (T) is recorded: W1, W3, W7 pre-dose and 6hrs (-1 hr) after end of infusion; W2, W5 & W6 record temperature pre-dose and at end of infusion; W4 and W8 record temperature at clinic visit.
6. For dosing weeks starting with W9 and for EOS, collect vital signs and temperature pre-dose only (day of visit for EOS).
7. ECHO or MUGA performed pre-study only for patients with a known history of cardiac insufficiency and symptomatic in the last 3 months, and only if prior ECHO or MUGA **not** available within 30 days of first dose.
8. ECG required +1hr (+30min) after end of infusion.
9. CT brain scan required to confirm if brain metastases have been stable for ≥ 30 days prior to W1D1. If a patient is asymptomatic at pre-study with no history of brain metastases, additional brain scanning for eligibility is not required.

10. Chemistry, hematology, urinalysis and coagulation panels are referenced in Section 5.11. It is not necessary to repeat W1D1 assessment if pre-study assessment was ≤3 days prior to W1D1. All safety labs must be performed pre-dose for clinic days while on study treatment. As of W2: permissible to perform D1 chemistry, hematology and urinalysis within 24 hours of dosing.
11. Coagulation within 3 days of first dose only in W1. Not needed for other weeks unless post-dose biopsy performed.
12. Pregnancy test is performed only at pre-study, prior to W1D1 dosing if needed and at EOS: repeat pregnancy test on W1D1 not necessary if pre-study test was ≤3 days prior to W1D1. Test should be repeated as needed for women of child-bearing potential if suspicion of pregnancy. Positive urine pregnancy tests should be confirmed with a serum pregnancy test.
13. For Phase 1, Phase 2a Stage 1 and for up to 10 patients in Phase 2a Stage 2, plasma PK will be collected on the dosing day in weeks 1, 3 & 7: On D1 pre-dose; after initiation of infusion at 30 min (during infusion) and 60 min (during infusion); at end of infusion; and after end of infusion at +30 min, +60 min, +3 hr, +6 hr (-1 hr), and +24 hr (D2). In addition, pre-dose plasma samples (trough samples) will be collected on Weeks 2, 5 & 6. Refer to Section 5.13 for complete details on PK time points.
14. For Phase 1 and for Phase 2a Stage 1 urine PK will be collected on the dosing day in weeks 1, 3 & 7. Collect a 15 mL spot urine pre-dose; then collect all urine from start of infusion (0 h) through 6 h post-infusion.
15. Collect 15 ml spot urine for PK during week 2, 5, and 6 only pre-dose.
16. Blood sample for biomarker in Phase 2a Stage 1 and Stage 2 only. During treatment collect only W1 and W3: D1 pre-dose and D2.
17. Blood for CTC in Phase 2a Stage 1 only. Collect blood for CTC only at Week 1 pre-dose, 4hrs (-1hr) after end of infusion, 24hrs (+/-4hrs) after end of infusion (Day 2); Week 2 pre-dose; Week 3 pre-dose and 4hrs (-1hr) after end of infusion; and Week 5 pre-dose.
18. Collect blood for MPS function test in phase 2a Stage 1 pre-dose only in Week 1 and 3.
19. Perform the tumor measurement every 8 weeks (+6 days), starting at Week 9 (e.g. W9, W17, etc.), until the patient discontinues study drug treatment due to disease progression. If a complete or partial response per RECIST 1.1 criteria or with methodologies consistent with tumor type is reported, then repeat evaluation 3-4 weeks later for confirmation at discretion of investigator. If stable response per RECIST criteria or with methodologies consistent with tumor type is reported, then continue repeat evaluation every 8 weeks. See Section 5.15.3 for alternative methodologies. In Phase 1, patients with non-measurable disease will require Investigator and Medical Monitor review to determine proper disease staging, if any is required. Bone scans will be required at each tumor evaluation for CRPC patients enrolled into Phase 2a.
20. EOS tumor measurement and staging is not required if previous evaluation was less than 22 days prior.
21. For prostate cancer patients only in Phase 2a: collect PSA pre-study; pre-dose at the start of every fourth week starting at Week 5 (e.g. W5, W9, W13, etc.); at EOS only if it has been > 14 days since the last PSA measurement; and during Follow-Up if applicable at the same time tumor evaluation is performed.
22. Collect tumor biopsy only if accessible and feasible to collect and with consent of patient; collect biopsy pre-study prior to first dose. Collect post-dose biopsy any time after the third dose is completed.
23. Tumor marker data will be collected per Institution guidelines only if appropriate for evaluation of disease for the specific tumor-type and if feasible; repeat as per standard of care.
24. Archived tumor tissue confirmed if available and patient has consented. Preparation of slides and shipment to central lab will not be triggered until Sponsor advises sites in writing.
25. During screening, patients will be provided with Day (-1) oral premedication. Patients will be instructed on when (prior to the first CRLX301 infusion) and how to take these medications by the study staff. On D1 or D2 (as applicable of given week), oral premedication will be provided to each patient for the

subsequent week's dosing event. Refer to Section 5.10.2 for complete details on premedication. **NOTE:** Site staff will call each patient within 72 hours prior to D(-1) to remind patient to take premedication.

26. **NOTE:** Prior to initiation of CRLX301 infusion, site will confirm that patient ingested premedication regimen the prior evening (D(-1)). If patient did not take premedication, CRLX301 infusion will be initiated at discretion of investigator. Each CRLX301 infusion should start as slow as possible with no more than 15mL infused over the first 15 minutes. Provided the patient does not experience any infusion related symptoms during these 15 minutes, the rate of infusion can be gradually increased to complete the infusion in approximately 120 minutes, inclusive of the 50mL flush. Refer to the Pharmacy Manual and Section 5.10.3.1 for complete administration instructions.
    NOTE: If hypersensitivity event occurs, **collect blood sample for tryptase evaluation within 3 hours of event**. If patient to be retreated, collect blood sample for tryptase prior to each subsequent infusion. See Table on Clinical Laboratory Test Parameters and Timing.
27. Patients who are discontinued from study treatment for reasons other than disease progression will continue to have tumor evaluation by RECIST 1.1 or with methodologies consistent with tumor type until another anti-cancer treatment is started, progression of disease, death, loss to follow up or withdrawal of consent, whichever comes first. Prostate cancer patients in Phase 2a only will also have PSA collected at the same time tumor evaluation is repeated.

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LIST OF ABBREVIATIONS AND SPECIAL TERMS

AE	Adverse event
AESI	Adverse Event of Special Interest
AIDS	Acquired immune deficiency syndrome
AST	Aspartate aminotransferase
ALT	Alanine aminotransferase
ALP	Alkaline phosphatase
ANC	Absolute neutrophil count
AUC	Area under the plasma concentration versus time curve
BP	Blood pressure
BSA	Body surface area
C	Cycle
°C	Degrees Celsius
C1D1	Cycle 1 Day 1
CxDx	Cycle “x” Day “x”
CFR	Code of Federal Regulations
C_{max}	Maximum concentration observed
CNS	Central nervous system
CRA	Clinical Research Associate
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
CTCs	Circulating tumor cells
D or d	Day/(s)
dL	Deciliter
DLT	Dose limiting toxicity
DVT	Deep venous thrombosis
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
EPR	Enhanced permeability and retention
EOS	End-of-Study

FDA	Food and Drug Administration
g	Gram
h	Hour(s)
hr(s)	Hour(s)
HSR	Hypersensitivity (Infusion) Reaction
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HR	Heart rate
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent ethics committee
IND	Investigational new drug (application)
IUD	Intrauterine device
IRB	Institutional review board
IV	Intravenous(ly)
kg	Kilogram
L	Liter
LDH	Lactate dehydrogenase
m	meter
mg	milligram
mg/m^2	milligrams per meter squared
min	Minute
mL	Milliliter
mm	Millimeter
mmHg	millimeter of mercury
MPS	Mononuclear phagocyte system
msec	millisecond
µL	microliter
MTD	Maximum tolerated dose
NCI	National Cancer Institute
nm	Nanometer
NSCLC	Non-small cell lung cancer
PD	Pharmacodynamic
PE	Physical Examination
PFS	Progression-free survival
PI	Principal Investigator
PK	Pharmacokinetic
PCS	Potentially clinically significant
PCWG2	Prostate Cancer Working Group 2

PR interval	Duration of time from P wave (atrial depolarization) to the beginning of the QRS complex (ventricular depolarization) in the heart's electrical cycle
PSA	Prostate-specific antigen
PT	Prothrombin time
PTT	Partial thromboplastin time
PV	Pharmacovigilance
Q3W	Dosing every 3 weeks
QT	Time interval between the start of the Q wave and the end of the T wave in the heart's electrical cycle
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using the Fridericia formula ($QTcF = QT/(RR)^{1/3}$)
QW	Weekly Dosing
RBC	Red blood cell
RECIST	Response evaluation criteria in solid tumors
RP2D	Recommended Phase 2 dose
RR	Respiratory rate
SAE	Serious adverse event
SAP	Statistical analysis plan
SOC	Standard of Care
SRC	Safety Review Committee
SUSAR	Serious unexpected suspected adverse reaction
T	Temperature
$T_{1/2}$	Elimination half-life
TEAE	Treatment-emergent adverse event
TGA	Therapeutic Goods Administration
TIA	Transient ischemic attack
ULN	Upper limit of normal
US/USA	United States
VS	Vital Signs
WBC	White Blood Cell

1. INTRODUCTION

1.1 Unmet Clinical Need

According to the International Agency for Research on Cancer, there were 12.7 million new cancer cases and 7.6 million cancer deaths in 2008, and the global cancer burden is expected to nearly double to 21.4 million cases and 13.15 million deaths by 2030.[1] The most common cancer worldwide is lung cancer contributing nearly 13% of the total number of new cases diagnosed among men and women, while among women only breast cancer leads at nearly 23%. The highest cancer rate for men and women together diagnosed in 2008 is Denmark, followed by Ireland and then Australia with the US having the seventh highest.[2]

In Australia an estimated 124,910 new cases of cancer will be diagnosed this year, with that number set to rise to 150,000 by 2020. In 2011, more than 43,700 people are estimated to have died from cancer making it a leading cause of death and accounting for about 3 in 10 deaths in Australia. The most 5 common cancers in Australia (excluding non-melanoma skin cancer) are prostate, colorectal, breast, melanoma and lung cancer and account for over 60% of all cancers.[2]

In the United States, cancer will become the leading cause of death in 16 years, surpassing heart disease, according to a new report from the American Society of Clinical Oncology. The number of new cancer cases is expected to increase nearly 45% by 2030, from 1.6 million cases to 2.3 million cases annually. Although there is a declining rate of deaths due to cancer and improvements in the 5-year survival rates, the overall incidence of cancer remains stable in women and with slight decline in men.[3] The need to continue to identify cancer therapies including use of advanced technologies, to improve survival and control of disease remains high as cancer continues to be a major health issue in the United States and other countries.

1.2 Docetaxel

The active pharmaceutical ingredient of CRLX301 is docetaxel which is a member of the taxane family derived from the European yew tree, *Taxus baccata.*[4] Taxanes disrupt the microtubular network required for mitotic and interphase cellular functions. Docetaxel is a strong inhibitor of microtubule disassembly leading to interference with cell division and cell death by apoptosis.[5] By virtue of its strong inhibition of microtubule disassembly, docetaxel is active against a variety of cancers and has been approved to treat several human solid tumor malignancies including androgen-independent prostate cancer, non-small cell lung cancer (NSCLC), and locally advanced or metastatic breast cancer.[6,7] It's marketed under the trade name of Taxotere® (hereafter referred to as commercial docetaxel). Unfortunately, the therapeutic response to docetaxel is associated with dose-limiting side effects such as myelosuppression, neutropenia, anemia and fluid retention.[8,9] In addition, the poor aqueous solubility of docetaxel requires the incorporation of polysorbate 80 and ethanol in the clinical formulation leading to increased toxicities such as hypersensitivity.[10]

1.3 CRLX301 and Nanoparticle Delivery of Docetaxel

[redacted]

1.4 Non-Clinical Pharmacokinetics, Pharmacology, Pharmacodynamics and Toxicology with CRLX301

1.4.1 Summary of non-GLP Studies

[redacted]

1.4.2 Summary of Pharmacokinetics in GLP Studies

[redacted]

1.4.3 Summary of Pharmacology, Pharmacodynamics and Toxicology in GLP Studies

[redacted]

[redacted]

1.5 Clinical Experience with CRLX301 for the Treatment of Advanced Solid Tumor

As of 26 March 2016, 20 patients have been treated with single agent CRLX301 in Schedule 1 (Q3W) IV in this first-in-human study. Doses tested include 7.5 mg/m^2 (n=1), 15 mg/m^2 (n=1), 30 mg/m^2 (n=3), 60 mg/m^2 (n=3), 75 mg/m^2 (n=6) and 90 mg/m^2 (n=6). All patients were evaluable for dose limiting toxicities (DLTs) and MTDs. Safety data from one additional patient treated on Schedule 2 Cohort 1 (CRLX301 IV weekly [QW, no break] 25mg/m^2) are included in the summary of the most common treatment-related AEs (TRAEs) in the paragraph below. See Section 1.8.3:Rationale for Evaluation of QW, 3 week on/1 week off for Schedule 2 for preliminary safety information from additional subjects enrolled in Schedule 2 after the 26 March 2016 data cut-off for the 17 August 2016 CRLX301 Investigator's IB.

The most common TRAEs (all grades) experienced by the 21 subjects treated as of 26 March 2016 were (% of subjects): fatigue (76%), infusion-related reaction (38%); and decreased appetite, nausea and dysgeusia, each in 33% of subjects. The majority of these events were of mild to moderate severity. TRAEs ≥ Grade 3 were reported for 9 (45%) subjects overall; all subjects were on Schedule 1 (Q3W). The most common treatment-related events ≥ Grade 3 were infusion-related reaction and neutropenia, each reported for 3 (14 %) subjects.

Two DLTs were observed during cycle 1 at the 90mg/m^2 dose level in 2 subjects (1 DLT each) treated on Schedule 1 (Q3W CRLX301). One subject experienced reversible grade 3 elevations in transaminases concomitant with grade 2 bilirubin (<3 days duration), and 1 subject experienced grade 4 febrile neutropenia (<3 days duration). Per protocol, 90mg/m^2 exceeded the MTD, and 75mg/m^2 was declared as the MTD and selected as the RP2D for CRLX301 when administered Q3W (Schedule 1). Common side effects related to docetaxel, such as fluid retention, were not observed. No new toxicities have been observed that have not been reported for docetaxel.

All 21 patients enrolled received pre-medication with dexamethasone 20 mg IV and one dose each of an anti-histamine and a histamine 2 receptor (H2) antagonist (IV or orally) within 30-90 minutes prior to CRLX301 administration. A total of 8 (38%) patients enrolled in Schedule 1 have experienced hypersensitivity infusion reactions (HSRs). Within the cohorts which initiated treatment at a dose <90 mg/m^2, the HSRs were either mild (grade 1; n=1) or moderate (grade 2; n=4), with one exception of a Grade 3 event occurring at 75mg/m^2. Within the 90 mg/m^2 cohort, 1 patient experienced a Grade 2 HSR, 1 patient experienced a Grade 3 HSR and 1 patient experienced a Grade 4 HSR (the latter event, described in detail in the Investigator's Brochure, did not occur until the dose had been reduced to 75mg/m^2). Most HSRs occurred at cycle 1 or cycle 2 and within the first 15 minutes of administration, similar to docetaxel. Four of the 8 patients were re-challenged with study drug at a slower infusion rate and/or with an increased premedication regimen; these patients either did not have recurrence of HSR or experienced additional episodes of mild to moderate HSR that were manageable. Two other patients had their first episode of HSR in later cycles and were not re-challenged due to study discontinuation as a result of progressive disease. The 2 subjects experiencing ≥ Grade 3 HSRs at the 90 mg/m^2 dose level were discontinued from study treatment and followed up per protocol.

Secondary to these HSR events, protocol CRLX301-101 was amended (Amendment 7) to incorporate changes in the required premedication regimen prior to administration of CRLX301, and to prolong the duration of each CRLX301 infusion.

A total of 7 serious adverse reactions considered at least possibly related to CRLX301 were reported for 6 subjects. These included the 2 DLTs described above, 3 cases involving infusion-related reactions (HSR), and 1 case involving a peripheral sensory neuropathy and peripheral motor neuropathy in a subject with multiple confounding factors (including a history of diabetes, gout and cardiovascular disease, and concomitant chronic colchicine and dexamethasone at the time of participation in CRLX301-101). Please see the latest version of the CRLX301 Investigator's Brochure for details on this case and other toxicities reported.

In terms of anti-tumor activity of study drug as of 26 March 2016, of 13 subjects evaluable for efficacy, stable disease lasting ≥ 3 cycles was observed in 6 patients with 2 patients experiencing prolonged stable disease (7 and 17 cycles). A patient with B-RAF mutant adenocarcinoma of unknown primary who was resistant to a prior B-RAF inhibitor had tumor shrinkage per RECIST and partial metabolic response per FDG-PET.

Dose level 75 mg/m^2 Q3W is the standard dose and dosing schedule of commercial docetaxel given to patients in multiple indications.[22] Given the preliminary safety events and anti-tumor activity (tumor shrinkage in 1 patient) observed at 75 mg/m^2 of CRLX301 treatment, the study continues with expansion of 75 mg/m^2 Q3W cohort to further explore the safety, tolerability, and preliminary anti-tumor activity of CRLX301 at the dose that is equivalent to standard dose of commercial docetaxel.

PK studies of CRLX301 were performed after administration of CRLX301 at 7.5, 15, 30, 60, 75 and 90 mg/m^2 IV x 1 over 1 h every 21 days. Plasma PK studies of total and released docetaxel were performed on cycles 1, 3 and 6. The PK (as measured by Cmax and AUC) of total docetaxel was linear from 7.5 to 90 mg/m^2; whereas, the PK of released docetaxel was more variable. There was no accumulation of total or released docetaxel from cycle 1 to 6. At the equivalent dose of 75 mg/m^2, the plasma AUC of total docetaxel after CRLX301 is ~100-fold greater than for commercial docetaxel. In addition after administration of CRLX301 at 75 mg/m^2, the plasma AUC of released docetaxel is similar to commercial docetaxel; however, most of the measured AUC after CRLX301 is associated with exposure from 24-168 h, suggesting slow release in plasma. The C_{max} of released docetaxel in plasma after CRLX301 was 21-fold lower than for commercial docetaxel, which might be associated with a decrease in toxicity with CRLX301. Refer to the IB for details about clinical PK

1.6 Study Rationale

The development of CRLX301 is focused on the utility of nanoparticles to increase the extended plasma stability of docetaxel with slower clearance and prolonged circulation time, to provide effective delivery of docetaxel into tumors for prolonged periods, enhancing anti-tumor activity while potentially reducing the toxicity observed with traditional taxanes. The development program is focused on the demonstration of clinical activity and improved safety of docetaxel when administered in this nanoparticle formulation.

Studies in animals have demonstrated the ability to maintain CRLX301 for prolonged periods while sustaining low released docetaxel concentrations in the blood optimizing the cell-cycle specific activity associated with continuous low drug exposure. These specific characteristics have demonstrated, *in vivo*, the intended improvement in anti-tumor activity of CRLX301 compared to delivery of docetaxel alone.

This study protocol would allow the first-in-human dosing of CRLX301 in patients with advanced solid tumor malignancies to evaluate the safety and to establish the MTD and/or RP2D of CRLX301 in an optimal dosing schedule. The dosing, safety and clinical outcomes data reported from the Phase 1 and Phase 2a treated patients may support the future planning of clinical trials to evaluate efficacy endpoints for development of CRLX301.

1.7 Rationale for Q3W Dosing and the Starting Dose Phase 1 Based on Clinical Experience with Docetaxel

Since a once every-three-week dose (Q3W) schedule is used as the standard dosing schedule for commercial docetaxel and the pre-clinical PK study showed that half-life of CRLX301 is longer than commercial docetaxel, Cerulean decided to evaluate a dosing schedule which is not more frequent than Q3W in this first-in-human study. Therefore, Q3W dosing schedule was chosen as the initial dosing schedule of CRLX301 in this Phase 1 study.

The recommended starting dose for Schedule 1 Q3W dosing in humans was based on the results of the CRLX301 nonclinical repeat dose toxicity studies in dogs, the more sensitive species, would be 5.8 mg/m^2/dose. However, Cerulean medical advisors and clinical trial investigators considered it to be unethical to expose patients to a starting dose of less than 10% of the approved dose of docetaxel (75 mg/m^2), an active chemotherapy agent, and that this ratio for starting dose should not exceed 50%.

The toxicological effects of CRLX301 reported in dogs (the more sensitive species) are all consistent with docetaxel findings, and are shown to be reversible within 3 weeks, with the exception of the testicular and skin effects at the HNSTD (1.75 mg/kg or 35 mg/m^2). Furthermore, there were no observed adverse effects on ECG or respiratory parameters up to 1.75 mg/kg (35 mg/m^2) in dogs, or adverse effects on neurologic function up to 10 mg/kg (60 mg/m^2) in rats. These evidences offer the opportunity for an actual starting dose to be potentially higher than the calculated starting dose at 5.8 mg/m^2 per dose.

A recent study reported that the mean ratio of MTD to starting dose and total number of required dose levels in clinical Phase 1 studies was significantly greater for nanoparticles compared to small molecules when using the usual method to determine clinical Phase 1starting dose from preclinical dog study results.[23] The CRLX301 preclinical results along with the report finding clinical Phase 1 studies of nanoparticles start at lower dose levels relative to the clinical MTD support using a higher starting dose in a clinical Phase 1 study of docetaxel in a nanoparticle. Accordingly, the starting dose employed in this initial Phase 1 evaluation of CRLX301 for Schedule 1 was 10% of the approved dose of docetaxel (75 mg/m^2). This dose is equivalent to 7.5 mg/m^2.

1.8 Rationale for Weekly Dosing (Schedule 2) and the Starting Dose Based on Clinical Experience with CRLX301

1.8.1 Rationale for Weekly Dosing

As per Section 1.5: Clinical Experience with CRLX301 for the Treatment of Advanced Solid Tumor, no DLT was observed for Q3W dosing in the 6 patients treated at dose level 75 mg/m^2 which is equivalent to the standard dose of commercial docetaxel. At dose levels below 75 mg/m^2, CRLX301 was well tolerated with minimal toxicity. One exception is the patient receiving chronic use of colchicine in the 60 mg/m^2 cohort who developed Grade 3 neuropathy (see Section 1.5: Clinical Experience with CRLX301 for the Treatment of Advanced Solid Tumor and the CRLX301 Investigator's Brochure for additional details). Myelosuppression effect was minimally observed at 30 and 60 mg/m^2 dose levels while stable disease was observed with 2 patients in each cohort. Based on this level of clinical activity and low observed toxicity to date, there is room to explore in parallel a more frequent (weekly) dosing schedule.

PK studies of CRLX301 were performed after administration of CRLX301 at 7.5, 15, 30, 60 and 75 mg/m^2 IV x 1 over 1 h every 21 days. Plasma PK studies of total and released docetaxel were performed on cycles 1, 3 and 6. After CRLX301 infusion, elimination half-lie and total docetaxel in plasma was approximately 5 -8 hours and the $T_{1/2}$ of released docetaxel was approximately 42 – 121 hours. However, the long estimate of T½ of released docetaxel is related to a consistent release of docetaxel from CRLX301 rather than a slower elimination of released docetaxel. The ability to administer CRLX301 on a weekly schedule is further supported by the measured concentration versus time profiles of CRLX301 at 30, 60 and 75 mg/m^2 IV every 21 days. In that study there was no detectable exposure of total docetaxel on day 8 of cycles 1, 3 or 6. This supports the ability to explore weekly dosing.

There's mounting evidence that higher frequency of treatment with chemotherapy agents at lower doses may be more optimal than therapy at higher doses administered less frequently. This is supported by the emerging data from evaluation of metronomic chemotherapy.[24] A study of weekly paclitaxel in the adjuvant treatment of breast cancer compared toxic effects of paclitaxel and docetaxel between Q3W and QW schedule and demonstrated that there were significantly less adverse events resulted from weekly dosing of docetaxel as opposed to Q3W dosing.[25] Paclitaxel is currently given to patients with once weekly dosing schedule as a common practice. With the NDC technology platform, the preclinical study showed that weekly dosing of CRLX301 in mice could lead to up to 10-fold increase in drug accumulation in mouse tumors for at least 72 hours post nanoparticle administration when compared to a docetaxel control, thus it's hypothesized that more frequently dosing of CRLX301 would lead to more cumulative delivery of NDC conjugated form of docetaxel to tumor while potentially associating with less toxicities resulted from released form of docetaxel.

Therefore, the protocol is amended to add Schedule 2 with weekly CRLX301 dosing. Schedule 2 dose escalation will initiate in parallel with the Schedule 1 Q3W dose escalation.

Once enrolled and assigned to either Schedule 1 or Schedule 2 dosing schedule, patients will not be allowed to switch dosing schedules during treatment.

1.8.2 Rationale for Starting Dose for Schedule 2 during Phase 1 (QW, no break)

To better calculate the initial starting dose for the QW, no break schedule, we have performed two separate PK simulations from the ongoing Q3W schedule. Each model was performed to simulate the concentration versus time profiles of total and released docetaxel in plasma after administration of CRLX301 at 20, 25, 30 and 40 mg/m^2 administered IV x1 per week for nine consecutive weeks. The AUC versus time profiles of total and released docetaxel were estimated for the 1st, 4th and 7th dose. These doses are the proposed doses that would be evaluated in the phase 1 clinical trial of CRLX301 on the weekly dosing schedule. The PK simulations suggest that administration of CRLX301 at 20 to 40 mg/m^2 IV x 1 weekly for 9 weeks will not result in accumulation of total or released docetaxel in plasma. The estimated total docetaxel AUCs after the 1st, 4th, and 7th doses of CRLX301 at 20 and 40 mg/m^2 are approximately 22% and 45% of the AUCs achieved after administration of CRLX301 at 75 mg/m^2 Q3W. In addition, the estimated released docetaxel AUCs after the 1st, 4th, and 7th doses of CRLX301 at 20 and 40 mg/m^2 are approximately 32% and 65% of the AUCs achieved after administration of CRLX301 at 75 mg/m^2 Q3W. The PK simulation further supports weekly dosing schedule as well as a starting dose in the range of 20 to 40 mg/m^2.

The planned starting dose for Schedule 2 weekly dosing Phase 1 dose escalation is 25 mg/m^2. This represents 1/3 of the dosing intensity of the MTD/RP2D following Q3W dosing.

Also for Schedule 1, dose level 30 mg/m^2 demonstrated to be well tolerated with minimal toxicity: 1 patient was on study for 3 cycles; 1 patient was on study for 7 cycles and 1 patient was on study for 10 cycles. Multi-dose PK data (up to 6 doses in 2 patients) at 30 mg/m^2 showed no detectable level of either total nor released docetaxel after the CRLX301 infusion by Day 8 in each treatment cycle. Therefore, 25 mg/m^2 is deemed a safe starting dose for Schedule 2, a weekly dosing schedule.

1.8.3 Rationale for Evaluation of QW, 3 week on/1 week off for Schedule 2

As of 11 November 2016, a total of 12 patients have been enrolled into Schedule 2 of CRLX301-101 (see Table 2). A review of safety data from Cohort 3 (45mg/m^2 QW) revealed new events of neuropathy in 3 patients after at least 3 weeks of treatment with CRLX301. The first subject developed Grade 1 peripheral neuropathy at week 6, which worsened to Grade 2 at week 9, leading to dose interruption. A second patient developed Grade 2 peripheral neuropathy at week 9, also leading to dose interruption, and a third patient developed Grade 1 intermittent peripheral sensory neuropathy at week 4. This latter patient also reported Grade 2 bilateral episcleritis, which led to dose interruption.

Based on these data, CRLX301 dosing has been revised from QW, no break to QW, 3 week on/1 week off for any patient enrolled into Schedule 2 Cohort 3 and continuing on treatment as of 11 November 2016. This change in dosing frequency will also apply to all patients enrolled into Schedule 2 Cohort 4 (54 mg/m^2). The dosing schedule for cohorts beyond Cohort 4 will be determined by the Safety Review Committee (SRC).

2. STUDY OBJECTIVES

2.1 Primary Objectives

- Phase 1: To determine the maximum tolerated dose (MTD) / recommended Phase 2 dose (RP2D) of CRLX301when 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

- Phase 2a: To further establish the safety and tolerability of the CRLX301 MTD / RP2D

2.2 Secondary Objectives

- To evaluate the pharmacokinetic (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

2.3 Exploratory Objectives

- 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.

3. INVESTIGATIONAL PLAN

3.1 Phase 1 Dose Escalation Study Design

3.1.1 Study Design Summary

Phase 1 of the study is an open-label, dose-escalation study examining two separate dosing schedules. Schedule 1 (Q3W dosing schedule) was initiated first and Amendment 6 incorporates Schedule 2 (QW, no break dosing schedule). As of Amendment 9, for patients still receiving treatment in Schedule 2 Cohort 3 (45mg/m^2), and for patients enrolled in Schedule 2 Cohort 4 (54mg/m^2), dosing will be on a once weekly, 3 week on/1 week off schedule. The dosing schedule for additional Schedule 2 cohorts will be determined by the SRC. A single MTD/RP2D will be determined for Schedule 2. See Section 1.8.3: Rationale for Evaluation of QW, 3 week on/1 week off for Schedule 2.

For Q3W dosing the first 2 cohorts utilized a 1+5 study design. A single patient was enrolled sequentially into cohort 1 and cohort 2. If either patient in cohort 1 or 2 had experienced a dose limiting toxicity (DLT) during Cycle 1, then the cohort would have been expanded to enroll additional patients up to a total of 6. Furthermore, if the initial patient in cohort 1 experienced a DLT in Cycle 1, then enrollment would have reverted to a 3+3 design for cohort 2.

As of planned cohort 3 for Q3W dosing and for all cohorts in QW dosing, a 3+3 dose escalation schema will be utilized.[26] Initially a minimum of 3 patients will be accrued into each cohort. It is permissible to enroll more than 3 patients initially to further explore the safety or PK profile of a particular dose level. If any 1 of the initial enrolled patients in a cohort experiences a DLT during Cycle 1 or the first 3 weeks, then the cohort will be expanded to enroll additional patients up to a total of 6.

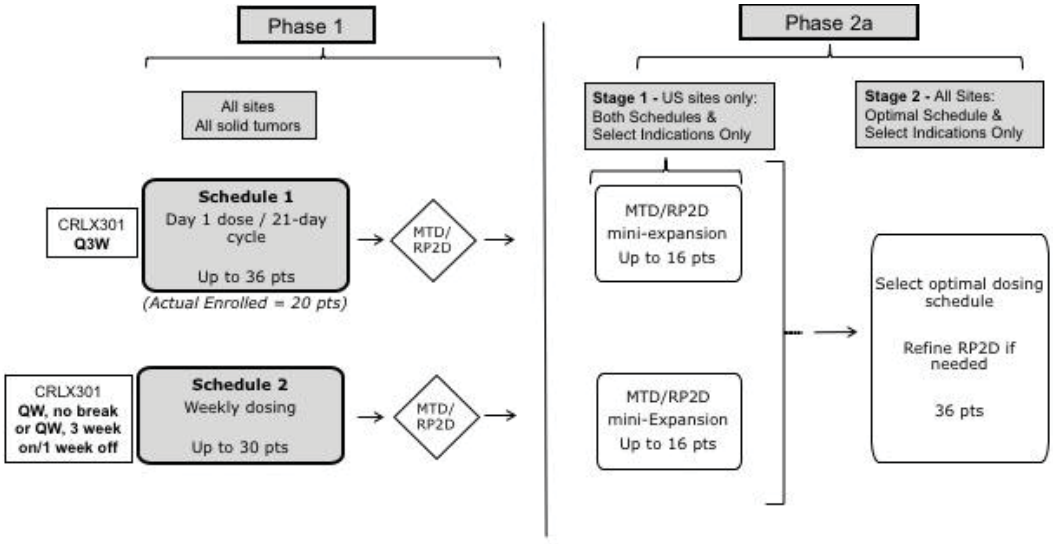
Subsequent cohorts will enroll a minimum of 3 patients with dose escalation until ≥2 patients in a cohort experience DLT(s) during Cycle 1 or the first 3 weeks. A DLT is defined as any adverse event (AE) possibly, probably, or definitely related to CRLX301 that results in an unacceptable toxicity (per criteria specified) and occurs at any point during Cycle 1 or the first 3 weeks post-initiation of study drug infusion.

Additionally, the Safety Review Committee (SRC) is responsible to determine whether or not there is a defined wait period between any or all patients into a new cohort. See Section 3.1.6: Study Safety Review Committee for details.

Enrollment in a particular dose cohort will be halted immediately when ≥2 patients within the cohort experience a DLT during Cycle 1 or the first 3 weeks. At this point, dose de-escalation will occur until <2 of 6 patients experience a DLT in a cohort. Then dose escalation with an additional cohort assigned to a mid-way dose level may be required to determine MTD and/or RP2D.

Phase 1 enrollment into both dosing schedules may run in parallel. Enrollment will be managed through close communication with participating clinical sites so that Investigators are aware of available patient slots in each of the dosing schedules.

Figure 1: Study Schematic



3.1.2 Definition of Maximum Tolerated Dose and Recommended Phase 2a Dose

The MTD is defined as the highest dose level at which fewer than 2 of 6 patients in a Phase 1 dose escalation cohort experiences a DLT during the first three weeks of treatment. This is the dose level for which the incidence of DLT is <33%.[23]

The RP2D is defined as the dose which will be assigned in Phase 2a as advised by the SRC based on AEs, anti-tumor activity of CRLX301 and available PK and 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.

3.1.3 Definition of Dose-Limiting Toxicity

A DLT is defined as any AE possibly, probably, or definitely related to CRLX301 that results in an unacceptable toxicity (per criteria below) and occurs at any point during the first 3 weeks of treatment post-initiation of study drug infusion. The event must be assessed by the Investigator and study Medical Monitor, and be determined to be unrelated to disease progression, intercurrent illness, or concomitant medications. All DLTs will be graded according to the current version of the Common Terminology Criteria for Adverse Events (CTCAE Version 4.03) (Appendix B).

Note that for any hematologic grade 3 or 4 events repeat lab values should be obtained every 48 - 72 hours or as clinically indicated to evaluate for DLT criteria and resolution.

DLTs may include but are not limited to the following:

- Grade 4 neutropenia >7 days
- Grade 3 or 4 neutropenia with fever (≥38.5ºC)
- Grade 4 thrombocytopenia, or ≥ Grade 3 thrombocytopenia in the presence of bleeding
- AST/ALT elevation of 5-10x ULN lasting > 24 hours
- Any single instance of AST or ALT elevation >10x ULN
- Any single instance of total bilirubin elevation > 3 x ULN
- Any single instance of AST/ALT elevation >3x ULN accompanied by bilirubin elevation >2x ULN that is not thought to be due to progressive disease
- Grade 3 nausea, vomiting, or diarrhea for >72 hours despite standard of care treatment
- Grade 4 nausea, diarrhea or vomiting of any duration
- Any non-hematological toxicity ≥Grade 3 of any duration, **excluding those above and the following:**
  - Grade 3 fatigue lasting <7 days
  - Grade 3 anorexia
  - Grade 3 dehydration as a result of nausea and vomiting
  - Grade 3 constipation
  - Grade 3-4 hypersensitivity/infusion reaction
  - Grade 3 electrolyte disturbance resolving to ≤ Grade 1 or baseline within 7 days (supplementation allowed)
- Any ≥ Grade 2 peripheral neuropathy > 14 days
- Any unresolved related AE that results in >21day delay to initiate the patient's second dose, excluding alopecia
- Any other ≥Grade 2 toxicity of any duration that in the opinion of the Investigator and upon review with the Medical Monitor is determined to be a clinically unacceptable risk.

3.1.4 Treatment Schedule

Eligible patients will receive an intravenous infusion of CRLX301 on:

- Schedule 1 (Q3W): Day 1 of a 21-day cycle

- Schedule 2 (QW): Day 1 of every week, no break or QW, 3 week on/1 week off * (depending on enrollment cohort)

and continue treatment as per assigned Schedule until progression of disease (unless the Investigator and sponsor agree it is acceptable for the patient to continue treatment) or other specified reason for study discontinuation (see Section 6.1: Reasons for Discontinuation from Treatment).

*For Schedule 2 (QW, 3 week on/1 week off), CRLX301 will be dosed weekly for the first 3 weeks of each 4-week period (e.g., week 1, week 2, week 3). No CRLX301 will be administered on week 4.

3.1.5 Phase 1 Dosing Cohorts

Schedule 1

Sequentially enrolled cohorts will receive increasing doses of CRLX301 in Cycle 1 until ≥2 patients experience DLTs. Eligible patients will be assigned to the currently open cohorts and assigned to the specified dose of CRLX301 per Table 1: Schedule 1 Q3W Provisional Phase 1 Dose Escalation Scheme. After halting dose escalation due to DLTs, dose de-escalation will occur until <2 patients out of 6 experiences a DLT in a cohort.

For determination of the MTD, an additional cohort may be enrolled and assigned to the dose level midway between the dose level at which <2 patients out of 6 experiences DLTs and the dose level at which ≥2 patients out of 6 experiences DLT.

The Schedule 1 Cohort 1 starting dose level was 7.5 mg/m^2; see Section 1.7: Rationale for Q3W Dosing and the Starting Dose Phase 1 Based on Clinical Experience with Docetaxel. The initial dose level was increased by 2 times to 15 mg/m^2 dose-level; thereafter, the dose level increments will be an additional 15 mg/m^2.

Schedule 2

The Schedule 2 Cohort 1 starting dose level is 25 mg/m^2, see Section 1.7: Rationale for Weekly Dosing (Schedule 2) and the Starting Dose Based on Clinical Experience with CRLX301.

3.1.5.1 Cohort Expansion for DLT

If at any time during the first three weeks of treatment on either Schedule a patient experiences a DLT, then additional patients will be enrolled up to a total of 6 treated at the same dose level. Upon expansion, the SRC will decide if enrollment between each additional patient will require a defined wait period or if additional patients may enroll as soon as eligible. If at any time during the first three weeks of treatment a second patient experiences a DLT then enrollment in that cohort will be halted immediately.

If none of the additional patients enrolled in the same cohort experiences a DLT in the first three weeks of treatment (i.e., <2 out of 6 patients in the cohort), then dose escalation may occur with enrollment of new patients at the next dose level per the Dose Escalation Scheme.

3.1.5.2 Cohort Dose Escalation Scheme

Before a decision is made to increase the dose a minimum of 1 patient (Schedule 1 Cohort 1 and 2 only) and a minimum of 3 patients (all subsequent Cohorts for Schedule 1 and for Schedule 2) must have been treated with the assigned dose of CRLX301 and have completed three weeks of treatment. For Schedule 1 this includes the Day 22 safety evaluation (21 days post-infusion) and for Schedule 2 this includes pre-dose or day of visit evaluations for Week 4. The SRC will review emerging safety data from the current cohort and data from on-going patients in previous cohorts before proceeding to enrollment in the subsequent cohort. Each dosing schedule will be reviewed independently.

Cohort dose escalation will follow the Dose Escalation Scheme tables (Table 1 and Table 2).

- If in Cohort 1, there are 2 patients who experience a DLT during the first three weeks of treatment, dose escalation will not occur. Subsequent cohorts may be dosed at a lower dose and/or at a less frequent schedule to be determined by the Sponsor, Medical Monitor, and Investigators and implemented per protocol amendment.
- If in Cohort 1 there is no more than 1 patient who experiences a DLT during the first three weeks of treatment, then dose escalation will occur.
- Similarly, for subsequent Cohort dose levels, if no more than 1 of up to 6 patients in the cohort experiences a DLT during the first three weeks of treatment, then dose escalation will occur with enrollment of new patients at the next dose level per the Dose Escalation Scheme.

Intermediate dose level cohorts are allowed as recommended by the SRC instead of escalating to the next planned dose cohort.

In the absence of DLT if the SRC or sponsor wants to further define the safety, efficacy, PK or PD profile of CRLX301 at a particular dose level, additional patients may be enrolled at the same, intermediate or lower dose levels following consultation between the investigator and sponsor.

Additionally, and for Schedule 1 only, based upon review of AEs and available PK data by SRC at the end-of cohort-review-meeting for the 30 mg/m^2 cohort, 100% dose escalation from 30 mg/m^2 to as high as 60 mg/m^2 (80% of the approved dose of docetaxel) for the next cohort was allowed if recommended by the SRC. No other planned cohorts may be skipped during Schedule 1 Phase 1 dose escalation.

For Schedule 2 only, based upon review of AEs and available PK data by SRC at the end-of cohort-review-meeting it is allowable to skip a proposed dose level in order to minimize the number of patients treated at sub-optimal dose levels. However, dose increment to the next higher dose level shall not exceed 40% at dose levels below 50 mg/m2 and will not exceed 20% at dose levels at or above 50 mg/m^2.

Table 1: Schedule 1 Q3W Provisional Phase 1 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 plus 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/m2 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 Phase 1 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	
2	35 mg/m^2	
3**	45 mg/m^2	
4**	54 mg/m^2	

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%)	
*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		

The final dose and schedule for cohorts beyond Cohort 4 will be selected by the SRC based upon review of AEs and available PK data from both dosing schedules.

3.1.6 Study Safety Review Committee

Members: The Investigators, Sponsor representative, Sponsor designated Medical Monitor and Sponsor designated PK expert will comprise the Study Safety Review Committee (SRC).

Phase 1 Meetings: This committee will discuss all DLTs, AEs, PK parameters if available, and other relevant data on regular teleconferences, no less frequently than after completion of enrollment and treatment in a cohort prior to dose escalation.

Phase 1 Decision-making role: The SRC is designated to make decisions for the Study for each dosing schedule regarding:

- confirmation of DLTs
- confirmation to proceed with enrollment in a new cohort with dose escalation
- confirmation of next dose level
- determine if any type of enrollment wait period will be imposed between patients in the next cohort or during expansion (based on emerging safety data)
- recommend if dose schedule modifications are needed according to the clinical and PK data available
- determination of the MTD and/or RP2D.

In the event the SRC is not in agreement, then the Sponsor Chief Medical Officer will make the final decision after consultation with additional medical advisors.

3.1.7 Dose Reductions

Patients experiencing a DLT in first 3 weeks will have the study drug interrupted and will be followed until recovery from their DLT to grade ≤1 or baseline. After that, if the investigator (along with the Sponsor) concludes that it is in the patient's best interest to resume study treatment, the patient may continue in the study at a lower dose level.

Patients who do not experience a DLT but are dosed in the same cohort where ≥2 patients experienced DLTs, will be dose de-escalated to the next lower already studied dose level at the next scheduled treatment, as per the Dose Escalation Scheme.

3.1.7.1 Dose De-escalation

If during later treatment beyond the DLT period, a patient experiences an unacceptable toxicity (defined as a toxicity that meets the same criteria of DLT for the first 3 weeks), the patient may continue in the next treatment cycle but must have a dose reduction to the next lower dose level as per the Dose Modification Scheme.

A maximum of 2 dose de-escalations will be permitted per patient. Patients who require >2 dose reductions will be discontinued from treatment and will be followed up per protocol.

3.2 Phase 2a Expansion Study Design

Phase 2a will be an open-label RP2D expansion study. Treatment guidelines for the RP2D expansion cohorts will be the same as those for the Phase 1 dose expansion cohorts.

Patients will be followed for safety, tumor response, and progression free survival (PFS) while on the study per RECIST version 1.1 guidelines or with methodologies consistent with tumor type. Patients will remain on study treatment until they experience progression of disease unless the Investigator feels the patient would benefit from continued treatment, unacceptable toxicity, or other specified reason for discontinuation (see Section 6.1: Reasons for Discontinuation from Treatment).

3.2.1 Phase 2a Stage 1 Expansion

Once either of the dosing schedules confirms 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 5 specific tumor types will be selected and only patients with the select 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 6 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 CTCs and MPS function (both of which require freshly collected whole blood samples) only US sites will enroll patients in Stage 1.

3.2.2 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 5 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.

4. STUDY POPULATION

4.1 Inclusion Criteria

Patients must meet the following criteria for inclusion:

1. Male or female adult patient ≥18 years of age
2. Diagnosis of histologically or cytologically confirmed, advanced solid tumor malignancy:
    a. For Phase 1: that is refractory to standard therapy and/or for whom no further standard therapy is available, especially for those which taxane chemotherapy may be a reasonable therapeutic choice, in the opinion of the Investigator
    b. For Phase 2a: advanced/metastatic tumors considered responsive to taxanes
    c. For prostate cancer patients in Phase 2a: that is castration resistant prostate cancer (CRPC*) and has not been previously treated with taxanes (taxane-naïve [unless approved by Sponsor]) but has been treated with abiraterone and/or enzalutamide. ***NOTE:** CRPC is defined as:
        i. **Castration:** Undergone surgical castration, or medical castration with testosterone < 50ng/dL
        ii. **Resistant**: Disease progression while castrate with radiographic progression defined by Prostate Cancer Working Group 2 (PCWG2) criteria, **OR** disease progression defined as rise in PSA with baseline PSA of at least 2 ng/mL, **OR** disease progression as per RECIST 1.1.
3. For patients enrolled in Phase 2a only at least one measurable target lesion as defined by RECIST 1.1 criteria for solid tumors, except for patients with advanced prostate cancer (as per the PCWG2 criteria). Tumors within a previously irradiated field should be designated as "non-target" unless progression is documented or a biopsy is obtained to confirm persistence at least 90 days following completion of radiation therapy.
4. If Patient has received:
    a. approved chemotherapy or small molecule targeted therapy; it has been ≥2 weeks since last dose before CRLX301 first dose
    b. investigational therapy; it has been ≥30 days before first dose
    c. local palliative radiation; it has been ≥14 days prior to first dose
    d. radiation or invasive surgery requiring general anesthesia; it has been ≥30 days before first dose
    e. chemotherapy with nitrosoureas or mitomycin C; it has been ≥45 days before first dose
5. ECOG Performance Status of 0 or 1

6. Life expectancy in opinion of Investigator of greater than 12 weeks
7. Patients with acceptable pre-study hematology and biochemistry labs ≤3 days prior to first dose defined as:
    a. absolute neutrophil count (ANC) ≥1500 cells/µL (1.5 x10^9/L), without growth factor support
    b. platelet count ≥100,000 cells/µL, without growth factor support
    c. hemoglobin ≥10 g/dL (100 g/L) for males, and ≥9 g/dL (90 g/L) for females
    d. total bilirubin within normal limits
    e. AST/ALT ≤1.5 x ULN
    f. creatinine 24-hour clearance ≥40 mL/min (measured or calculated)
    g. PT/PTT ≤1.2 x ULN
8. Contraception requirements:
    a. Women of child-bearing potential, defined as women physiologically capable of becoming pregnant, must use highly effective methods of contraception during study treatment and for 30 days after the last dose of study treatment. Highly effective methods of contraception include:
        i. Total abstinence (when this is the preferred and usual lifestyle of the subject). Withdrawal and periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) are not acceptable methods of contraception.
        ii. Female sterilization (defined as having had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy, or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
        iii. Male sterilization for at least 6 months prior to screening. The vasectomized male partner should be the sole partner for that subject.
        iv. Use of oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception. In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment.
    b. Male subjects must use condoms during the study treatment period and for 120 days following the last dose of study drug.

9. Negative urine pregnancy test ≤3 days prior to first dose (women of childbearing potential only)
10. Ability to understand and willingness to sign a written informed consent form
11. Able to comply with study visit schedule and assessments.

4.2 Exclusion Criteria

Patients who meet any of the following criteria will not be eligible to participate in the study:

1. Uncontrolled grade 2 or greater toxicity except alopecia related to any prior treatment (i.e. chemotherapy, targeted therapy, radiation or surgery) within 7 days prior to C1D1 unless approved by the Medical Monitor
2. Prolongation of QT/QTc interval (QTc interval >450 msec. for males and >470 msec. for females) using the Fredericia method of QTc analysis. If single reading is above these minimum ranges, then repeat test in triplicate and evaluate eligibility based on average value
3. Women who are pregnant or nursing
4. Any known HIV infection or AIDS or any concurrent infection requiring IV antibiotics
5. Any chronic or concurrent acute liver disease, including viral hepatitis
6. Primary brain malignant tumors
7. Known metastases to the brain / CNS confirmed by CT requiring treatment or radiation therapy, or that have not been confirmed stable on imaging for ≥ 30 days prior to first dose
8. Uncontrolled hypertension >150 (systolic) and >100 (diastolic) mmHg
9. Concurrent participation in any other investigational study, unless non-interventional study and approved by Sponsor
10. Concurrent treatment with the following medication, unless approved by Sponsor:
    a. Anticoagulant
    b. Tubulin binding agents (e.g. colchicine)
    c. Strong CYP3A4 inhibitors (see Appendix C)
11. History of stroke, deep venous thrombosis (DVT), transient ischemic attack (TIA), or myocardial infarction, within 6 months prior to first dose
12. History of other cancer type, except for cutaneous basal cell or squamous cell carcinoma, or cervical in situ or very low/low risk prostate cancer within the last 2 years prior to first dose
13. Uncontrolled concurrent disease or illness including but not limited to:

a. symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia
b. unstable or untreated cardiac conditions or ejection fraction of <50% as determined by echocardiogram (ECHO) or multiple gated acquisition scan (MUGA); NOTE: ECHO or MUGA required at screening only in subjects with known history of cardiac insufficiency **and** symptomatic in 3 months prior to screening.
c. diabetes mellitus
d. coagulation disorder
e. psychiatric illness that would limit compliance with study requirements, as determined by the Investigator

14. History of severe hypersensitivity reaction to taxanes
15. For Phase 2a Stage 2: treatment with a taxane within 6 months of first dose; **NOTE:** advanced prostate cancer patients must be taxane-naïve.
16. Peripheral neuropathy defined as one or more of the following unless approved by the Sponsor:
    a. Active peripheral neuropathy within 30 days prior to first dose defined as:
        i. Motor neuropathy of any grade (e.g., distal extremity weakness, loss of deep tendon reflex)
        ii. ≥Grade 2 neurosensory symptoms (e.g., pain, numbness, paresthesia, dysesthesia, etc.)
    b. History of ≥ Grade 3 neurologic reactions to prior chemotherapy; in particular, any neurological reactions that required a dose reduction or discontinuation from prior taxane therapy.
17. Other severe, acute, or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or study drug administration or that may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for the study.

4.3 Number of Patients

Phase 1: Up to 66 patients may be enrolled in the Phase 1 dose escalation cohorts. Up to 36 patients may be enrolled for Schedule 1 (Q3W) and up to 30 patients may be enrolled for Schedule 2 (QW, no break or QW, 3 week on/1 week off). The exact number of patients is dependent on the actual number of patients per cohort and total cohorts investigated in both dosing schedules based on toxicities experienced.

Phase 2a: 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 5 specific tumor types.

4.4 Replacement of Patients

Phase 1: Patients enrolled in the Phase 1 dose escalation cohorts who discontinue prior to completion of 3 weeks on treatment for any reason other than a DLT are deemed not evaluable for MTD and will be replaced.

Phase 2a: Patients enrolled in both Stages of the Phase 2a RP2D expansion cohort who discontinue from the study for any reason at any time will not be replaced.

5. STUDY PROCEDURES

See Schedule of Procedures.

5.1 Informed Consent and HIPAA

Written informed consent, and HIPAA authorization (United States only) to use or disclose protected health information, must be obtained from a prospective patient before any study-specific procedures are performed for that individual. Standard of care assessments performed before informed consent is obtained may be utilized to screen for study eligibility. Patients will read the Informed Consent Form (ICF), and the HIPAA authorization (as applicable), after being given an explanation of the study. Before signing the ICF and HIPAA authorization form, patients will have an opportunity to discuss the contents of the ICF and HIPAA form with study center staff. Patients will be made aware that they may withdraw from the study at any time. Patients who agree to participate in the study will sign the most recently approved ICF and the HIPAA authorization form and will be provided with a copy of the fully executed documents. The original, executed ICF and HIPAA will be maintained in the respective patient's clinical study file. .

Refer to Section 12: Ethical Considerations

Once screening procedures have begun, patients will be provided with Day(-1) premedication along with instructions to be followed once eligibility is confirmed. **NOTE:** Research staff will call each patient within 72 hours prior to Day(-1) to remind the patient to take premedication.

5.2 Eligibility, Study Enrollment, and Patient Number Assignment

Patients will be assigned screening numbers consecutively by the Investigator or designee at the time the patient signs the ICF. For all patients screened, the Investigator or designee will record the eligibility criteria assessment in the medical record. A screening and enrollment log will capture screening number, date of enrollment or determination as ineligible, and the assigned subject enrollment number, if enrolled.

Enrollment for this study is defined as any patient that has received at least one dose of CRLX301.

Each eligible, enrolled patient in the study will be uniquely identified by a patient identification number. Patients will be assigned a study number by the Sponsor only after screening eligibility is confirmed (repeat assessments being performed within 3 days of first dose may still be pending). Once assigned, a patient identification number will not be reused.

See the Investigator Site File for Enrollment forms and complete enrollment instructions. The Sponsor and Medical Monitor may review eligibility and have final determination regarding whether a patient is eligible as appropriate.

NOTE: The following information in Sections 5.3 through 5.21 is to be recorded on the eCRF for enrolled patients only.

5.3 Current Cancer Diagnosis, Prior Therapies, and Responses

Record cancer history including but not limited to:

- current cancer diagnosis
- date of diagnosis
- disease stage at time of diagnosis
- disease stage at pre-Study

Record all anti-cancer therapy received including but not limited to:

- names of drugs
- description of surgery
- anatomic sites for radiation
- start and stop dates
- dosing
- best response to each treatment

5.4 Other Medical History

Record medical history including but not limited, to:

Demographics: date of birth, gender, race, and ethnic origin

Clinically significant prior diagnoses, prior surgeries, and concurrent medical conditions or illnesses noting current severity

Allergies and known hypersensitivity reactions to any medications

Any other cancer history (not current cancer), including prior therapies received, outcome of those therapies, and progression-free interval on those therapies

5.5 Concomitant Medications and Therapies

5.5.1 Concomitant Medications

Record concomitant medications including:

Medications administered to the patient within 30 days prior to the planned first dose of study drug. Include name of medication, indication, dose if available, route and frequency of administration, and start dates and stop dates if applicable.

Concomitant medications taken by the patient during the study period including all medications, supplements, and blood products from first dose through 30 days post the last dose of study drug.

5.5.1.1 Concomitant Procedures

Any other non-cancer related medical or surgical procedure received by the patient during the study period. Information to be recorded includes: the name of the medication or procedure, indication, dose and frequency if applicable, and duration of treatment.

5.5.2 Concurrent Cancer Symptom Management

Palliative and supportive care for disease-related symptoms and pain management should be continued or initiated as clinically indicated during the study with the following exceptions:

- Patients may not be treated with erythropoietin, darbepoetin (Aranesp®), or other erythrocyte-, neutrophil- or platelet-stimulating agents during the first three weeks of therapy. However, they may be used in subsequent cycles/weeks of treatment per investigator discretion or institutional standard guidelines.
- Patients requiring palliative radiation therapy must be pre-approved by the Sponsor and study Medical Monitor.

5.5.3 Prohibited Concurrent Medications or Therapies

Patients are prohibited from:

- Receiving any other cancer treatment during the study period. This includes but is not limited to:
  - any approved antineoplastic or biologic therapies
  - radiation therapy
  - surgical procedures
  - investigational chemotherapy or biologic therapy
- Erythropoietin, darbopoietin or other erythrocyte, neutrophil-, or platelet-stimulating agents during the first three weeks of treatment
  - These may be used in subsequent cycles/weeks as per investigator discretion or institutional standard guidelines. Please refer to Section 5.10.4.1: CRLX301 Treatment Modifications for Hematologic Toxicity for additional information.
- Strong CYP3A inhibitors during the study period unless sponsor approval is obtained in writing prior to enrolling the patient or initiating treatment (Appendix C)
- Other tubulin binding agents during the study period (e.g. colchicine)

5.6 Physical Examination and BSA

Patients will undergo a complete physical examination, which will be completed by the investigator who is a professionally trained physician or health professional listed on Form FDA 1572 and licensed to perform physical examinations, pre-study and at the End-of-Study visit. Complete physical examination will include the major body systems, including skin, height (pre-Study only), weight, and ECOG Performance Status (Appendix A).

In addition, a limited physical examination will occur every three weeks (end of each cycle for Schedule 1 or pre-dose every 3 weeks for Schedule 2 – QW, no break) or every four weeks (pre-dose every 4 weeks for Schedule 2 – QW, 3 week on/1 week off). Limited physical examinations will include general appearance, heart, lungs, abdomen, and any symptom directed examination of body/system organ(s). Symptom directed exams will require the patient to report on any signs/symptoms that they may have and, based on the patient's report, the Investigator will conduct physical examinations of relevant body/system organ(s). Height and weight will be used to calculate Body Surface Area (BSA). BSA will be calculated for the first dosing day and recalculated only if body weight changes by more than 10% and the change is attributed to dry weight. (Section 7.2.1: Body surface Area Calculation.)

5.7 Vital Signs

Vital signs measurement includes diastolic and systolic blood pressure (BP), heart rate (HR), and respiratory rate (RR). These will be assessed by study center staff as per the time points in the Schedule of Procedures and/or Table 3 and Table 4.

BP and HR will be measured with patients in the sitting or supine position (patients must be sitting or supine for at least 5 minutes), using the same arm throughout the study, and before any corresponding blood sample is collected.

All vital sign assessments will be recorded on the eCRF, including any additional assessments completed for evaluation of potential infusion reactions or possible AEs.

Table 3: Schedule 1 (Q3W) Vital Sign Assessment

Study Day	Timing	Window
Cycle 1 Day 1	Prior to start of CRLX301 IV infusion *Including Temperature	none
	30 min after initiation of CRLX301 infusion	±5 min
	60 min into infusion	±5 min
	End of infusion	±5 min
	60 min (1 hour) after completion of CRLX301 infusion	±5 min
	180 min (3 hours) after completion of CRLX301 infusion	±10 min
	360 min (6 hours) after completion of CRLX301 infusion *Including Temperature	-1 hr
All other cycles Day 1	Prior to start of CRLX301 IV infusion * Including Temperature	none
	60 min/1 hour after completion of CRLX301 infusion	±5 min
All cycles Day 8	7 days after completion	N/A: day of visit
All cycles Day 22	21 days after completion and prior to initiation of CRLX301 for subsequent treatment cycle	On day of visit, pre-dose
EOS	Day of Visit * Including Temperature	N/A: day of visit

*Temperature collection required per protocol.

Table 4: Schedule 2 (QW, no break) Vital Sign Assessment

Study Day	Timing	Window
Week 1, 4 & 7 **Day 1**	Prior to start of CRLX301 IV infusion *Including Temperature	none
	30 min after initiation of CRLX301 infusion	±5 min
	60 min after initiation of CRLX301 infusion	±5 min
	End of infusion	±5 min
	60 min (1 hour) after completion of CRLX301 infusion	±5 min
	180 min (3 hours) after completion of CRLX301 infusion	±10 min
	360 min (6 hours) after completion of CRLX301 infusion *Including Temperature	-1 hr
Week 2, 3, 5, 6 **Day 1**	Prior to start of CRLX301 IV infusion * Including Temperature	none
	End of CRLX301 infusion * Including Temperature	±5 min
Week 8 & subsequent weeks **Day 1**	Prior to start of CRLX301 IV infusion * Including Temperature	none
EOS	Day of Visit * Including Temperature	N/A: day of visit

* Temperature collection required per protocol.

Table 5: Schedule 2 (QW, 3 week on/1 week off) Vital Sign Assessment

Study Day	Timing	Window
Week 1, 3 & 7 **Day 1**	Prior to start of CRLX301 IV infusion *Including Temperature	none
	30 min after initiation of CRLX301 infusion	±5 min
	60 min after initiation of CRLX301 infusion	±5 min
	End of infusion	±5 min
	60 min (1 hour) after completion of CRLX301 infusion	±5 min
	180 min (3 hours) after completion of CRLX301 infusion	±10 min
	360 min (6 hours) after completion of CRLX301 infusion *Including Temperature	-1 hr
Week 2, 5 & 6 **Day 1**	Prior to start of CRLX301 IV infusion * Including Temperature	none
	End of CRLX301 infusion * Including Temperature	±5 min
Week 4 & 8	Day of Visit * Including Temperature	N/A: day of visit
Week 9 & subsequent dosing weeks **Day 1**	Prior to start of CRLX301 IV infusion * Including Temperature	none
EOS	Day of Visit * Including Temperature	N/A: day of visit

Every effort should be made to perform vital signs at the specified time points. When vital sign collection timing coincides with blood PK collection timing, collection of the PK on time point is the preferred priority if clinically feasible. However, vital signs collected outside of the allowable window, or *after* a coinciding plasma PK sample be logged as a minor protocol deviation with explanation.

5.8 Electrocardiogram

Standard 12-lead ECG will be performed for safety as per the time points in the Schedule of Procedures. The paper speed will be a standard 25 mm/second; the ECG tracing will be kept at the study center. Measurements will be recorded for the following parameters in lead II or lead III: heart rate, PR interval, QRS duration, QT interval, and QTc (using the Fredericia method of QTc analysis). If any reading is abnormal, then the ECG will be repeated in triplicate and the average value of the 3 readings will be reported.

ECGs will be clinically interpreted by the Investigator or designee and patient eligibility determined per QTc interval. Once enrolled, all ECGs should be interpreted prior to the patient leaving the clinic.

Repeat ECG as clinically indicated if there are changes in cardiac medical condition or if the patient has reported concomitant medications with documented cardiac toxicities since the pre-study ECG.

5.9 Echocardiogram (ECHO) or Multi Gated Acquisition Scan (MUGA)

ECHO or MUGA is required during pre-study for patients with known cardiac disease who are symptomatic within 3 months of planned first dose. Confirm sufficient cardiac function if testing has not already been performed within 30 days of first dose. If a patient is asymptomatic at pre-study with no history of impairment of cardiac function, this procedure for eligibility is not required.

5.10 Study Treatment and Dose Assignment

5.10.1 Cohort and Dose Assignment

Phase 1:

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.

Phase 2a:

All patients will be assigned to the CRLX301 dose level that is determined to be the RP2D. Patient dosing schedule will be provided in writing from the Sponsor to the Investigator when the patient's study identification number is assigned. The same treatment guidelines and assessments will apply as those specified in Phase 1.

5.10.2 Premedication Prior to CRLX301 Treatment for Both Schedules

As a precaution to minimize the risk and/or severity of infusion-related hypersensitivity reactions, all patients will be provided premedication to allow for dosing the night prior (Day (-1), and also on day of CRLX301 infusion.

Once screening procedures have begun, patients will be provided with Day (-1) premedication along with instructions to be followed once eligibility is confirmed. **NOTE:** Research staff will call each patient within 72 hours prior to Day (-1) to remind the patient to take premedication.

Prior to initiation of the CRLX301 infusion on day of dosing, sites should confirm that patient ingested premedication regimen the prior evening (Day (-1)). If patient did not take the premedication, the CRLX301 infusion will be initiated at discretion of the investigator. On day of dosing, premedication will be administered 30-90 minutes prior to the CRLX301 infusion.

Table 6: Premedication Schedule for Q3W and QW Schedules

Class	Preferred Medication	Dose	Route
Night Prior to CRLX301 Infusion Day (-1)			
corticosteroid	dexamethasone	8 mg	oral
antihistamine	diphenhydramine	50 mg	oral
H2 antagonist	ranitidine	50 mg	oral
30-90 minutes Prior to CRLX301 Infusion			
corticosteroid	dexamethasone	8 mg	IV
antihistamine	diphenhydramine	50 mg	IV
H2 antagonist	ranitidine	50 mg	IV
OPTIONAL: Antiemetic with a 5-HT3 receptor	dolasetron	100 mg	IV
	ondansetron	8-24 mg	IV
	SOC	SOC	oral

If the subject has not experienced any infusion related reaction after the first three infusions of CRLX301, the dose of dexamethasone (both the night before and on day of CRLX301 dosing) may be tapered to 4mg for subsequent CRLX301 infusions. If the subject continues to tolerate the subsequent three infusions of CRLX301, without experiencing any infusion related reaction, all “night prior” premedication may be stopped at the investigator's discretion. On the day of CRLX301 dosing, premedication are to continue throughout the study.

The example medications, route of administration, and dose indicated should be the medication-of-choice if clinically feasible. **Note**: It is particularly important to administer the premedication on the day of CRLX301 dosing via IV to achieve the quickest onset and maximum bioavailability of these medications to effectively prevent hypersensitivity/infusion reaction. The oral route is not recommended, especially for patients who have gastrointestinal tract (GI) tumor involvement, GI disease history and/or active GI symptoms (e.g., nausea, vomiting, diarrhea) that may negatively impact the absorption of the medications. If not clinically feasible or not site standard practice, the Investigator should discuss appropriate options with the medical monitor prior to Cycle 1 Day 1 dosing for each patient. A prospective approval from the Medical Monitor or sponsor Medical Director may be provided in writing to acknowledge alternate route or alternate medication. All premedication will be recorded on the eCRF as concomitant medications with the name of the medication, dose, time administered, and the indication reported as "CRLX301 premedication".

Please refer to Section 5.10.4.2: CRLX301 Treatment Modifications for Non-Hematologic Toxicity for management of any hypersensitivity reactions to CRLX301.

5.10.3 CRLX301 Administration, Management of Infusion Related Reactions and Treatment Compliance

5.10.3.1 CRLX301 Administration

Each CRLX301 infusion should start as slow as possible with no more than 15mL infused over the first 15 minutes. Provided the subject does not experience any infusion related symptoms during these 15 minutes, the rate of infusion can then be **gradually** increased to complete the infusion in approximately 120 minutes, inclusive of 50mL flush. If a subject has a history of infusion related reactions to other drug treatments, or has many environmental allergies (e.g., food, pollen), the total infusion time may be slowed during the first CRLX301 infusion and for all subsequent infusions, at the discretion of the investigator. If the Day (-1) premedications have been stopped and the patient has tolerated at least 3 infusions without Day (-1) premedications, the CRLX301 infusion rate may be increased (while maintaining the rule of no more than 15mL in first 15 minutes) to complete infusion in no less than 60 minutes, at discretion of investigator.

5.10.3.2 Management of Infusion Related Reactions

Table 7: Management of Infusion Related Hypersensitivity Reactions

NCI CTCAE Grade	Treatment	Retreatment Rules
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Collect data on tryptase as soon as possible (within 3 hours from onset of event)	Retreatment may be considered. The investigator may consult an allergist to assess if potential desensitization needs to be done prior to retreatment. At investigator's discretion, infusion rate may be slower for all subsequent dosing. The use of premedication may be increased as indicated. Tryptase should be repeated prior to each subsequent infusion.
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs.	**Immediately interrupt infusion** and provide appropriate medical therapy as indicated. Collect data on tryptase as soon as possible (within 3 hours from onset of event) Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within a few hours, at Investigator's discretion, study drug may be resumed and administered at a slower rate (i.e. 2x slower rate). The rate may be slowly increased to complete administration of full dose. **OR** Hold dose administration on the day of the hypersensitivity event, and resume treatment at next scheduled day at same dose level.	Retreatment may be considered. The investigator may consult an allergist to assess if potential desensitization needs to be done prior to retreatment. Infusion rate should be initiated at a slower (i.e. 2x slower rate) for subsequent dosing. The use of premedication may be increased as indicated. Tryptase should be repeated prior to each subsequent infusion.

NCI CTCAE Grade	Treatment	Retreatment Rules
Grade 3 Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	**Immediately Stop Infusion** and provide appropriate medical therapy. Collect data on tryptase as soon as possible (within 3 hours from onset of event). Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated.	Review with study Medical Monitor to determine whether to discontinue from study treatment. Confirm that rate of administration was appropriate and premeds were given as suggested. Retreatment is allowed only for subjects with clinical benefit from study drug and only after successful desensitization. Infusion rate should be initiated at a slower (i.e. 2x slower rate) for all subsequent dosing. The use of premedication may be increased as indicated. Tryptase should be repeated prior to each subsequent infusion.
Grade 4 Life-threatening; pressor or ventilatory support indicated	**Immediately Stop Infusion** and provide appropriate medical therapy as indicated. Collect data on tryptase as soon as possible (within 3 hours from onset of event) Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated.	Retreatment not allowed. Subject to be permanently discontinued from study treatment and followed up per protocol.

Please also note the following:

- Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.

- A blood sample for tryptase should be drawn within 3 hours of onset of any infusion related reaction. Further, if a subject is to be re-treated, repeat blood sample for tryptase prior to each subsequent infusion.

- For any ≤Grade 2 reaction, CRLX301 infusion may also be halted for the day, and the subject may return at the next scheduled visit for the next dose either as per study-specific CRLX301 administration procedures or per an Institutional desensitization protocol. For any subject that has experienced infusion related reaction while on study, all subsequent doses may be administered at a slower rate.

5.10.3.3 Treatment Compliance

All patients must meet hematology, bilirubin, AST, ALT and alkaline phosphatase eligibility criteria prior to receiving the first dose of CRLX301. Required hematology and chemistry lab results must be obtained within 3 days of the first dose date and within 24 hours of subsequent doses.

Patients will receive all doses under the direct supervision of the Investigator and designated study personnel. The intravenous infusion start time, stop time, volume infused, calculated dose and actual dose will be recorded.

5.10.4 Dose Delay or Reductions or Treatment Discontinuation for Toxicity

Modification and/or delay of treatment with CRLX301 will be based upon determination of hematologic and/or non-hematologic toxicities. Patients will continue to receive the same dose level of CRLX301 in Schedule 1 and in Schedule 2 as they were assigned at study entry unless a dose modification is required to manage AEs. In order to maintain dose-intensity and cumulative dose-delivery on this study, reasonable efforts will be made to minimize dose reduction and treatment delays as specified below. Any patient whose treatment is delayed must be evaluated *at least* weekly until adequate hematologic and non-hematologic parameters have recovered. All AEs and laboratory findings should be reviewed prior to dosing to determine whether any treatment modifications are required. The investigator should carefully assess all treatment-associated toxicities and, whenever possible, determine if they can reasonably be attributed to study drug.

Dose delays for up to 21 days from the planned initiation of the next dose are permitted. Any dose delay of >21 days from planned date of next dose may result in withdrawal of the patient from further treatment upon review and discussion with Medical Monitor.

Subsequent dosing days:

For subsequent dosing days after the first dose, if a patient experiences ongoing Grade ≥2 related AE in Schedule 1 (Q3W) or Grade >2 related AE in Schedule 2 (QW, no break or QW, 3 week on/1 week off), this will require a dose delay; if

the AE resolves to adequate hematologic and non-hematologic parameters in ≤21 days, this may require dose reduction. Refer to the information below for both hematologic and non-hematologic toxicity management.

It is also up to Investigator discretion to delay or reduce the dose for any Grade 1 AE.

If the AE does not resolve to adequate hematologic and non-hematologic parameters, and results in >21 day delay to initiation of the next dose Day 1, then the patient is withdrawn from further study treatment.

A maximum of 2 dose reductions will be permitted per patient. If a patient experiences repeat toxicities after 2 dose reductions, then subsequent treatment with CRLX301 will be halted and the patient will be withdrawn from the study. Patients who do not experience a DLT but are dosed in the same cohort where ≥2 patients experienced DLTs, will be dose de-escalated to the next lower dose level at the next planned dosing date, as per the Dose Escalation Scheme. This does not constitute 1 of the 2 permitted dose reductions for toxicity described above. Similarly, a change in dosing schedule from QW, no break to QW, 3 week on/1 week off dosing will not constitute 1 of the 2 permitted dose reductions.

Review all proposed dosing changes with the Medical Monitor and record on the eCRF.

5.10.4.1 CRLX301 Treatment Modifications for Hematologic Toxicity

For both schedules:

Treatment decisions will be based on the absolute neutrophil count (ANC) (rather than the total white cell count (WBC) and the platelet count.

Refer to Section 5.5.3: Prohibited Concurrent Medications or Therapies

The use of hematopoietic cytokines and protective reagents are restricted to after first 3 weeks and as noted below:

Patients will NOT receive prophylactic growth factors [filgrastim (G-CSF), sargramostim (GM-CSF), pegfilgrastim (Neulasta)] unless they experience recurrent neutropenic complications despite the treatment modifications specified below.

Patients will NOT receive prophylactic thrombopoietic agents.

Patients may receive erythropoietin (EPO), iron supplements, and/or transfusions as clinically indicated for management of anemia. Treating physicians should be aware of prescribing information for the erythropoiesis stimulating agents (including Aranesp, Epogen, and Procrit) which note that there is a potential risk of shortening the time to tumor progression or disease-free survival, and that these agents are administered only to avoid red blood cell transfusions. They do not alleviate fatigue or increase energy. They should not be used in patients with uncontrolled hypertension. They can cause an increased incidence of thrombotic events in cancer patients on chemotherapy. The updated package inserts should be consulted.

Table 8: Schedule 1 (Q3W): CRLX301 Dose Delay or Reduction for Hematologic Toxicity

Absolute Neutrophil Count on Cycle 1 Day 22 or Subsequent Cycles		**Platelet Count on Cycle 1 Day 22 or Subsequent Cycles**	**CRLX301 Dose for Next Cycle[1]**
Grade 2 <1500 and ≥1000 cells/µL	And	≥100,000 cells/µL	Hold dose until neutrophil count is ≥1500 cells/µL (Grade 1), then give full dose.
Grade 3 ≥500 and <1000 cells/µL	And	Grade 1 ≥75,000 cells/µL	Hold dose until neutrophil count is ≥1500 cells/µL. If event duration is >7 days, consult Medical Monitor to confirm need for dose reduction by 1 dose level. If event duration ≤7 days, then resume dosing at full dose. If associated with fever, then reduce dose
Grade 3 ≥500 and <1000 cells/µL	And	Grade 2 ≥50,000 and < 75,000 cells/µL	Hold dose until neutrophil count is ≥1500 cells/µL and platelet count is ≥75,000 cells/µL. If event duration >7 days, consult Medical monitor to confirm need for dose reduction by 1 dose level. If event duration ≤7 days, then resume dosing at full dose. If associated with fever, then reduce dose
Grade 4 <500 cells/µL	Or	Grade 3 ≥25,000 and <50,000 cells/µL	Hold dose until neutrophil count is ≥1500 cells/µL and platelet count is ≥75,000 cells/µL If duration > 7 days, then consult Medical Monitor to consider dose reduction by 1 dose level.
Any Grade or none at all	And	Grade 4 ≤25,000 cells/µL	Study treatment to be discontinued

[1] In cases of dose delay if cytopenia persists for >21 days from planned initiation of next cycle, then patient is withdrawn from study treatment.

Schedule 2 (QW, no break or QW, 3 week on/1 week off): CRLX301 Dose Delay or Reduction for Hematologic Toxicity:

- CRLX301 will not be given unless ANC is ≥1000/mm³ and the platelet count is ≥75,000/mm³.
- If CRLX301 treatment is held, missed doses will not be made up.
- During the first 3 weeks of treatment, GCSF use is not allowed. If the CRLX301 dose is held due to insufficient ANC and/or platelet counts, then monitor counts weekly until they are adequate for treatment. Restart dosing at the same dose level

if delay is < 2 weeks. If the dosing delay is ≥2 weeks, contact the Medical Monitor to discuss the appropriate dose to be given to the subject.

- After the first 3 weeks of treatment, if the CRLX301 dose is held due to insufficient ANC and/or platelet counts, monitor counts at least weekly until they are adequate for treatment. In the event where counts not recovered to adequate count within 7 days, GCSF should be instituted. If counts recover adequately within the next 7 days, then CRLX301 will be administered in the same dose used prior to the hold. However, if subjects do not recover within 7 days after GCSF support, subjects might restart dosing at a reduced dose level after the ANC and/or platelet recovers to adequate counts with GCSG support or be taken off study if dosing delay is more than 3 weeks.
- Therapy will be delayed for a maximum of 3 weeks until the required ANC (despite GCSF support) and platelet count values are achieved. Subjects who fail to recover adequate counts despite of GCSF support with a three-week delay will be removed from study therapy.

5.10.4.2 CRLX301 Treatment Modifications for Non-Hematologic Toxicity

For both schedules:

- Patients with nausea, emesis, diarrhea, constipation, dehydration, electrolyte disturbance should receive appropriate medical management without dose modification. However, patients with persistent (> 72 hours) ≥Grade 3 toxicity—in spite of optimal medical management require a reduction of 1 dose-level and delay in subsequent therapy until recovered to Grade 1.
- If a Grade 3 recovered to adequate hematologic and non-hematologic parameters by the planned next dosing day and this is the first episode of such event, dose reduction is not required. It is up to the investigator's discretion to reduce the dose or not.
- There will be no required dose modifications for alopecia, fatigue or hypersensitivity reaction.

Table 9: Schedule 1 (Q3W) CRLX301 Dose Delay or Reduction for Non-Hematologic Toxicity

Non-Hematologic Event CRITERIA	**CRLX301 Dose for Next Cycle**
There will be no dose modifications for alopecia or fatigue.	
During cycle, onset of Grade 2 event that is now recovered to ≤Grade 1 by the scheduled dosing day; and no dose adjustment during previous cycle	Full dose
Grade 2 toxicity resulting dose delay	Hold dose until recovery to ≤Grade 1 and consult with Medical Monitor, may or may require dose reduction. If dose delay >21 days, withdraw from the study
≥ Grade 2 peripheral neuropathy:	Hold dose until recovery to ≤Grade 1, and require dose reduction by 1 level. If dose delay >3 weeks, then withdraw from study.
During week onset of Grade 3 event that is now recovered to ≤Grade 1 by the scheduled dosing day; and no dose adjustment during previous cycle	For the first episode of Grade 3 toxicity, full dose. If the same Grade 3 toxicity in previous cycle, then requires dose reduction. (exception: fatigue, alopecia, hypersensitivity reaction)
Grade 3 toxicity resulting in dose delay	Hold dose until recovery to ≤Grade 1 and requires dose reduction Exceptions: fatigue, alopecia, dehydration as a result of nausea and vomiting; constipation; electrolyte disturbance resolving to ≤ Grade 1 or baseline within 7 days (supplementation allowed)
During cycle if bilirubin >1.2 x ULN, or AST and/or ALT >1.5 × ULN concomitant with alkaline phosphatase >2.5 × ULN	Hold dose, and if either of these are unresolved >21 days from planned initiation of next cycle, then withdraw from study treatment
Grade 4 event	Withdraw from study treatment

Table 10: Schedule 2 (QW, no break or QW, 3 week on/1 week off) CRLX301 Dose Delay or Reduction for Non-Hematologic Toxicity

Grade of Event	Intervention
Nausea & Vomiting (unresponsive to adequate medical management)	
≤Grade 2	No change in dose. Investigator's discretion whether to hold dose or administer dose per schedule if Grade 2 persists, may discuss with study Medical Monitor.
Grade 3 or 4	**Hold** until resolved to <Grade 2, **Resume at same dose level** if resolved to ≤Grade 1 within 2 weeks. **Resume at one dose level lower** if resolved to ≤Grade 2 within 3 weeks **If not resolved** with 3 weeks, then **review** with study Medical Monitor to determine whether to discontinue study treatment or follow for resolution and consider dose modification to reduced dose level.
Grade 3 or 4	**Stop** infusion immediately and administer medical support as indicated per institutional guidelines. **Hold** dose administration on day of event. **Review** with study Medical Monitor to determine whether to discontinue from study drug treatment. Confirm that rate of administration was appropriate and premeds were given as suggested.
Peripheral neuropathy	
≥Grade 2 peripheral neuropathy	**Hold** dose until recovery to ≤Grade 1, and require dose reduction by 1 level.
Liver functional test abnormality	
If Bilirubin >1.2 x ULN, or AST and/or ALT >1.5 × ULN concomitant with alkaline phosphatase >2.5 × ULN	**Hold** dose, and if either of these are unresolved for >21 days from planned next dose date, then withdraw from study treatment
Other CTCAEs other than those above (unresponsive to adequate medical management)	
≤Grade 2	No change in dose. **Review** with study Medical Monitor whether to hold dose or administer dose per schedule
Grade 3 or 4	**Hold** until resolved to ≤ Grade 1, **Resume** at one dose level lower, if resolved within 3 weeks **If not resolved** within 3 weeks, then **review** with study Medical Monitor to determine whether to discontinue study treatment or follow for resolution and consider dose modification to reduced dose level.

5.11 Clinical Laboratory Tests

Blood and urine samples for safety assessments will be collected and analyzed by each site's institutional or local laboratory's standard procedures. The following Table 11: Schedule 1 (Q3W) Clinical Laboratory Test Parameters and Timing, Table 12: Schedule 2 (QW, no break) Clinical Laboratory Test Parameters and Timing and

Table 13: Schedule 2 (QW, 3 week on/1 week off) Clinical Laboratory Test Parameters and Timing detail the clinical laboratory tests to be performed according to the Schedule of Procedures.

Table 11: Schedule 1 (Q3W) Clinical Laboratory Test Parameters and Timing

Lab Test	*Parameters*[5]	*Timing*
Chemistry	Sodium, potassium, calcium, chloride, glucose, blood urea nitrogen (BUN[2]) or urea, creatinine, total protein, alkaline phosphatase, albumin, total bilirubin, direct and indirect bilirubin **(NOTE**: recording of indirect bilirubin is optional), aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), inorganic phosphorus, uric acid, cholesterol, triglyceride levels, and tryptase[4]	• Pre-study[3] • Cycle 1: Day 1 (pre-dose)[3] • Cycles 1 – 7: Day 8, 15 and 22 • As of Cycle 8 and subsequent cycles: Day 1 pre-dose only • EOS
Hematology	Absolute and differential white blood cell count, red blood cell count, hemoglobin level, hematocrit level, platelet count, and reticulocyte count	
Coagulation	Prothrombin time (PT), partial thromboplastin time (PTT), and international normalized ratio (INR)	• Pre-study[3] • Cycle 1: Day 1 (pre-dose)[3] • Prior to post-dose biopsy (as applicable)
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	• Pre-study[3] • Cycle 1: Day 1 (pre-dose)[3] • Cycles 1 – 7: Day 1 (or Day 22) and 8 • As of Cycle 8 and subsequent cycles: Day 1 pre-dose only • EOS
Pregnancy test[1]	Urine pregnancy test or Serum β-hCG as confirmation of positive urine test	• Pre-study[3] • Cycle 1: Day 1 (pre-dose)[3] • EOS

1. Only for women of childbearing potential
2. Urea acceptable if BUN is not standard
3. Repeat if >3 days prior to C1D1
4. Tryptase only required in subjects who experience an infusion related reaction
5. Contact the Medical Monitor to discuss if any parameter results require >24 hrs. for turn-around

Table 12: Schedule 2 (QW, no break) Clinical Laboratory Test Parameters and Timing

Lab Test	*Parameters*	*Timing*
Chemistry & Hematology	See Table 9	• Pre-study • Week 1: Day 1 (pre-dose)[1] • Week 2 & subsequent weeks: Day 1 pre-dose • EOS
Coagulation		• Pre-study • Week 1: Day 1 (pre-dose)[1] • Prior to post-dose biopsy (as applicable)
Urinalysis		• Pre-study • Week 1 Day 1 (pre-dose)[1] • Week 2 & subsequent weeks: Day 1 pre-dose • EOS
Pregnancy test[2]		• Pre-study • Week 1 Day 1 (pre-dose)[1] • EOS

[1] Repeat only if >3 days prior to W1D1
[2] Only for women of childbearing potential

Table 13: Schedule 2 (QW, 3 week on/1 week off) Clinical Laboratory Test Parameters and Timing

Lab Test	*Parameters*	*Timing*
Chemistry & Hematology	See Table 9	• Pre-study • Week 1: Day 1 (pre-dose)[1] • Week 2 & subsequent dosing weeks: Day 1 pre-dose • Week 4 and Week 8 visits • EOS
Coagulation		• Pre-study • Week 1: Day 1 (pre-dose)[1] • Prior to post-dose biopsy (as applicable)
Urinalysis		• Pre-study • Week 1 Day 1 (pre-dose)[1] • Week 2 & subsequent weeks: Day 1 pre-dose • Week 4 and Week 8 visits • EOS
Pregnancy test[2]		• Pre-study • Week 1 Day 1 (pre-dose)[1] • EOS

[1] Repeat only if >3 days prior to W1D1
[2] Only for women of childbearing potential

Additional blood and urine safety samples should be collected if clinically indicated.

All blood and urine samples for safety analyses will be analyzed by each center's local laboratory. Samples will be collected, processed, and stored according to the institutional instructions provided by the clinical laboratory. All reference ranges will be provided to the Sponsor for all lab parameters measured.

The Investigator will assess and document the clinical significance of any values outside the reference ranges provided by the clinical laboratory and grade according to the CTCAE Version 4.03.

5.12 Abnormal Results

The clinical significance of any abnormal findings found in the physical examination, clinical laboratory evaluations, vital sign assessments, and ECGs must be evaluated and documented by the Investigator. Onset of new abnormal findings not recorded in the medical history or worsening of baseline symptoms or concurrent medical conditions will be recorded on the eCRF as AEs (see Section 8: Adverse Events).

Abnormal findings that are considered not clinically significant by the Investigator may be reviewed by the Medical Monitor.

5.13 Pharmacokinetic Sample Collection

5.13.1 Patients with PK Collection

Phase 1:

All patients enrolled in Phase 1 dosing cohorts will have blood and urine samples collected for PK analysis.

All supplies for PK sample collection and handling will be provided as well as a study-specific PK Manual prepared by the Sponsor designated PK laboratory. Samples from each patient will be batched, stored as per instructions, and shipped after collection. Shipments will be triggered by the Sponsor to meet the needs of data review for of the end of cohort meetings. Details for collection, processing, storage, handling and shipment will be specified in the PK Manual.

Phase 2a:

All patients enrolled in Stage 1 expansion will have blood and urine samples collected for PK analysis.

Only a subset of patients enrolled in Stage 2 expansion will have blood samples for PK collected. The number of patients undergoing blood collection for PK will be based on the samples obtained from Stage 1 and whether or not the same dosing schedule and dose level will be examined in Stage 2.

If Schedule 1 is selected for Stage 2, PK samples will be collected until it is confirmed that at least 10 patients have completed serial PK sampling at both Cycle 1 and at least 1 repeat dose (Cycle 3 or 6).

If Schedule 2 is selected for Stage 2, PK samples will be collected until it is confirmed that at least 10 patients have completed serial PK sampling at both first dose and at least one additional serial sampling day.

No urine samples will be collected from patients enrolled in Phase 2a Stage 2.

For all patients in the study, an unscheduled single plasma PK sample should be collected if they present in the clinic with any SAE that is possibly related to infusion of CRLX301, provided the visit does not already have a PK collection scheduled.

Also, based on emerging data in the clinic and available PK data, the sponsor may remove collection of one or some blood PK sample time points without issuing a protocol amendment. The sites and patients would be alerted in writing.

5.13.2 PK Sample Collection Times

The required blood and urine sample collections for PK analysis are specified in the Tables below for each dosing schedule. Sample collection date and time, the time of the start and end of the CRLX301 IV infusion and the total volume of urine collected must be recorded on the eCRF and sample collection forms. Every effort should be made to collect plasma PK samples at the specified time points. PK samples collected outside of the allowable window will be logged as a minor protocol deviation.

Table 14: Schedule 1 (Q3W) Blood PK Sample Collection Times (Phase 1 and subset of patients in Phase 2a)

Cycle 1, 3 & 6	Timing	Window
Day 1	Prior to start of CRLX301 IV infusion (pre-dose)	None
	During infusion of CRLX301: 30 min after initiation of infusion	±5 min
	During infusion of CRLX301: 60 min after initiation of infusion	±5 min
	End of infusion (immediately after turning off infusion pump)	±5 min
	After infusion of CRLX301: 30 min after completion of infusion	±5 min
	60 min after completion of infusion	±5 min
	180 min (3 hours) after completion of infusion	±30 min
	360 min (6 hours) after completion of infusion	-1 hr
Day 2	Approximately 24 hours after completion of infusion	±4 hrs.
Day 3	2 days after completion of infusion (48 hours after completion of infusion)	N/A: day of visit
Day 8	7 days after completion of infusion (168 hours after completion of infusion)	N/A: day of visit
Day 15	14 days after completion of infusion (336 hours after completion of infusion) **Cycle 1 only**	N/A: day of visit
Day 22 **(i.e., D1 of cycle 2, 4, 7)**	21 days after completion of infusion (504 hours after completion of infusion)	day of visit / must be pre-dose if continuing treatment
A single PK sample may be collected, as able, if patient experiences a CRLX301 related SAE		

Table 15: Schedule 1 (Q3W) Urine PK Sample Collection Times (Phase 1, Phase 2a Stage 1, and subset of patients in Phase 2a Stage 2 only)

Cycle 1, 3 & 6	Timing
Day 1	Spot Urine collection (>15 mL) pre-dose, prior to CRLX301 infusion
	Collect all urine from start of CRLX301 infusion (0 min.) to 6 hours (-1 hr) after completion of infusion or to time of discharge if earlier. Note: record the total volume of urine collected and the start and stop time for the collection of urine.
Day 8	Spot Urine collection (>15 mL), 7 days after completion of infusion

Table 16: Schedule 2 (QW, no break) Blood PK Sample Collection Times (Phase 1 and subset of patients in Phase 2a)

Timing		Window
Week 1, 4 & 7		
Day 1	Prior to start of CRLX301 IV infusion (pre-dose)	None
	During infusion of CRLX301: 30 min after initiation of infusion	±5 min
	During infusion of CRLX301: 60 min after initiation of infusion	±5 min
	End of infusion (immediately after turning off infusion pump)	±5 min
	After infusion of CRLX301: 30 min after completion of infusion	±5 min
	60 min after completion of infusion	±5 min
	180 min (3 hours) after completion of infusion	±30 min
	360 min (6 hours) after completion of infusion	-1 hr
Day 2	Approximately 24 hours after completion of infusion	±4 hrs.
Week 2, 3, 5, 6		
Day 1	Prior to start of CRLX301 IV infusion (pre-dose)	None
A single PK sample should be collected, as able, if patient experiences a CRLX301 related SAE.		

Table 17: Schedule 2 (QW, no break) Urine PK Sample Collection Times (Phase 1 and Phase 2a Stage 1 Only)

	Timing
Week 1, 4 and 7	Spot Urine collection (>15 mL) pre-dose, prior to CRLX301 infusion
Day 1	Collect all urine from start of CRLX301 infusion (0 min.) to 6 hours (-1 h) after completion of infusion or to time of discharge if earlier. Note: record the total volume of urine collected and the start and stop time for the collection of urine.
Week 2, 5 and 8 **Day 1**	Spot Urine collection (>15 mL), pre-dose

Table 18: Schedule 2 (QW, 3 week on/1 week off) Blood PK Sample Collection Times (Phase 1 and subset of patients in Phase 2a)

Timing		Window
Week 1, 3 & 7		
Day 1	Prior to start of CRLX301 IV infusion (pre-dose)	None
	During infusion of CRLX301: 30 min after initiation of infusion	±5 min
	During infusion of CRLX301: 60 min after initiation of infusion	±5 min
	End of infusion (immediately after turning off infusion pump)	±5 min
	After infusion of CRLX301: 30 min after completion of infusion	±5 min
	60 min after completion of infusion	±5 min
	180 min (3 hours) after completion of infusion	±30 min
	360 min (6 hours) after completion of infusion	-1 hr
Day 2	Approximately 24 hours after completion of infusion	±4 hrs.
Week 2, 5 & 6		
Day 1	Prior to start of CRLX301 IV infusion (pre-dose)	None
A single PK sample should be collected, as able, if patient experiences a CRLX301 related SAE.		

Table 19: Schedule 2 (QW, 3 week on/1 week off) Urine PK Sample Collection Times (Phase 1 and Phase 2a Stage 1 Only)

	Timing
Week 1, 3 & 7 **Day 1**	Spot Urine collection (>15 mL) pre-dose, prior to CRLX301 infusion
	Collect all urine from start of CRLX301 infusion (0 min.) to 6 hours (-1 h) after completion of infusion or to time of discharge if earlier. Note: record the total volume of urine collected and the start and stop time for the collection of urine.
Week 2, 5 & 6 **Day 1**	Spot Urine collection (>15 mL), pre-dose

Detailed instructions for collection and shipment of PK samples will be provided in the study designated PK Laboratory Manual. Supplies for collection of blood and urine samples, labels, and shipping materials will be provided to the clinical site.

5.14 Estimated Total Blood Volume Collected

The Tables below show an estimate of the most blood volume to be collected if a patient underwent pre-study activities, completed 7 cycles (Schedule 1), 21 weeks (Schedule 2 - QW, no break) or 20 weeks (Schedule 2 – QW, 3 week on/1 week off) of treatment, the EOS visit and Follow-Up, if applicable. Actual blood volume collected is dependent upon what phase /stage of the study the patient is enrolled, whether they undergo additional coagulation testing for post-dose biopsy, whether pregnancy serum collection is required and if additional safety labs need to be repeated, etc.

Table 20: Schedule 1 (Q3W) Estimated Blood Volume

Assessment	Blood volume per time point (mL)	Pre-study	C1	C2	C3	C4	C5	C6	C7	EOS	Follow-Up
Hematology/ Chemistry	15	15	45	45	45	45	45	45	45	15	
Pregnancy serum test (if applicable)	5	5	--	--	--	--	--	--	--	5	
Coagulation	5	5	5 -before post-dose biopsy (if applicable)							--	
PK - plasma	6	--	72	6	66	6	--	66	6	--	
CTC	10	--	40	30	--	--	--	--	--	10	
MPS	10	--	10		10	--	--		--	--	
Biomarker	10	--	20	--	20	--	--	--	--	10	
PSA*	1	1		1	1	1	1	1	1	1	1**

*Phase 2a prostate cancer patients only
**PSA amount collected in follow-up varies; depends on length of participation in follow-up

Table 21: Schedule 2 (QW, no break) Estimated Blood Volume

Assessment	Blood volume per time point (mL)	Pre-study	Weeks							EOS	Follow-Up
			1-3	4-6	7-9	10-12	13-15	16-18	19-21		
Hematology/ Chemistry	15	15	45	45	45	45	45	45	45	15	
Pregnancy serum test (if applicable)	5	5	--	--	--	--	--	--	--	5	
Coagulation	5	5	5 -before post-dose biopsy if applicable								
PK - plasma	6	--	66	66	54	--	--	--	--	--	
CTC	10	--	40	30	--	--	--	--	--	10	
MPS	10	--	10	10		--	--	--	--	--	
Biomarker	10	--	20	20	--	--	--	--	--	10	
PSA*	1	1		1	1	1	1	1	1	1	1**

*Phase 2a prostate cancer patients only
**PSA amount collected in follow-up varies; depends on length of participation in follow-up

Table 22: Schedule 2 (QW, 3 week on/1 week off) Estimated Blood Volume

Assessment	Blood volume per time point (mL)	Pre-study	Weeks					EOS	Follow-Up
			1-4	5-8	9-12	13-16	17-20		
Hematology/ Chemistry	15	15	60	60	45	45	45	15	
Pregnancy serum test (if applicable)	5	5	--	--	--	--	--	5	
Coagulation	5	5	5 -before post-dose biopsy if applicable					--	
PK - plasma	6	--	114	66	--	--	--	--	
CTC	10	--	60	10	--	--	--	10	
MPS	10	--	20	--	--	--	--	--	
Biomarker	10	--	40	--	--	--	--	10	
PSA*	1	1	--	1	1	1	1	1	1**

*Phase 2a prostate cancer patients only
**PSA amount collected in follow-up varies; depends on length of participation in follow-up

5.15 Evaluation of Target Tumors

5.15.1 CT Scans

For patients undergoing tumor evaluation via RECIST v.1.1, CT scans for tumor measurement will be recorded following RECIST v.1.1 guidelines. CT scans are to be collected pre-study, and then repeated every 8-9 weeks until the patient discontinues study drug treatment due to disease progression:

Schedule 1: First evaluation during Cycle 3 Day 15 (+6 days) and perform within 1 weeks prior to Day 22 of Cycle 6, Cycle 9 etc.

Schedule 2 (QW, no break): First evaluation during Week 9 (post-dose) and complete before Week 10 dose, then during Week 18 (post-dose), Week 27 (post-dose), etc.

Schedule 2 (QW, 3 week on/1 week off): First evaluation complete before Week 9 dose, then prior to Week 17 dose, prior to Week 25 dose, etc.

Repeat CT Scans for tumor measurement at End-of-Study visit if prior CT scan and tumor evaluation is >3 weeks.

If a complete or partial response per RECIST v.1.1 criteria is reported, then repeat CT scan approximately 3 - 4 weeks later for confirmation, per Investigator discretion.

If stable response per RECIST v.1.1 criteria is reported, then continue repeat CT scan 8-9 weeks later for confirmation, per Investigator discretion.

Patients who are discontinued from study treatment for reasons other than disease progression will continue to have tumor evaluation by RECIST1.1 until another anti-cancer treatment is started, progression of disease, death, loss to follow up or withdrawal of consent, whichever comes first. Therefore, continued evaluations may be possible for some patients after the End-of-Study visit.

5.15.2 Bone Scans

Bone scans for tumor measurement will also be required and recorded for any CRPC patient enrolled into Phase 2a following PCWG2 criteria (see Section 5.15.3: Alternative Evaluation Methods). Bone scans are to be collected pre-study, and then repeated every 8-9 weeks until the patient discontinues study drug treatment due to disease progression:

Schedule 1: First evaluation during Cycle 3 Day 15 (+6 days) and perform within 1 weeks prior to Day 22 of Cycle 6, Cycle 9 etc.

Schedule 2 (QW, no break): First evaluation during Week 9 (post-dose) and complete before Week 10 dose, then during Week 18 (post-dose), Week 27 (post-dose), etc.

Schedule 2 (QW, 3 week on/1 week off): First evaluation complete before Week 9 dose, then prior to Week 17 dose, prior to Week 25 dose, etc.

Repeat bone scans for tumor measurement at End-of-Study visit if prior bone scan and tumor evaluation is >3 weeks.

5.15.3 Alternative Evaluation Methods

If an alternative tumor evaluation methodology consistent with the tumor type is preferred, the Investigator will review this with the Medical Monitor when the patient enters the study, and plan to use the same methodology during the entire study period. The same schedule for evaluations will apply as for CT Scans.

For Phase 2a prostate cancer patients, the alternative tumor evaluation method will be the PCWG2 criteria (see reference #33). PSA in prostate patients will be collected pre-study, every three to four weeks as per the Schedule of Procedures and at the EOS visit only if it has been >21 days since the last PSA measurement.

Patients who are discontinued from study treatment for reasons other than disease progression will continue to have tumor evaluation by the selected alternative evaluation method until another anti-cancer treatment is started, progression of disease, death, loss to follow up or withdrawal of consent, whichever comes first. Therefore, continued evaluations may be possible for some patients after the EOS visit.

5.16 Tumor Marker Data

Tumor marker data is collected only if appropriate for tumor-type and if already being performed as part of the patients Standard of Care. This includes treatment response markers (e.g. CA-125 for ovarian cancer, CA19-9 for pancreatic cancer, etc.) and tumor genotype markers (e.g. BRAF mutation status for melanoma, KRAS mutation status for colon cancer, EGFR status for lung cancer, etc.) The data should be entered into the eCRF. If tumor marker data is available prior to the first dose of CRLX301 (baseline) then additional data should be entered into the eCRF as available.

5.17 Pharmacodynamic (PD) Sample: Pre- and Post-Dose Biopsy

Additional pharmacodynamic evaluations may be conducted by the Sponsor if tumor biopsies are obtained pre- and post- CRLX301 infusion. The tissue will be used for additional research to include evaluation of markers for efficacy (e.g. proliferation, apoptosis, and cell cycle) and CRLX301 localization; it may also include genetic testing related to the cancer diagnosis for research purposes only, no other genetic testing on tumor tissue will be performed. Individual patient results of any disease related genetic testing will not be provided to the Investigators or patients.

Tumor biopsy is optional and is only required if accessible and feasible to collect and with consent of the patient. Collect a tissue sample pre-study prior to the first dose. Collect the post-dose biopsy as defined in the Schedule of Procedures

Detailed instructions on tissue preparation and shipping will be provided to the site separately.

5.18 Blood Sample Collection for Additional Biomarker Research

For Phase 2a only additional blood samples will be collected for additional exploratory research. Blood will be separated into peripheral blood mononuclear cells (PBMCs) and plasma.

Pre- and post-study treatment blood samples will be used for analysis of genomic DNA for genetic alterations pertinent to the subject's cancer diagnosis. A targeted panel of genes will be processed using next generation sequencing (NGS) to allow germline and tumor-specific mutations, amplifications and translocations (among other alterations) to be identified with high sensitivity and specificity. Plasma collected at progression will be used to determine whether new mutations may identify a potential marker for disease progression during treatment.

A total of 6 mL of blood will be collected at each time point as per the Schedule of Procedures for each dosing schedule.

For both schedules a total of 60 mL of blood will be collected during the study as per the time points detailed in each Schedule of Procedures.

The samples will be shipped to a central laboratory. Detailed instructions on collection, processing, and shipping of samples will be provided to the sites prior to enrollment into Phase 2a.

5.19 Archived Tumor Tissue

Collection of archived tumor tissue is optional. For all patients who consent, up to 12 slides from previously archived tumor tissue may be collected. Availability of archived tissue is not required in order to participate in the study. The site will be instructed to indicate during the pre-study visit if archived tissue is available, when the tissue was collected, and that the patient has consented to use of the tissue. Additional exploratory research may include evaluation of markers for efficacy (e.g. proliferation, apoptosis, and cell cycle) and CRLX301 localization; it may also include genetic testing related to the patient's cancer diagnosis for research purposes only, no other genetic testing will be performed. Individual patient results of any disease related genetic testing will not be provided to the Investigators or patients.

The trigger for preparation and shipment of slides will be a request in writing from the sponsor. The written request must occur prior to each site's completion of the study. Detailed instructions on collection, preparation of slides, and shipping of samples will be provided to the sites at a future date.

5.20 Circulating Tumor Cells (CTCs)

Whole blood will be collected for CTC analysis from patients enrolled in Phase 2a Stage 1 expansion only. The samples will be used to explore pharmacodynamic effects of CRLX301 on tumor cells.[27, 28] Fresh whole blood samples will be shipped to a central vendor. The samples must be shipped on the same day of collection in order to be analyzed within 24 hours. Refer to the Schedule of Procedures for each dosing schedule for collection time points. Detailed instructions will be provided in the study binder prior to initiation of Phase 2a Stage 1.

5.21 Mononuclear Phagocyte System (MPS) Function

Whole blood will be collected for MPS function analysis from patients enrolled in Phase 2a Stage 1 expansion only. The samples will be used to explore whether or not MPS plays a role in the clearance of CRLX301.[29, 30, 31] Fresh whole blood samples will be shipped to a central vendor. The samples must be shipped on the same day of collection in order to be analyzed within 24 hours. Refer to the Schedule of Procedures for each dosing schedule for collection time points. Detailed instructions will be provided in the study binder prior to initiation of Phase 2a Stage 1.

5.22 End-of-Study Visit

All dosed patients will have an End-of-Study (EOS) Visit 30 days (+10d) post last dose of study drug or at the time of early withdrawal if the patient cannot feasibly or is unwilling to return for the visit at the later date.

If a patient discontinues from study drug and receives an investigational treatment or anti-cancer therapy prior to the 30 days post last dose of CRLX301 End-of-Study visit, such treatment must be recorded on the eCRF. Every attempt should be made to complete the End-of-Study visit 30 days post the last dose of CRLX301 prior to initiating other cancer treatment. AEs that occur after the initiation of new cancer treatment will not be collected.

Patients will be followed for AEs and SAEs including clinically significant abnormal laboratory values. In addition, any dosed patients who discontinue from the study due to an AE deemed to be related to study drug must be followed to report the final outcome of the AE as resolved, or symptoms returned to baseline or determined to be due to a chronic condition, or death.

Discontinued patients who fail to return for an End-of-Study Visit within the designated time period must be requested in writing to return. A copy of the letter will be kept by the study center with the source documentation.

The reason for discontinuation from the study will be recorded on the End-of-Study page of the Case Report Form (eCRF).

The following procedures will be performed at the End-of-Study Visit:

- Physical examination
- ECOG performance status
- Assess AEs and vital signs
- Assess concomitant medication use
- Collect blood and urine samples for hematology, chemistry and urinalysis, and pregnancy test if applicable
- 12-lead ECG
- Collect blood for biomarker (Phase 2a only)
- Collect blood for CTC (Phase 2a Stage 1 only)
- Collect PSA for CRPC patients only if prior PSA measurement is >14 days
- Repeat CT Scans (or alternative method consistent with tumor type) for tumor measurement if prior evaluation is > 21 days; and complete tumor response assessment
- Collect blood for PSA for Phase 2a prostate cancer patients if prior evaluation is >21 days

- Record current patient contact as well as an alternate contact person.

5.23 Follow Up (as applicable)

Patients who are discontinued from study treatment for reasons other than disease progression will continue to have tumor evaluation by RECIST1.1 or by alternative response evaluation for specific tumor type every 8-9 weeks or per Investigator discretion until another anti-cancer treatment is started, progression of disease, death, loss to follow up or withdrawal of consent, whichever comes first. Therefore, continued tumor evaluations may be possible for some patients after the EOS Visit.

PSA will also be collected for CRPC patients only on Phase 2a. PSA during follow-up will be done on the same scheduling as tumor evaluation.

6. DISCONTINUATION FROM TREATMENT AND STUDY WITHDRAWAL

6.1 Reasons for Discontinuation from Treatment

Eligible patients who are enrolled into the study will be discontinued from study treatment if any of the following occur:

- Documented radiographic or clinical progression of disease unless there is evidence of clinical benefit from the study drug and the investigator believes it is in the patient's best interest to continue the treatment despite disease progression
- Grade 4 hypersensitivity/infusion related reaction (may also be discontinued for Grade 3; see Table 7)
- AE with clinically unacceptable toxicities (unless there is evidence of sustained therapeutic benefit and the investigator believes it is in the patient's best interest to continue the treatment despite the toxicity) including:
    - unresolved related AE ≥Grade 2 that causes a delay of >21 days from planned initiation of next dose of CRLX301
    - repeat toxicities after 2 dose reductions
    - bilirubin >1.2 ULN, or AST and/or ALT >1.5 × ULN concomitant with alkaline phosphatase >2.5 × ULN; if either of these are unresolved for >21 days from planned next dose date
    - any other clinically unacceptable toxicity (in agreement with the Sponsor/Medical Monitor)
- Withdrawal of consent
- Subject non-compliance with study schedule
- Protocol violation, (including lack of compliance or excessive deviations with study schedule) in agreement with the Sponsor/Medical Monitor and/or Study Director
- Lost to follow-up (after repeated efforts for >30 days have been made to contact the patient including letters sent by registered mail)
- Request for discontinuation by a regulatory agency (i.e. FDA)
- Investigator decision (in consultation with the Safety Medical Monitor and/or Medical Director and the patient) if there are changes in the patient's medical condition and/or intercurrent illness that render the patient unacceptable for further treatment. The reason for removal must be documented in the eCRF.

6.2 Survival Status

Last known survival status will be recorded on the eCRF at the End-of-Study Visit or post Follow-Up period as applicable. If a patient dies during the study, the cause of death and date will be recorded on the eCRF and every effort should be made to collect written documentation such as a death certificate.

7. STUDY DRUG AND PHARMACY INSTRUCTIONS

7.1 Study Drug

[redacted]

7.2 Study Drug Dose Calculation and Administration

7.2.1 Body surface Area Calculation

Body surface area (BSA) calculations will be performed according to institutional practices. Every attempt should be made to follow the updated ASCO clinical practice guidelines including the guideline for dosing obese patients.[32]

BSA is calculated according to the following method or alternate method as per the institutional practices:

$$BSA\ (m^2) = 0.20247 \times height\ (m)^{0.725} \times weight\ (kg)^{0.425}$$

A change in body weight of >10% will require recalculation of BSA if the change is attributed to dry weight.

Refer to the Pharmacy Manual for detailed dose calculation instructions.

7.2.2 CRLX301 Dose Reconstitution

[redacted]

7.2.3 CRLX301 Administration

Allowable exceptions for administering the CRLX301 infusion at a slower rate include Investigator discretion for patients who have history of infusion related reactions to other drug treatment(s) or who have environmental allergies (e.g., food, pollen).

7.3 Study Drug Accountability

The PI or appropriately trained designee will maintain an accurate record of the receipt of the investigational products shipped by the Sponsor's contracted drug distribution center, including the date and quantity received. In addition, an accurate drug disposition record will be kept that specifies the amount administered to each patient and the date of administration. This inventory record must be available for inspection at any time, and copies of this record will be provided to the Sponsor at the conclusion of the study. Also at the completion of the study, the PI (or appropriately trained designee) will provide the Sponsor with a complete record of investigational product accountability.

Empty or partially used vials of study drug will be destroyed at the study center per study center procedures and documentation of destruction will be reviewed by the Sponsor designated Study Monitor.

All unused study drug must be accounted for by the site and verified by the Sponsor designated Study Monitor prior to destruction at the study center or returned to the appropriate depot. Determination of destruction or return will be provided by the Sponsor.

8. ADVERSE EVENTS

8.1 Definition of Adverse Events and Adverse Reactions

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.

An adverse reaction is any adverse event caused by a drug.

A suspected adverse reaction is any adverse event for which there is a reasonable possibility that the drug caused the adverse event.

8.2 Evaluation of Adverse Events

The investigator will determine the seriousness, severity (intensity), and causality of an AE to the use of the study drug based on the definitions described below.

8.2.1 Serious Adverse Events (SAE) and Suspected Unexpected Serious Adverse Reactions (SUSAR)

An SAE is any untoward medical occurrence that at any dose results in any of the following outcomes, regardless of relationship to study drug.

Notify Sponsor via the study designated SAE Submission Line email or fax within 24 hours per instructions in the Investigator Site File; and document events on eCRF.

Death: All deaths, regardless of cause or relationship, must be reported for patients on study and for deaths occurring within 30 days of last study drug dose.

Note: Death is an outcome of an AE, and not an AE in itself. Reports of death due to disease progression or progressive disease must be associated with a diagnosis caused by progression of disease, e.g., respiratory failure. The event(s) that caused death (e.g., illness, accident) is the SAE. Death due to progressive disease will not be considered an SAE. Death due to any other cause(s) must also be reported as an outcome of the reportable SAE.

Life-threatening adverse drug event: This includes any adverse drug event that places the patient, in the view of the investigator, at immediate risk of death from the reaction as it occurred (i.e., this does not include a reaction that had it occurred in a more severe form, might have caused death).

Inpatient hospitalization or prolongation of existing hospitalization: "In-patient hospitalization" means the patient has been formally admitted to a hospital for medical reasons, for any length of time. This may or may not be overnight. It does not include presentation to and care within an emergency department. Complications that occur during hospitalizations are AEs. If a complication prolongs hospitalization, it is a SAE.

Persistent or significant disability/ incapacity: A disability is defined as any substantial disruption of a person's ability to conduct normal life functions.

Congenital anomaly/birth defect: Includes spontaneous miscarriage**,** Structural or functional anomalies, including metabolic disorders, which are present at the time of birth.

Important medical event: An event that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug event when, based upon appropriate medical judgment, it may jeopardize the patient and may require medical or surgical intervention to prevent any of the outcomes listed in this definition or meets the criteria for a SUSAR.

Serious unexpected serious adverse reaction (SUSAR) is any adverse event for which there is a reasonable possibility that the study drug caused the adverse event of which the specificity or severity is not consistent with those noted in the current protocol and/or IB, and meets one of the above criteria for serious. This refers to any AE that has not been previously observed, (e.g., included in the IB), rather than from the perspective of such an event not being anticipated from the pharmacological properties of the product.

Notify sponsor via the study designated SAE Submission Line email or fax by the next business day.

8.2.2 Unexpected Suspected Adverse Reaction

An unexpected suspected adverse reaction is any adverse event for which there is a reasonable possibility that the study drug caused the adverse event, the specificity or severity of which is not consistent with those noted in the current protocol and/or Investigator's Brochure. This refers to any AE that has not been previously observed, rather than from the perspective of such an event not being anticipated from the pharmacological properties of the product. Unexpected suspected adverse reaction(s) which are not serious are submitted to the Sponsor on the Serious Adverse Event /Adverse Event of Special Interest form and noted as not serious.

Notify sponsor or sponsor representative via the study designated SAE Submission Line email or fax the next business day; document on eCRF.

8.2.3 Other Adverse Events of Special Interest

For all patients, the following adverse events are categorized as Adverse Events of Special Interest (AESI)

- infusion-related hypersensitivity reaction(s) of any Grade
- ≥Grade 2 non-infective cystitis
- ≥Grade 2 bilirubin, ALT, or AST elevation
- ≥Grade 3 fluid retention (in the form of edema, pleural effusion, or weight gain)

Notify sponsor or sponsor representative within 3 business days of any non-serious AESIs by documenting on the eCRF.

8.2.4 Non-Serious Adverse Events

All other AEs, not fulfilling the previous definitions, are classified as non-serious.

Document non-serious AEs on the Adverse Event page of the case report form (eCRF).

8.2.5 Laboratory Adverse Events

All laboratory results must be filed in the patient's medical record and monitored. The Investigator or designee must review laboratory results in a timely manner demonstrated by signature / date and assignment of clinical significance assessment. Non-clinically-significant laboratory abnormalities, i.e., minor deviations from the normal range, are expected and it is likely that no medical intervention will be required. Abnormal laboratory results should not be considered AEs unless they are associated with a diagnosis.

Any grade laboratory abnormality that is considered to be clinically significant by the Investigator will be recorded on the AE eCRF. An abnormal test result will be considered an AE if:

It is not associated with an already reported AE, diagnosis, or pre-existing condition;

There is a change in concomitant medication or intervention is needed, in direct response to a Grade 3 or 4 laboratory result;

Investigator considers the laboratory result to be clinically significant.

All such laboratory abnormalities should be repeated and reassessed for "seriousness" by the Investigator or designee as soon as possible. If a result meets the regulatory definition of "serious", it should be reported as an SAE following regulatory and protocol requirements. Repeat laboratory tests should be performed regularly to monitor patient status.

8.2.6 Severity of Adverse Events

The severity of each AE will be graded by the Investigator according to the NCI-CTCAE Version 4.03.

For AEs not listed in the NCI-CTCAE, the following similar grading system should be used:

Grade 1 Mild AE

Grade 2 Moderate AE

Grade 3 Severe AE

Grade 4 Life-threatening or disabling AE

Grade 5 Death related to AE

Severity, which is a description of the intensity of manifestation of the AE, is distinct from *seriousness*, which implies a patient outcome or AE-required treatment measure associated with a threat to life or functionality. An AE assessed as Grade 4 based on the NCI-CTCAE grades may or may not be assessed as serious based on the seriousness criteria.

The severity rating must be recorded on the appropriate AE reporting page of the patient's CRF.

8.2.7 Relationship to Study Drug

The Investigator will attempt to assess the relationship of the event and record it as unrelated, unlikely-related, possibly related, probably related, and definitely related.

Unrelated: This category applies to those AEs which, after careful medical consideration, are clearly felt to be due to extraneous causes (disease, environment, etc.) that are unrelated to the administration of study drug.

Unlikely-related: This category applies to those AEs which, after careful medical consideration, are felt unlikely to be related to the administration of the study drug. The relationship of an AE to the study drug can be considered unlikely if (must have first 2 criteria below):

- It does not follow a reasonable temporal sequence from administration of the drug
- It could readily have been a result of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient
- It does not follow a known response pattern to the suspected drug
- It does not reappear or worsen when the drug is re-administered

Possibly related: This category applies to AEs which, after careful medical consideration, are considered not likely to be related, but the possibility cannot be ruled out with certainty. The relationship of an AE to the study drug can be considered possible if (must have first 2):

- It follows a reasonable temporal sequence from administration of the study drug;
- It could readily have been a result of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient;
- It follows a known response pattern to the suspected study drug.

Probably related: This category applies to AEs which, after careful medical consideration, are felt with a high degree of certainty to be related to the administration of the study drug. The relationship of an AE to the study drug can be considered probable if (must have first 3 criteria below):

- It follows a reasonable temporal sequence from administration of the drug;
- It could not be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors or other modes of therapy administered to the patient;
- It disappears or decreases upon cessation of drug, dose delay, or dose reduction;
- It follows a known response pattern to the suspected drug.

Related: This category applies to AEs, which, after careful medical consideration, are felt to be related to the administration of the study drug. The relationship of an AE to the study drug can be considered related if (must have first 3 criteria below):

- It follows a reasonable temporal sequence from administration of the drug or drug levels have been established in body fluids or tissues;
- It could not be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors or other modes of therapy administered to the patient;
- It disappears or decreases upon cessation of drug, dose delay, or dose reduction and appears upon re-challenge;
- It follows a known response pattern to the suspected drug.

8.3 Expedited Reporting of SAEs, Patient Death and Unexpected AE

8.3.1 Time-Frame for Reporting

Any SAE, unexpected (and severe) AE experienced by the patient from time of informed consent through 30 days after receiving the last dose of study drug, regardless of relationship to study drug, or any death that occurs more than 30 days after the last dose of study drug, and is believed to be study drug-related, must be **promptly reported within 24 hours of the Investigator becoming aware of the event** to the study designated SAE Submission Line email or fax.

AEs that do not meet the definition for severe or unexpected should be collected from the time of first dose through 30 days after the last dose of study drug.

If a non-serious AE is reported from time of informed consent up to the first dose it should be recorded in medical history.

8.3.2 Information to be Submitted for Reportable Event

At the time of the initial contact(s), the Investigator must report to the Medical Monitor information for completion of an expedited Safety Report. The Sponsor representative will require all of the following information about the patient and the event:

- Patient identification code, gender, and age or date of birth
- Height, weight, or body surface area (where required for dose calculation)
- Underlying diagnosis and extent of disease
- Lot number and expiration date of study drug
- Dose, route, frequency, and duration of study drug administered
- Date of study drug administration
- Description of event, including date of onset and duration
- Date of death (if applicable)
- Intervention(s) required
- Concomitant therapy (including regimen[s] and indication)
- Pertinent laboratory data/diagnostic study (including dates)
- Pertinent medical history
- Study drug status (dose interrupted, discontinued)
- Did event abate after interruption of study drug administration (if applicable)
- Did event recur after study drug was reintroduced (if applicable)

In addition to the above information, the sponsor will require the investigator's assessment of the following:

- Severity of the AE
- Relationship of the AE to study treatment
- Outcome of the AE

Study center staff must transmit an SAE report form to the Sponsor within 24 hours of knowledge of the event, even if an initial report is made by telephone, as well as any relevant Pregnancy Report forms. Refer to the Investigator Site File for copies of the forms and instructions for reporting to the Sponsor.

SAE Report Forms and Pregnancy Report Forms should be submitted to the study designated SAE submission email or fax.

Supplemental information should be submitted as soon as available.

8.4 Recording Adverse Events

All AEs and SAEs will be recorded, evaluated, and documented by the Investigator on source documents and on designated eCRF pages.

Patients are to be questioned regarding any AEs or SAEs at every scheduled and non-scheduled visit. Patients will be asked to volunteer information through open-ended questioning. AEs will also be identified by physical examination and review of laboratory results. The Investigator or designee will record all pertinent information on the appropriate AE reporting page of the patient's eCRF whether or not they are considered causally related to the investigational product.

The Investigator should attempt to establish a diagnosis of the AE based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE verbatim term rather than individual signs/symptoms.

For every AE, the Investigator must document the following:

- Diagnosis or description of event
- Onset date
- Assessment of the severity
- Assessment causal relationship to the investigational product
- Assessment of seriousness of the event (i.e. whether it is an SAE)
- Method of treatment taken for the AE
- Action taken related to study drug include the following: dose interruption, dose delay, dose reduction, or study drug discontinuation

- Outcome of event and end date; all SAEs must be followed until resolution, patient death or until the SAE is deemed stable or irreversible
- Phase 1 during Cycle 1 only: any event which meets the criteria as a DLT will be noted as such on the eCRF

8.5 Exposure to Study Drug during Pregnancy

The Investigator must report any pregnancy (including the pregnancy of a male patient's partner), even if no AE has occurred, on a Pregnancy Report Form within 24 hours of the Investigator becoming aware of the pregnancy. See the Investigator Site File for a copy of the form and instructions on how to submit this information to the Sponsor.

Female patients who become pregnant while on the study will be immediately discontinued from study treatment, and complete the End-of-Study visit at 30 days post-last dose follow-up period, reporting all AEs including any related to the pregnancy. In addition, the Investigator will make every attempt to confirm the outcome of the pregnancy and report this on a follow-up Pregnancy Report form.

8.6 End-of-Study Post-treatment Safety Follow-up

In this study, the post-treatment safety follow-up period is defined as 30 days after the last dose of CRLX301. All AEs occurring during the study period from the time of the first dose to the last day of the 30-day post-treatment follow-up period will be reported. All patients should be instructed to report AEs or SAEs occurring during the 30-day post-treatment safety follow-up period.

If a patient discontinues from study drug and is planning to receive an investigational treatment or anti-cancer therapy prior to the 30 days post last dose of CRLX301 every attempt should be made to complete the End-of-Study visit prior to initiating other cancer treatment. AEs that occur after the initiation of new cancer treatment will not be collected.

Unresolved study drug related (see Section 8.2.7: Relationship to Study Drug for definition) AEs and SAEs at the time of treatment discontinuation or new study drug-related AEs and SAEs that occur during the 30 day post last dose follow-up period will be followed until they have, in opinion of the Investigator, resolved to baseline, stabilized, or are deemed to be irreversible.

9. EVALUATION OF ANTI-TUMOR ACTIVITY

Tumor response evaluations will be performed by following RECIST guidelines, version 1.1 or by alternate methodology consistent for tumor type. A patient will be considered evaluable for efficacy if the patient received at least 1 dose of study drug and had either:

- a pre-study CT scan and at least 1 follow-up CT scan assessment during the study period. CT scan assessments should be completed every 8 - 9 weeks if possible; and, whenever feasible a CT scan should be repeated 4 weeks after a partial or complete response is observed. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

- a pre-study alternative response evaluation consistent with tumor type and at least one follow-up alternative response evaluation during the study period.

NOTE: the rest of this section describes evaluation of anti-tumor activity via RECIST1.1. If an alternative response evaluation is used, please refer to the appropriate criteria. For example, for prostate cancer, see reference #33 for the PCWG2 criteria.

9.1 Measurable Disease and Target Lesions

9.1.1 Measurable Disease

Measurable lesions are defined as those that can be accurately measured in at least 1 dimension (longest diameter to be recorded) as >20 mm by chest x-ray or as >10 mm with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Tumor lesions that are situated in a previously irradiated area may or may not be considered measurable.

To be considered pathologically enlarged and measurable, a malignant lymph node must be >15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

9.1.2 Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, and lend themselves to reproducible repeated measurements. It may be that, on occasion, the largest lesion does not lend itself to reproducible measurement in which case the next largest lesion that can be reproducibly measured should be selected. The sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions should be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is included. The baseline sum diameters will be used as a reference to further characterize any objective tumor regression in the measurable dimension of the disease.

9.2 Response Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have a reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, using the baseline sum diameters as a reference.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as a reference the smallest sum on study (this includes the baseline sum if that is the smallest on the study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of 1 or more new lesions is also considered progression).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR, nor sufficient increase to qualify for PD, taking as a reference the smallest sum diameters while on the study.

9.3 Evaluation of Best Overall Response and Disease Control Rate

The best overall response is the best response 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).

The duration of overall response is measured from the time the measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented.

Duration of stable disease is measured from the start of the treatment until the criteria for progression are met, taking the smallest measurements recorded since the treatment started, including the baseline measurements, as a reference.

The objective response rate is the proportion of all patients with PR or CR, from the start of treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the start of treatment).

The disease control rate is the proportion of all patients with SD for 8-9 weeks, or PR, or CR, from the start of treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the start of treatment).

9.4 Progression-Free Survival

Progression-free survival (PFS) is defined as the duration of time from the start of treatment to the time of progression or death, whichever occurs first while on the study.

10. STATISTICAL METHODS

A detailed description of analysis methods will be prepared by the Sponsor designated study biostatistician in the study Statistical Analysis Plan.

Schedules 1 and 2 will be analyzed separately. As appropriate analysis for each cohort in Phase 1 and for each of the MTD expansion cohorts will be reported separately. For Schedule 2, a single MTD/RP2D will be determined, but other analyses will be reported separately for QW, no break cohorts and QW, 3 week on/1 week off cohorts.

10.1 Patient Populations

10.1.1 Safety Population

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

10.1.2 Pharmacokinetic Analysis Population

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

10.1.3 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.

10.1.4 MTD and/or RP2D Efficacy Evaluable Populations

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 1 follow-up tumor assessment via imaging or methodologies consistent with specific tumor type.

10.2 Endpoints

10.2.1 Phase 1

The primary endpoint is the frequency of dose limiting toxicities as a function of CRLX301 dose.

10.2.2 Phase 2a

The primary endpoint is safety and tolerability, evaluated by the following parameters:

- Type, frequency and severity of adverse event(s)
- Laboratory parameters (hematology and chemistry, especially those associated with bone marrow and hepatic function)
- Vital signs

- Physical examination
- 12-lead ECG

The secondary endpoints are:

- PK parameters in plasma: area under the concentration versus time curve (AUC), maximum concentration (Cmax), half-life ($t_{1/2}$), volume of distribution (Vd), clearance (CL) for both total and released docetaxel after single dose and multiple doses when available for each dosing schedule.
- Efficacy measures: best overall response, duration of overall response, duration of stable disease, objective response rate, disease control rate, and progression free survival as per RECIST, version 1.1 or alternative response evaluation criteria for specific tumor types

10.3 Patient Disposition

All enrolled patients will be listed with the cohort treatment assignment, last cycle/week and date, date of the End-of-Study Visit, reason for discontinuation.

Eligibility data will be listed for each patient.

10.4 Demographics and Other Baseline Characteristics

Demographic parameters (e.g., age, race, ethnicity, sex) and other baseline characteristics will be summarized by cohort group for the Safety Population. Descriptive statistics (n, mean, median, SD, minimum, and maximum) will be presented for continuous variables. Frequency distributions (counts and percentages) will be presented for categorical variables.

Medical history and pregnancy test data will be listed for all patients.

10.5 Protocol Deviations

Individual listings for protocol deviations will be presented for each subject. Protocol deviations will be summarized using the Safety Analysis Population.

10.6 Extent of Exposure and Treatment Compliance

Exposure of the Safety Population to the investigational product during the study period will be summarized for treatment duration, calculated as the number of days from the date of the first dose of investigational product taken to the date of the last dose taken, inclusive. Descriptive statistics (n, mean, median, SD, minimum, and maximum) will be presented.

The intravenous infusion start time, stop time, and volume infused will be recorded. Treatment compliance will not be calculated.

10.7 Efficacy Analyses

Exploratory analyses of efficacy will be undertaken by evaluating the RECIST findings or by alternative response evaluations for specific tumor types. All RECIST findings for target lesions or specific tumor type response evaluations will be listed. In addition, the following parameters will be determined:

- Best overall response
- Duration of overall response
- Duration of stable disease
- Objective response rate
- Disease control rate
- Progression free survival

For the analysis of best overall response, objective response rate and disease control rate, summary tables presenting the number and proportion of responders and non-responders, together with the two-sided 95% Pearson-Clopper confidence intervals for response rates will be produced.

The analysis of time to event endpoints, such as duration of overall response, duration of stable disease, and progression free survival, will be based on the survival function, which is the probability to stay event-free beyond a certain point in time. The survival function will be estimated by the Kaplan-Meier method. The survival function will be summarized for 25^{th} percentile, median, and 75^{th} percentile and their 95% confidence intervals. The plot of Kaplan-Meier estimates of survival functions will be presented.

10.8 Pharmacokinetic Analyses

Plasma samples will be collected from all patients in Phase 1 and a subset of patients in Phase 2a to evaluate the PK of total and unconjugated docetaxel in plasma. PK parameters will be calculated using noncompartmental analysis with the software program WinNonlin (version 15.3 or higher). Actual sampling times will be used to calculate PK parameters in this study. The plasma PK parameters will include area under the concentration versus time curve (AUC), maximum concentration (Cmax), half-life ($t_{1/2}$), volume of distribution (Vd), clearance (CL) for both total and unconjugated. Urine samples will be collected from patients in Phase 1 to evaluate the urinary excretion of total and unconjugated docetaxel. PK parameters in urine will include the maximum concentration (Cmax), amount of drug in the urine, % of drug eliminated in the urine.

For PK data the arithmetic mean, standard deviation (SD), median, minimum, maximum, coefficient of variation (CV%), geometric mean and geometric coefficient of variation (geo CV%) values will be presented. Details of the PK analyses will be provided in the Statistical Analysis Plan (SAP).

10.9 Safety Analyses

The safety analysis will be performed based on the Safety Population as specified in the SAP. Safety variables will include AEs, clinical laboratory parameters, vital signs, and ECG parameters. For each safety parameter, the last assessment made before the first dose of the investigational product for each period will be used as the baseline for all analyses of that safety parameter.

10.9.1 Adverse Events

An AE (classified by preferred term) that occurs during the treatment period will be considered a TEAE if it was not present before the first dose of investigational product or if it was present before the first dose of investigational product but increased in severity during the treatment period. If more than 1 AE is reported before the first dose of study drug and is coded to the same preferred term, the AE with the greatest severity will be used as the benchmark for comparison with the AEs that were also coded to that preferred term and that occurred during the period. An AE that occurs more than 30 days after the last dose of investigational product will not be counted as a TEAE, unless recommended by the Safety Medical Monitor or Investigator.

The number and percentage of patients reporting TEAEs by cohort will be tabulated by system organ class and preferred term; by system organ class, preferred term, and severity; and by system organ class, preferred term, and relationship to the investigational product. If more than 1 AE is coded to the same preferred term for the same patient, the patient will be counted only once for that preferred term using the most severe and most related occurrence for the summarization by severity and by relationship to the investigational product.

Listings will be presented for patients with SAEs and patients with AEs leading to discontinuation. A listing of all AEs by patient will also be presented.

10.9.2 Clinical Laboratory Parameters

Descriptive statistics for clinical laboratory values and changes from the baseline values will be presented by cohort for each clinical laboratory parameter.

The number and percentage of patients who have post-baseline potentially clinically significant (PCS) clinical laboratory values will be tabulated by cohort. The criteria for PCS laboratory values will be detailed in the SAP. The percentages will be calculated relative to the number of patients who have available non-PCS baseline values and at least 1 post-baseline assessment. The numerator will be the total number of patients with available non-PCS baseline values and at least 1 post-baseline PCS value. A supportive listing of patients with post-baseline PCS values will be provided, including the patient number and baseline and post-baseline values by cohort for the Safety Population.

Urinalysis and Coagulation results will be listed by patient.

10.9.3 ECOG

Descriptive statistics for ECOG performance at baseline (pre-study) and changes from pre-study to End-of-Study will be presented by cohort.

10.9.4 Vital Signs

Descriptive statistics for vital signs (systolic and diastolic BP, pulse rate, weight, respiration rate, and temperature) at baseline (pre-study) and changes from pre-study to End-of-Study will be presented by cohort. Descriptive statistics for interim vital signs (systolic and diastolic BP, pulse rate) during the PK profiling period (time between first dose of investigational product and the End-of-Study) at baseline (pre-dose) and changes from baseline at post-dose will be presented by cohort.

Vital sign values will be considered to be PCS if they meet both the observed value criteria and the change from baseline value criteria that will be detailed in the SAP. The incidence of PCS values will be presented. The percentages will be calculated relative to the number of patients who have baseline values and at least 1 post-baseline assessment. The numerator will be the total number of patients with at least 1 PCS post-baseline value. For the Safety Population, a supportive listing of patients with PCS post-baseline values will be provided, including the patient number and baseline and post-baseline values, by cohort for pre-Study and End-of-Study assessments and by treatment for assessments during the PK profiling period.

10.9.5 Electrocardiograms

Descriptive statistics for ECG parameters (HR, PR interval, QRS duration, QT interval, and QTc) will be reported.

10.9.6 Physical Examination

Individual data listings for physical examination results will be presented for each subject.

10.9.7 Weight and Height

Weight, height, BMI and BSA will be listed and summarized by cohort.

10.9.8 Prior and Concomitant Medication

Prior medication will be defined as any medication taken within 14 days prior to the first dose of the study drug and stopped prior to the first dose of study drug.

Concomitant medication will be defined as any medication taken during the study between the date of the first dose of study drug and the date of the End-of-Study Visit. Any medications started after the End-of-Study Visit will not be considered concomitant medications.

Individual data listings will be presented for each subject, with separate listings for prior medications and concomitant medications. In addition, concomitant medications will be summarized by Anatomical Therapeutic Chemical (ATC) classes and PT using frequency counts and percentages. For the summaries of concomitant medications, subjects who take the same medication (in terms of PT) more than once will be counted only once for that medication.

10.10 Biomarker and Pharmacodynamic Exploratory Analyses

Descriptive statistics will be provided depending on the available data from evaluation of biomarker samples, available tumor biopsies and archived tissue samples for presence of study drug in the samples.

Analyses and parameters will be detailed in the SAP.

10.11 Interim Analysis

No interim analysis is planned for this study.

10.12 Missing data

Missing data will not be imputed for this study.

11. CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

If any amendments to this protocol are necessary, the Sponsor will propose them in writing to the Investigator. Any amendments proposed by the Investigator will be reviewed and approved by the Sponsor prior to submission for IRB review and implementation. No protocol amendment may be implemented (with the exceptions noted below) before it has been submitted to the Regulatory Agency and approved by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC). In addition the Investigator signature page must be signed and submitted to the Sponsor.

If the protocol is amended to eliminate or reduce the risk to patients, the amendment may be implemented before IRB/IEC review and approval. However, the IRB/IEC must be informed in writing of such an amendment, and approval must be obtained within reasonable time limits.

Protocol waivers will be allowed only in extremely rare circumstances where patient benefit is established and there is complete agreement between the Investigator and the Sponsor.

Protocol deviations brought to the attention of the Sponsor after their occurrence will only be recognized and assessed for ethical, medical, scientific, and regulatory implications and for impact on the patient's participation in the study, and will be documented. Such deviations cannot be waived.

Protocol violations (which are deviations that have a major impact on the patient's rights, safety, or well-being or the integrity and authenticity of the study data) can never be waived.

12. ETHICAL CONSIDERATIONS

This study will be performed in accordance with the protocol, the Declaration of Helsinki, the International Conference on Harmonization **(**ICH) Harmonized Tripartite Guideline for GCP, and all applicable local regulatory requirements. The study will be conducted in full compliance with Therapeutic Goods Administration (TGA)/ United States Food and Drug Administration(FDA) guidelines for GCP and in accordance with the ethical principles that have their origins in the Declaration of Helsinki and 21 CFR §312.120.

12.1 Independent Ethics Committee / Institutional Review Board

It is the responsibility of the Investigator to obtain the approval of the IEC / IRB before the start of the study. A copy of the approval letter will be supplied to the Sponsor, along with a roster of IEC / IRB members. During the course of the study, the Investigator or designee will provide timely and accurate reports to the IEC / IRB on the progress of the study at appropriate intervals (not to exceed 1 year) and at the completion of the study. Investigator or designee will notify the IEC / IRB of serious AEs (SAEs) or other important safety findings. The study protocol, informed consent form (ICF), information sheet advertisements (if any), and amendments (if any) will be approved by the IRB at each study center in conformance CFR, Title 21, Part 56.

12.2 Patient Information and Consent

Before the start of any study-related procedures are undertaken, the Investigator or designee must obtain written, informed consent from each patient in accordance with US federal regulations (21 CFR §50) and the ICH document "Guidance for Industry – E6 Good Clinical Practice: Consolidated Guidance". Informed consent will be obtained by discussing with the patient the purpose of the study, the risks and benefits, the study procedures, and any other information relevant to the patient.

The Investigator or designee must explain to the patient that for purposes of evaluating the study results, that patient's private health information obtained during the study may be shared with the Sponsor, regulatory agencies, and IECs / IRBs, before enrolling that patient into the study. It is the US Investigator's (or designee's) responsibility to obtain permission to use private health information per the Health Information Portability and Accountability Act (HIPAA) from each patient, or if appropriate, the patient's legal representative.

The patient or his/her legal representative will document his/her informed consent by signing the current version of the written, IRB-approved ICF. The person who conducted the informed consent discussion with the patient and/or patient's legal representative (if applicable) must also sign the ICF. The patient is given a fully executed copy of the ICF bearing all appropriate signatures, and the original must be maintained in the clinical master files at the site.

The Investigator, or designee, is responsible for the content of the ICF, but the original and any updated versions must be approved by the Sponsor prior to submission to the IRB/IEC. The ICF should also include any additional information required by local laws relating to institutional review. All active patients participating on the protocol must be re-consented each time the ICF is updated and re-approved by the IRB/IEC.

13. STUDY MANAGEMENT AND INVESTIGATOR OBLIGATIONS

13.1 Principal Investigator and Clinical Sites

The Principal Investigator (PI) at each study center (clinical site) will be responsible for ensuring that the investigation is conducted according to the signed Investigator's statement, the protocol, and ICH GCP guidelines.

The Principal Investigator at each clinical site will be responsible for the management of the study, which will include but not be limited to oversight of other designated study Investigators and study staff conducting any activities related to the study, maintenance of the study file and patient records, correspondence with the IRB, and completion of the electronic case report forms (eCRFs).

13.2 Study Safety Review Committee

Members: The Investigators, Sponsor representative, Sponsor designated Medical Monitor and Sponsor designated PK expert will comprise the Study Safety Review Committee (SRC).

A description of this committee's role is defined in Section 3.1.6: Study Safety Review Committee.

13.3 Data Monitoring

Before the first patient is dosed in the study, a Sponsor representative will meet with the Investigator and clinical site study staff to review the procedures for conducting the study and to train the staff on recording the data on the eCRFs using the electronic data capture (EDC) system. The Sponsor representative will periodically monitor the progress of the study by conducting on-site visits. The Sponsor representative will also be able to review query statuses remotely, which may warrant more frequent communication with the Investigators and clinical site study staff.

The Investigator will make available to the Sponsor representative the source documents, the signed consent forms, all other study-related documents, and the computer that accesses the eCRFs. The Investigator or designee will be responsible for reviewing eCRFs, resolving data queries generated by the Sponsor via the system, providing missing or corrected data, approving all changes to the data, and endorsing the patient data within the EDC system. This approval method will include applying an electronic signature, a uniquely assigned username and a password that together will represent a traditional handwritten signature.

13.4 Data Recording and Documentation

Data collection will involve the use of the Sponsor EDC system, to which only authorized personnel will have access. In addition to periodic monitoring occurring within the system by Sponsor personnel, programmatic edit checks will be used to review the data for completeness, logic, and adherence to study protocol. As a result of this monitoring and these checks, queries may be issued electronically to the clinical study center and answered electronically by that study center. The identifying information (assigned username, date, and time) for both the originator of the query (if created during the monitoring process) and the originator of the data change (if applicable), as well as the Investigator's approval of all changes performed on his or her patients' data, will be collected.

All data collected in the context of this study will be stored and evaluated according to regulatory requirements and applicable guidance for electronic records. Data will be stored and evaluated in such a way as to guarantee patient confidentiality in accordance with the legal stipulations applying to confidentiality of data. Study records (e.g., copies of eCRFs, regulatory documents, etc.) will be retained at the study center, along with adequate source documentation, according to FDA and ICH requirements. All study records must be available for inspection by the Sponsor, its authorized representatives, and FDA officials.

13.5 Retention and Review of Records

The PI must maintain the documentation relating to this study. If the Sponsor, the FDA, or another regulatory authority wishes to review any documentation relating to the study, the PI must permit access to such records.

The PI must retain a copy of all records that support the CRFs for this study (e.g., ICFs, clinical laboratory reports, source documents, investigational product dispensing records) for a period of at least 15 years after study completion unless local regulations or study center policies require a longer retention period or otherwise notified in writing by the Sponsor.

If the PI retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a suitable alternate custodian employee of the study center or to a suitably qualified and responsible third party. The Sponsor must be notified in writing of the name and address of the new custodian before such transfer is made.

No study records shall be destroyed without notifying and giving the Sponsor the opportunity to arrange long-term storage for such study records or to authorize in writing the destruction of records after the required retention period.

13.6 Patient Confidentiality

All patient records will only be identifiable by a unique patient identification number. Patients' names or identifying information other than the data as specified for the eCRF collection are not to be transmitted to the Sponsor. The PI will keep a master patient list on which the patient number and full name, address, and telephone number of each patient are listed.

14. STUDY SPONSORSHIP

The Sponsor for this study is:

CERULEAN PHARMA AUSTRALIA PTY LTD

[redacted]

Cerulean Pharma Inc. (parent company)

[redacted]

The Sponsor Medical Director and contact person is:

[redacted]

The Sponsor Back-up Medical Director and contact person is:

[redacted]

14.1 Study Audits and Inspections

The study may be evaluated by the Sponsor and/or designees and government inspectors who must be allowed access to eCRFs, source documents, and other study files. Sponsor audit reports will be kept confidential. The Investigator should promptly notify Sponsor of any audits scheduled by any regulatory authorities, and promptly forward copies of audit reports.

14.2 Study Termination

The Sponsor reserves the right to terminate the study in its entirety or at a specific study center at any time.

14.3 Reporting and Publication

All data generated in this study will be the property of the Sponsor. An integrated clinical and statistical report will be prepared at the completion of the study.

Publication of the results by the Investigators will be subject to the signed contractual agreement between the PI and the Sponsor.

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APPENDICES

APPENDIX A

ECOG Performance Status

Level	ECOG*
0	Normal activity
1	Symptoms but ambulatory
2	In bed <50% of time
3	In bed >50 % of time
4	100 % bedridden
5	Dead

* As published in American Journal of Clinical Oncology:
Oken M, Creech RH, Tormey DC, Horton J, Davis TE, McFadden E, Carbone PP. Toxicity and response criteria of the eastern cooperative oncology group. *Am J Clin Oncol.* (CCT) 1982; 5:649-655.

Credit to Eastern Cooperative Oncology Group, Robert Comis MD, Group Chair

APPENDIX B

National Cancer Institute's Common Terminology Criteria for Adverse Events NCI-CTCAE Version 4.03

NCI Common Terminology Criteria for Adverse Events (CTCAE) v.4 data files and related documents can be accessed at:

http://evs.nci.nih.gov/ftp1/CTCAE/About.html

The quick reference document for version 4.03 can be accessed at:

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

APPENDIX C

CYP3A Inhibitors

http://www.straighthealthcare.com/cytochrome-p450-3a4.html

- **CYP3A STRONG INHIBITORS**
  - Boceprevir (Victrelis®) [7,9]
  - Clarithromycin (Biaxin®) [1,9]
  - Cobicistat (part of Stribild®) [7]
  - Conivaptan (Vaprisol®) [9]
  - Fluvoxamine (Luvox®) - likely a strong inhibitor [7]
  - Grapefruit Juice (in large amounts, > 1 liter a day, and in high concentrations) [9]
  - Indinavir (Crixivan®) [1,9]
  - Itraconazole (Sporanox®) [1,9]
  - Ketoconazole (Nizoral®) [1,9]
  - Lopinavir and Ritonavir (Kaletra®) [9]
  - Nefazodone (Serzone®) [1,9]
  - Nelfinavir (Viracept®) [1,9]
  - Posaconazole (Noxafil®) [9]
  - Quinupristin (Synercid®) [7]
  - Ritonavir (Norvir®, Viekira Pak™) [7, 9]
  - Saquinavir (Invirase®) [9]
  - Telaprevir (Incivek®) [7,9]
  - Telithromycin (Ketek®) [1,9]
  - Voriconazole (Vfend®) [7,9]

- **CYP3A MODERATE INHIBITORS**
  - Aprepitant (Emend®) [9]
  - Atazanavir (Reyataz®) [7,9]
  - Ciprofloxacin (Cipro®) [9]
  - Darunavir (Prezista®) [9]
  - Diltiazem (Cardizem®, Cartia®, etc) [5,9]
  - Dronedarone (Multaq®) [7]
  - Erythromycin (E.E.S.®, Ery-Tab®, etc) [9]
  - Fluconazole (Diflucan®) [9]
  - Fosamprenavir (Lexiva®)
  - Grapefruit Juice (in lower concentrations and smaller amounts) [9]
  - Imatinib (Gleevec®) [9]
  - Verapamil (Calan®, Covera-HS®, Verelan®, etc) [9]

- **CYP3A WEAK INHIBITORS**

- Alprazolam (Xanax®) [9]
- Amiodarone (Cordarone®) [9]
- Amlodipine (Norvasc®) [9]
- Atorvastatin (Lipitor®) [6,9]
- Bicalutamide (Casodex®) [9]
- Cilostazol (Pletal®) [9]
- Cimetidine (Tagamet®) [9]
- Cyclosporine (Neoral®,etc) [9]
- Dihydroergotamine (DHE-45®, Migranal®) [5,7]
- Ergotamine (Cafergot®) [5,7]
- Fluoxetine (Prozac®) [9]
- Ginkgo (supplement) [9]
- Goldenseal (Hydrastis canadensis, root) [9]
- Imipramine (Tofranil®) [11]
- Isoniazid [9]
- Nilotinib (Tasigna®) [9]
- Oral contraceptives [9]
- Ranitidine (Zantac®) [9]
- Ranolazine (Ranexa®) [9]
- Tipranavir (Aptivus®) [9]
- Zileuton (Zyflo®) [9]

- **CYP3A INHIBITORS (CLASS UNCERTAIN)**
- Azithromycin (Zithromax®) [5]
- Bromocriptine (Cycloset®, Parlodel®) [7]
- Chloramphenicol [2]
- Delavirdine (Rescriptor®) [7]
- Desipramine (Norpramin ®) [5]
- Danazol [5]
- Felodipine (Plendil®) [5]
- Iloperidone (Fanapt®) - *in vitro* studies only [7]
- Linagliptin (Tradjenta®) [7]
- Nicardipine (Cardene®) [5]
- Nifedipine (Adalat®, Procardia®, etc) [7]
- Quinidine [5]
- Simeprevir (Olysio®) - intestinal CYP3A4 inhibitor [7]
- Zafirlukast (Accolate®) (*in vitro* data only) [7]

- 1 - Flockhart DA. Drug Interactions: Cytochrome P450 Drug Interaction Table. Indiana University School of Medicine (2007). http://medicine.iupui.edu/clinpharm/ddis/table.aspx. Accessed [2011].
- 2 - SuperCYP website
- 3 - PMID 9884161
- 4 - PMID 12011477

- 5 - PMID 18043468 - big 3a chart
- 6 - PMID 21182938
- 7 - Manufacturer's Package Insert (for drug labeled)
- 8 - PMID 19074530
- 9 - FDA drug development and drug interactions
- 10 - PMID 15557548
- 11 - PMID 17471183
- 12 - PMID 18505790